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PRINCIPAL INVESTIGATOR: Hans P.A. Van Dongen, PhD

CONTRACTING ORGANIZATION: Washington State University

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14. ABSTRACT Sleep loss, which is common in military operations, causes significant deficits in situational awareness and decision making, but the underlying mechanisms are not well understood. In this project, healthy young adults were assigned to laboratory-based sleep deprivation or a control condition. Study participants were tested on a suite of performance tasks, specifically developed for the study, while well-rested and during 38 hours of sleep deprivation. We found that impairments due to sleep deprivation could not be explained as mere downstream consequences of degraded vigilant attention. Reduced binding of acquired knowledge may also contribute to sleep deprivation-induced deficits. Expectation-driven cognitive processing may have both advantageous or disadvantageous consequences, depending on the context. However, cognitive flexibility training did not appear to be a viable countermeasure for the effects of sleep deprivation on situational awareness and decision making. Based on our findings, we developed a novel framework for understanding the effects of sleep deprivation on operationally relevant task performance. This provides a foundation for future interventions to increase resilience against operational performance impairment and help improve the safety and success of US military missions around the globe, and could benefit millions of Americans who are frequently deprived of sleep due to medical conditions or professional demands.					
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1. INTRODUCTION

Sleep loss, which is common in military operations, causes significant deficits in situational awareness and cognitive flexibility in decision making, especially in fast-paced, dynamically changing circumstances. The development of countermeasures against these deficits is hampered by an incomplete understanding of the underlying cognitive and brain mechanisms.

Many decision-making contexts require that individuals use cues from their environment, paired with knowledge of previous decision outcomes, to form expectation-driven decision making strategies. This experience-based form of decision making enhances performance outcomes (e.g., decision making efficiency or accuracy) when circumstances are stable. However, real-world decision-making circumstances are often dynamic and fast-paced, requiring the ability to rapidly update and adapt decision-making strategies. Studies conducted by our laboratory have revealed that sleep deprivation impairs the ability to form expectation-driven decision making patterns and diminishes the ability to adapt these patterns to changing contingencies (Whitney et al., 2015, 2017; Satterfield et al., 2018; Honn et al., 2019).

Previous models of sleep deprivation and cognition have posited that vigilant attention is the principal contributor to performance impairment regardless of task requirements (Lim & Dinges, 2010). However, the extant literature has pointed to a wide range of cognitive deficits ranging from working memory failure to enhanced susceptibility to interference; from increased impulsivity to executive function deficits; and many other, seemingly distinct aspects of cognition (Jackson & Van Dongen, 2011). To reconcile these paradoxical perspectives and better understand the causes of sleep loss-induced performance impairment, we began a line of research with support from the Department of Defense.

Importantly, we brought to light the importance of the *task impurity problem*, which entails that performance on a task may be degraded by sleep deprivation due to deficits in any or all of the cognitive components involved in performing the task (Whitney &

Hinson, 2010). Thus, for example, a working memory task may be impacted by sleep deprivation because of degraded working memory function, or because of degraded other cognitive processes such as stimulus encoding or sustained attention. Correctly interpreting the effect of sleep deprivation on task performance necessitates a decomposition of the effects of sleep deprivation on the dissociable components of cognition that make up performance of the task (Jackson et al., 2013).

As part of this line of research, we showed that sleep deprivation substantially degrades sustained attention (Hudson et al., 2019), attentional arousal (Ratcliff & Van Dongen, 2009), the fidelity of information processing (Chavali et al., 2017), and the quality of information stored in memory (Ratcliff & Van Dongen, 2018). However, the effects of sleep deprivation are negligible for semantic encoding (Honn et al., 2018), working memory scanning (Tucker et al., 2010), and resistance to proactive interference (Tucker et al., 2010; Fournier et al., 2018).

Our previous studies further indicated that sleep loss causes significant impairment in attentional control, which refers to the ability to allocate attention to goal-relevant information. That is, we observed profound deficits in decision making during sleep deprivation when changing circumstances required the reallocation of attentional resources. This occurred in an AX continuous performance task (AX-CPT) paradigm, which required subjects to make a conditioned response to a particular cue-probe combination (A–X) and then adjust to a switch of the valid cue-probe combination (Whitney et al., 2017). It also happened in go/no-go reversal learning tasks, in which subjects were to use response accuracy feedback to learn a given stimulus-response mapping and subsequently adapt to an unannounced reversal of the stimulus-response mapping (Whitney et al., 2015; Honn et al., 2019).

Through the assessment of genetic polymorphisms associated with inter-individual differences in vulnerability to impairment on these tasks, we showed that the deficits in attentional control exposed by these studies were independent of the deficits in sustained attention caused by sleep loss (Whitney et al., 2017; Satterfield et al., 2018). These findings revealed that sleep deprivation produces multiple, distinct impairments in

cognitive processing, and that situational awareness and cognitive flexibility in decision making may be impacted by sleep deprivation due to reduced sustained attention and/or, in particular, degraded attentional control.

In the present research project, we sought to further clarify these mechanisms by means of a carefully controlled laboratory experiment, and to provide a scientific basis for the development of targeted countermeasures. N=91 young adults (50 men, 51 women), aged 21–38 years (mean $\pm$ SD: 26.7 $\pm$ 5.2 years), were randomized to a sleep deprivation condition (n=60) or a control condition (n=31). The subjects were tested on performance tasks specifically developed for this study, both at baseline and during 38 hours of total sleep deprivation (or equivalent well-rested control). A subset of the subjects assigned to the sleep deprivation condition received cognitive flexibility training.

As described in section 3, the results of the study provided new insights into the mechanisms underlying the situational awareness and decision making deficits people experience under fast-paced, dynamically changing conditions, and provided a foundation for increasing resilience against operational performance impairment due to sleep deprivation. This will help to improve the safety and success of US military missions around the globe, and will also benefit the millions of Americans who are frequently deprived of sleep due to sleep disorders, other medical conditions, and/or professional demands.

2. KEYWORDS

Sleep deprivation, performance impairment, attentional control, situational awareness, mission success, resilience

3. ACCOMPLISHMENTS

What were the major goals of the project?

Sleep loss, which is common in military operations, causes significant deficits in situational awareness and cognitive flexibility in decision making, especially in fast-paced, dynamically changing circumstances. The development of countermeasures against these deficits is hampered by an incomplete understanding of the underlying cognitive and brain mechanisms. To address this issue and develop a foundation to increase resilience against operational performance impairment due to sleep deprivation, we sought to address the following specific aims:

Aim 1: Demonstrate dissociable effects of sleep loss on vigilant attention and dynamic attentional control and isolate their influences in operationally relevant performance.

Aim 2: Show that effects of sleep loss on the use of proactive and reactive control are responsible for failures of situational awareness and risky decision errors.

Aim 3: Explore cognitive flexibility training as a method to protect against sleep loss-induced failures of situational awareness and risky decision errors.

In a carefully controlled, laboratory sleep deprivation experiment, we significantly refined our understanding of the underlying mechanisms and formed a knowledge base for the development of targeted countermeasures. This contributes significantly to our long-term objective of establishing a scientific framework for improving the safety and success of US military missions.

Stated goals not met: none.

What was accomplished under these goals?

Laboratory sleep deprivation study

N=91 young adults (50 men, 51 women), aged 21–38 years (mean $\pm$ SD: 26.7 $\pm$ 5.2 years) completed a 4-day in-laboratory study. They were randomized (at a ratio of 2:1) to a 38-hour total sleep deprivation condition (n=60) or a control condition (n=31). Subjects randomized to the sleep deprivation condition were further randomized to receive cognitive flexibility training (n=30) or no such training (n=30). A schematic of the study design is shown in Figure 1.

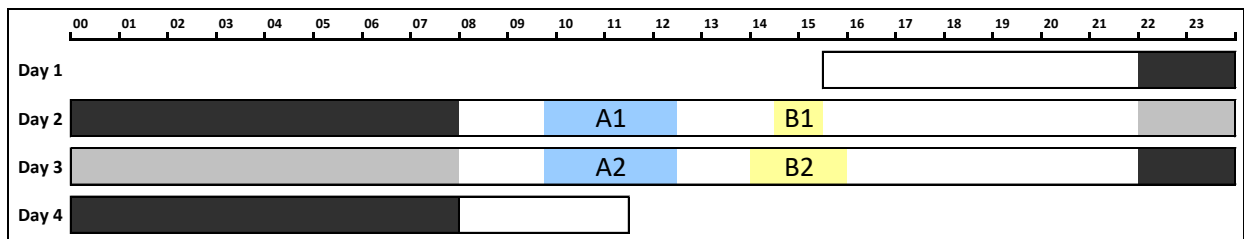


Figure 1: Schematic of the 4-day in-laboratory study design. Bars indicate time in the laboratory; white denotes scheduled wakefulness, black denotes scheduled sleep, gray denotes scheduled sleep in the control condition only. Cognitive performance was measured in test batteries administered in the late morning (A1, A2) and early afternoon (B1, B2) of day 2 (baseline) and day 3 (sleep deprivation or well-rested control). Cognitive flexibility training (if assigned) occurred in the beginning of test bout B2, and the effects of the training (if assigned) were assessed at the end of test bout B2.

Subjects were in the laboratory for 4 days / 3 nights continuously, under constant observation and physiological monitoring. In the sleep deprivation condition, subjects had one night with 10 hours time in bed for baseline sleep, then underwent 38 hours of total sleep deprivation (equivalent to missing one night of sleep), and then were given one recovery night with 10 hours time in bed for sleep. Those in the control condition had 10 hours in bed for sleep on all three nights. Subjects were tested on a range of cognitive performance tasks at baseline and after sleep deprivation (or well-rested control). Half the subjects in the sleep deprivation condition received cognitive flexibility training prior to testing on some of the cognitive flexibility tasks during sleep deprivation,

which included an operationally relevant task requiring situational awareness and cognitive flexibility.

New paradigm for understanding deficits in situational awareness and cognitive flexibility in decision making due to sleep deprivation

The central premise of our study was that sleep deprivation induces changes in attentional control that are critically involved in loss of situational awareness and in poor decision making. We argued that the effects of these changes will be especially profound when individuals making decisions are weighing risks in fast-paced, dynamically changing circumstances such as military encounters. Based on the data obtained in through this project, we identified how sleep deprivation affects the fundamental attentional control processes that govern both the development of situational awareness and the flexible updating of situational awareness based on changing conditions.

To understand how situational awareness of current goals and conditions is constructed, we must understand: (1) how people use environmental cues, including feedback arising from the outcomes of actions, to associate current goals and task elements within the focus of attention, and (2) how people manage the inherent tradeoff of balancing the maintenance of current task-relevant information in the focus of attention versus updating of information to adapt to shifting events, goals and contingencies. High OPTEMPO tasks, in which multiple related decisions must be made over time and circumstances can change unpredictably, are especially challenging for managing the maintenance-updating tradeoff in the control of attention.

Multiple lines of existing evidence (Braver et al., 2009; Jimura & Braver, 2010; Cools & D'Esposito, 2011; Armbruster et al., 2012; Braver, 2012; Whitney et al., 2017; Whitney et al., 2019) indicate that processes of binding goals and task elements into a coherent situational model, and the ability to update the situational model, are highly dependent on the neural pathways among the hippocampus (HPC), prefrontal cortex (PFC), and striatum. During early experiences with a novel task environment, the ability to

recognize the goal-relevant features and organize, or bind, them into mental representations that guide performance is critically dependent on HPC–PFC connections (Brown et al., 2016; Mack et al., 2017). When task goals change, or representations of task elements need updating, again the HPC is critical, in conjunction with striatal processing, to update the information maintained in the focus of attention by the PFC. The role of the HPC in dynamic attentional control may seem surprising given that it has long been regarded as the critical brain region for declarative memory, but it is now well established that the HPC is implicated in the process of binding and re-binding of elements across a wide range of tasks, including tasks that involve overcoming perceptual interference or competition from established responses. The key pathways are summarized in the dynamic attentional control framework shown below in Figure 2, which presents a new paradigm for understanding the effects of sleep deprivation on situational awareness and cognitive flexibility in decision making.

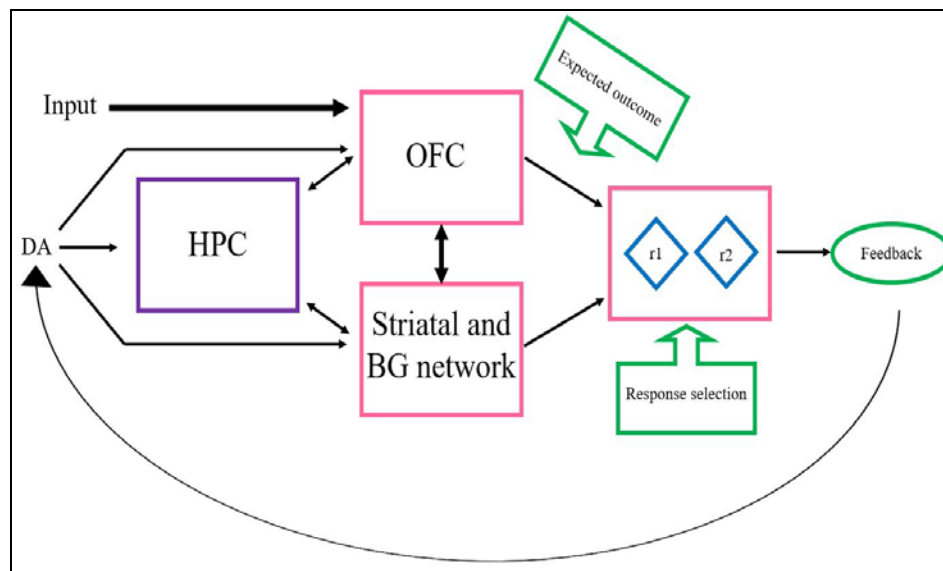


Figure 2: Dynamic attentional control framework. In decisions between two response options (r1 and r2), the orbitofrontal cortex (OFC), hippocampus (HPC), and striatal–basal ganglia (BG) network play complementary roles. Feedback over trials produces expected outcomes for each response option. These expectations are created by HPC binding of choice options and outcomes. The expectations, along with current goals and strategies, are maintained in working memory via dopamine (DA) dependent processing in the OFC. Feedback contrary to expectations destabilizes working memory and allows for flexibility in responding. The processes responsible for flexibility are dependent on DA circuits in the striatal–BG network and the HPC. See Whitney et al. (2019).

The data we obtained through our study are consistent with the conclusion that the effects of sleep deprivation on multiple cognitive tasks can be understood in terms of a bias produced with the dynamic attentional control pathways displayed in Figure 2. Because sleep deprivation leaves the ability to maintain and use information in the focus of attention, or working memory, relatively spared, but impairs binding of contingencies and cognitive flexibility, performance under sleep deprivation is characterized by perseveration on familiar and well-established patterns. What this implies for situational awareness in operational contexts is that sleep-deprived people will be especially error-prone when conditions are dynamically changing and highly trained responses no longer fit the current circumstances.

Both developing choice–outcome associations and adapting to shifting response contingencies are clearly manifested in the laboratory tasks we have used in our previous research and in the data collected through the present project. Our data show that when sleep-deprived, subjects have slower and less effective acquisition of choice–outcome associations, and those associations, when established, may be less flexible than those of rested subjects. That is, in general sleep-deprived subjects can maintain their current task association in the focus of attention, but this maintenance comes at the expense of updating the current associations to match decision feedback and changing contingencies in the environment. The evidence we collected in support of this new paradigm is described in the sections below.

Sleep deprivation does not necessarily change risk seeking/avoidance or framing bias, but risky decision making is impacted by more than just declines in vigilant attention

We investigated the effects of sleep deprivation on the Framed Gambling Task (FGT), which is a risky decision making task that requires the acquisition of knowledge from outcomes of gamble choices to obtain optimal performance (e.g., Wilson et al., 2018a; Wilson et al., 2018b). To help understand the results we obtained in the present study, we first discuss the results of an earlier laboratory study with healthy adult subjects (study 2 in Satterfield et al., 2015), in which the task was administered twice: once

during baseline, and once 24 hours later after 26 hours of wakefulness (n=8) or well-rested control (n=9).

On every trial in each test bout, a choice was offered between a sure option (e.g., gain \$50) on the one hand, and one of two gamble options on the other hand. Of the two gamble options, one was a good gamble and the other a bad gamble, as defined by expected (average) gains or losses. The two gamble options were differentiated visually (i.e., a blue deck labeled “x” and a green deck labeled “y”), but initially, the expected outcomes for each of the gamble options was ambiguous. Subjects thus had to acquire knowledge about the probabilistic gains and losses obtained from choices of these options in order to determine which gambles were advantageous and which were disadvantageous, versus the alternative sure option.

The sure option was included to create a framing bias in decision making – when the sure option is a loss, people are predisposed to choose the gamble, whereas when the sure option is a gain, people are predisposed to avoid gambling (Tversky & Kahneman, 1981; Kühberger, 1998; Levin et al., 1998). Optimal decision making on the FGT requires that subjects overcome the pre-existing framing bias and only gamble when the gamble is a good choice but not when it is a bad choice. By design, the good gamble option in the FGT was always the better choice, even if a sure gain was the alternative; and the bad gamble was always the worse choice, even if a sure loss was the alternative.

Thus, performance on the FGT was deemed accurate if the subject gambles when the good gamble is offered and takes the sure option when the bad gamble is offered. To be able to perform accurately, subjects had to acquire, maintain, and update information about the gamble options. Probe questions were included to determine whether subjects had accurate estimations of the good and bad gamble outcomes. The task contained 4 blocks of 18 trials each. The probe questions appeared after trial block to measure knowledge acquisition over time.

As shown in Figure 3, performance on the FGT was not significantly degraded by sleep deprivation. As expected, accurate choices improved across trial blocks (of 18 trials) during each test bout (repeated-measures ANOVA, effect of trial block, $F_{1,15}=7.05$, $p=0.018$). Accuracy also improved across test bouts (effect of test bout, $F_{2,30}=11.94$, $p<0.001$), in both the sleep deprivation and control groups. The effects of sleep deprivation were not statistically significant (effect of session by group, $F_{1,15}=0.012$, $p=0.915$; effect of session by group by block, $F_{2,30}=0.640$, $p=0.534$).

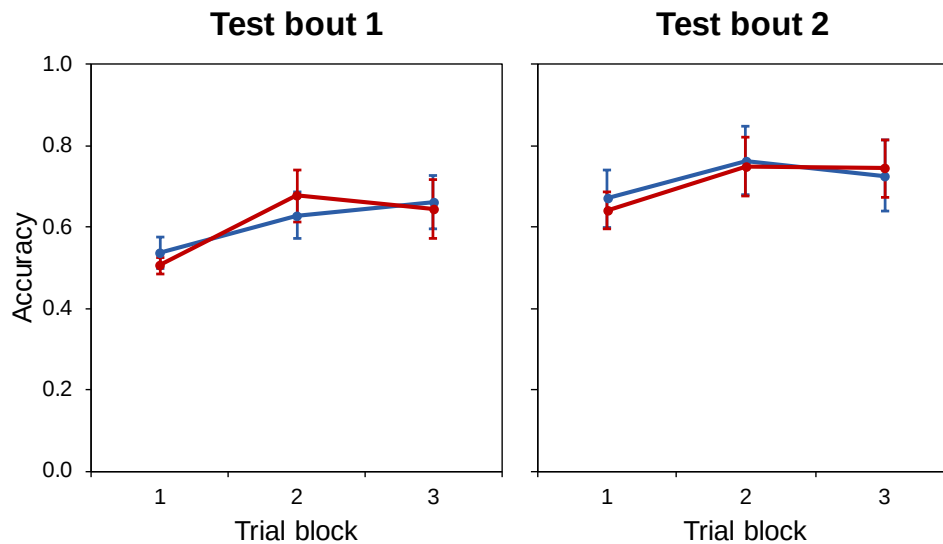


Figure 3: FGT accuracy (means $\pm$ SE) over three blocks of 18 trials each during test bout 1 (baseline) and test bout 2 (sleep deprivation or well-rested control) in the sleep deprivation group (red) and the control group (blue).

There was a positive correlation between choice accuracy and the accuracy of gamble estimates as assessed with the probe questions ($r=0.61$, $p<0.001$). Thus, sleep-deprived subjects, like well-rested subjects, obtained the required choice feedback information and were able to update and maintain accurate knowledge on which to base their gamble choices, allowing them to make accurate gambles and overcome their pre-existing framing bias.

These results must be interpreted with the understanding that the FGT implemented in the earlier study did not have any response deadline – i.e., decision making on each trial was not time-limited. However, the time pressures often associated with making decisions in real-world contexts may contribute to errors in decision making, especially

while sleep-deprived (Satterfield et al., 2013). In the present project, therefore, we implemented a modified version of the FGT with a response deadline of 2 seconds – the “speeded FGT.” During the laboratory study (Figure 1), the speeded FGT was administered twice: once at baseline and once 24 hours later after 27 hours of wakefulness (n=56) or well-rested control (n=30).

Even with the severe response deadline of the speeded FGT, subjects showed the expected improvement across trial blocks (effect of trial block, $F_{1,84}=20.44$, $p<0.001$). However, in the second test bout, sleep-deprived subjects showed lower accuracy (interaction of group by test bout, $F_{2,84}=4.15$, $p=0.045$) and less improvement across trial blocks (interaction of group by test bout by trial block, $F_{2,168}=3.97$, $p=0.021$) than the well-rested controls; see Figure 4.

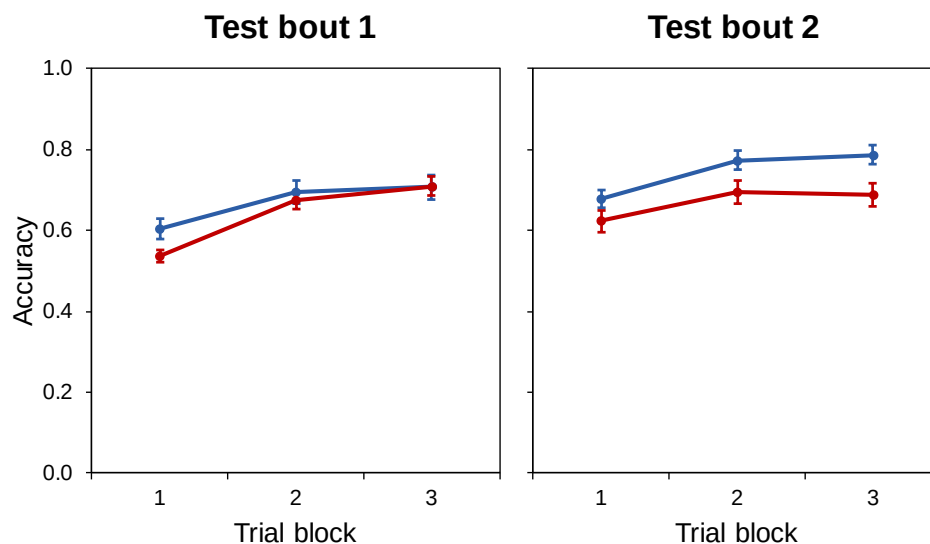


Figure 4: Accuracy (means $\pm$ SE) on the *speeded* FGT over three blocks of 18 trials each during test bout 1 (baseline) and test bout 2 (sleep deprivation or well-rested control) in the sleep deprivation group (red) and the control group (blue).

Taken together, these results indicate that sleep-deprived subjects can meet the multiple cognitive demands of risky decision making in the FGT, when other constraining factors are limited (Figure 3). In this task setting, sleep loss, by itself, does not alter propensity to gamble – it does not change the degree of risk seeking or risk avoidance – nor does it significantly affect pre-existing framing bias. However, when the

time available to acquire, update, and utilize task-relevant information is constrained by a decision making deadline, impairment due to sleep deprivation emerges (Figure 4). While some sleep-deprived subjects remain resilient in the face of this challenge, more individuals begin to show compromised performance when a response deadline is imposed.

Furthermore, the probe questions revealed that accurate choice outcome information, while necessary, is not sufficient for optimal decision making performance on the FGT. Under conditions with minimal task constraints, sleep-deprived individuals can acquire and properly utilize risky decision making task information. Time pressure changes this, suggesting that time pressure interacts with sleep deprivation to degrade the acquisition of task-relevant information, or the utilization of this information, or both.

Poor task performance during sleep deprivation has previously been attributed to a generic, downstream effect of the deterioration of vigilant attention (Lim & Dinges, 2010). While this would seem to be inconsistent with the lack of a sleep deprivation effect on FGT accuracy in the task version without response deadline, in that version of the task it is possible that sleep-deprived subjects are able to maintain accuracy because of a speed–accuracy tradeoff. However, this does not explain how sleep-deprived subjects are able to acquire and utilize task-relevant knowledge on the task equally well as well-rested subjects – these aspects of the task are not implicated in the effects of sleep deprivation based on whether or not the task has a response deadline. As such, the effects of sleep deprivation on speeded FGT performance cannot be attributed to downstream effects of the deterioration of vigilant attention alone. Rather, it appears that sleep-deprived individuals are slower and less effective in acquiring, updating, and maintaining associative bindings between choices and outcomes of those choices.

Sleep deprivation-induced reduction in knowledge acquisition contributes to, but does not fully explain, errors in decision making

As we have shown previously (Whitney et al., 2015; Satterfield et al., 2018; Honn et al., 2019), sleep deprivation causes errors in decision making on traditional reversal-learning tasks that require subjects to make decisions based on acquired knowledge, then to update relevant knowledge to accommodate a reversal in task contingencies. In this project, we investigated this further. During the laboratory study (Figure 1), we administered the Two-Card Reversal (TCR) task, in which subjects were required to learn through feedback which of two decks of gamble options more consistently resulted in gains and which more consistently resulted in losses. There were five trial blocks of 12 trials each. Over halfway through the task (immediately before the fourth trial block), the deck contingencies reversed without warning. Prior to this reversal, we probed subjects' knowledge of the values associated with the decks. The TCR task was administered twice: once at baseline and once 24 hours later after 26 hours of wakefulness (n=44) or well-rested control (n=24).

Regardless of test bout or condition, performance improved over trial block in the pre-reversal phase (repeated-measures ANOVA with Greenhouse-Geisser correction on degrees of freedom, effect of trial block, $F_{2,41,149.30}=52.36$, $p<0.001$). As expected, the subjects also exhibited an immediate decline in accuracy when the deck contingencies reversed (Bonferroni-adjusted contrasts, pairwise comparison between trial block 3 and trial block 4: mean difference $\pm$ SE: 0.327 ± 0.037 , $p<0.01$). During test bout 2, we found that overall performance was worse in the sleep deprivation group as compared to the well-rested control group (pairwise comparison between sleep deprivation group and control group in test bout 2: mean difference $\pm$ SE: 0.10 ± 0.034 , $p=0.004$). Moreover, pre-reversal performance improved from test bout 1 to test bout 2 in the control group (pairwise comparison between session 1 and session 2 in blocks 1–3 in the control group: mean difference $\pm$ SE: 0.075 ± 0.029 , $p=0.014$), but not in the sleep deprivation group ($p=0.34$). See Figure 5.

Compared to well-rested controls, poorer performance in the sleep deprivation group was accompanied by poorer knowledge of the deck outcomes ($t_{62.73}=3.77$, $p<0.001$). In a linear regression model with condition, level of knowledge, and their interaction, knowledge was the only significant predictor of performance in test bout 2 ($t_{62}=3.45$, $p<0.001$). Thus, subjects made more advantageous decisions when they demonstrated more explicit knowledge of the deck contingencies.

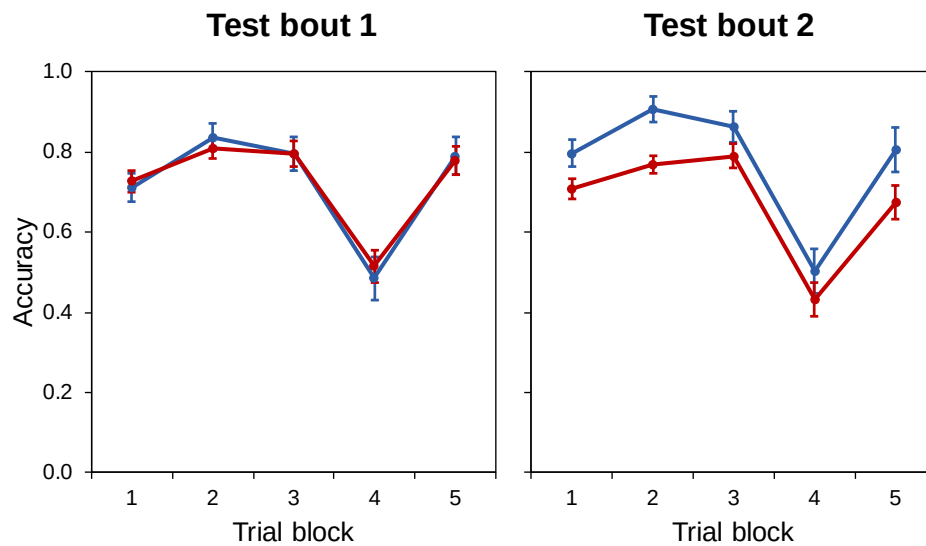


Figure 5: TCR task performance accuracy (means $\pm$ SE) over five trial blocks of 12 trials each, with reversal of contingencies immediately before trial block 4, during test bout 1 (baseline) and test bout 2 (sleep deprivation or well-rested control) in the sleep deprivation group (red) and the control group (blue).

These results suggest that for most individuals, sleep deprivation hinders the ability to accumulate decision-relevant knowledge, which causes errors in decision making.

However, knowledge alone may not be sufficient to ensure effective TCR task performance. As shown in Figure 6, several subjects in the sleep deprivation group showed adequate knowledge of the deck choices before the reversal, but nonetheless failed to make advantageous decision on the TCR task. Only about 60% of sleep-deprived subjects in the highest tertile of level of knowledge were also in the highest

tertile of decision making performance. This suggests that an additional process other than knowledge acquisition is also necessary for good TCR task performance.

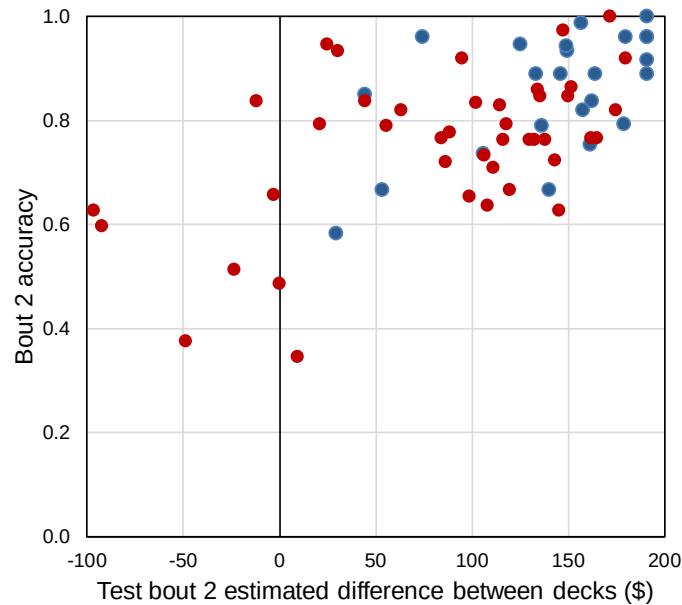


Figure 6: Relationship between level of knowledge, which is the estimated difference between decks (calculated as good deck estimation – bad deck estimation) and performance accuracy on the TCR task during the second test bout, in sleep-deprived individuals (red) and well-rested controls (blue). The actual difference between the good and bad decks is 100.

Expanding on our previous investigations into the effects of sleep deprivation on cognitive flexibility (Whitney et al., 2015; Honn et al., 2019), we also administered a simplified go/no-go reversal learning (GNGr) task, in which subjects used outcome feedback for decisions to detect and adapt to an unannounced reversal of the go and no-go response mappings. The specifics of the task are described elsewhere (Whitney et al., 2015). Here we reduced the stimulus sets to a bare minimum of two pairs of numbers, i.e., as simple and undemanding as possible while avoiding a ceiling effect in performance. In addition, we announced in advance and provided extensive practice with the pre-reversal stimulus sets during an additional phase of trial blocks at the beginning of the task. Further, after each trial in the practice phase we asked subjects to recall and report the stimulus that was presented. There were 32 trials in the practice

phase, 40 or 48 trials in the pre-reversal phase (depending on task version, so that the reversal would not happen at the same point in the task each day), and 40 trials in the post-reversal phase. For analysis, each phase was divided into 4 trial blocks. This version of the GNGr task was administered twice: once at baseline and once 24 hours later after 27 hours of wakefulness (n=45) or well-rested control (n=25).

Even on this simplified GNGr task, sleep-deprived subjects showed impairment in the pre- and post-reversal phases during test bout 2; see Figure 7. The fraction of hits (correct responses to “go” stimuli) were analyzed with a mixed-effects ANOVA with fixed effects for group (sleep deprivation or control), test bout (1 or 2), and phase (practice, pre-reversal, and post-reversal), and their interactions, with a random effect over subjects on the intercept. There was a trend towards more hits in the control group than the sleep deprivation group (mean $\pm$ SE: control group = 0.89 ± 0.026 , sleep deprivation group = 0.83 ± 0.020 ; fraction of hits by group: $F_{1,8040}=3.23$, $p=0.072$). There was a significant effect of hits by test bout (mean $\pm$ SE: test bout 1 = 0.88 ± 0.017 , test bout 2 = 0.84 ± 0.017 ; fraction of hits by test bout: $F_{1,8040}=36.41$, $p<0.001$) and by phase, with the highest rate of hits pre-reversal (mean $\pm$ SE: practice phase = 0.84 ± 0.017 , pre-reversal phase = 0.90 ± 0.017 , post-reversal phase = 0.83 ± 0.017 ; fraction of hits by phase: $F_{2,8040}=38.81$, $p<0.001$). There was also a group by test bout interaction, with the sleep deprivation group performing worse in test bout 2 (fraction of hits by group by test bout: $F_{1,8040}=48.83$, $p<0.001$). There was no significant interaction of group by phase ($p=0.58$), test bout by phase ($p=0.87$), or group by test bout by phase ($p=0.93$). Pairwise comparisons between groups by phase showed no difference during test bout 1 in the practice ($p=0.71$), pre-reversal ($p=0.75$), or post-reversal phases ($p=0.79$). In test bout 2, the sleep deprivation group had a significantly lower fraction of hits in all 3 phases (practice: $t_{8040}=3.06$, $p=0.002$; pre-reversal: $t_{8040}=3.20$, $p=0.001$; post-reversal: $t_{8040}=2.86$, $p=0.004$).

Similarly, there was a trend towards significance for false alarms (FAs; incorrect responses to “no go” stimuli) by group (mean $\pm$ SE: control group = 0.096 ± 0.011 , sleep deprivation group = 0.12 ± 0.009 ; fraction of FAs by group: $F_{1,8040}=3.08$, $p=0.079$) and by test bout (mean $\pm$ SE: test bout 1 = 0.10 ± 0.008 , test bout 2 = 0.12 ± 0.008 ; fraction

of FAs by test bout: $F_{1,8040}=3.09$, $p=0.079$). There was a significant effect of FAs by phase (mean $\pm$ SE: practice phase = 0.081 ± 0.009 , pre-reversal phase = 0.098 ± 0.008 , post-reversal phase = 0.15 ± 0.008 ; fraction of FAs by phase: $F_{2,8040}=30.20$, $p<0.001$) and significant group by test bout interaction ($F_{1,8040}=27.69$, $p<0.001$). There was a trend toward a significant test bout by phase interaction ($F_{2,8040}=2.46$, $p=0.085$), and no significant interaction of group by phase ($p=0.35$) or group by test bout by phase ($p=0.53$). Similar to hits, pairwise comparisons of FAs between groups by phase showed no difference during test bout 1 in the practice ($p=0.11$), pre-reversal ($p=0.83$), or post-reversal phases ($p=0.70$). In test bout 2, the sleep deprivation group had a significantly greater fraction of FAs in all 3 phases (practice: $t_{8040}=2.39$, $p=0.017$; pre-reversal: $t_{8040}=2.86$, $p=0.004$; post-reversal: $t_{8040}=2.86$, $p=0.004$).

Probe recall accuracy in the practice phase was high in both test bouts, even after sleep deprivation. There was a significant difference in accuracy by session (mixed-effects ANOVA, $F_{1,4408}=4.38$, $p=0.036$) and a significant group by session interaction ($F_{1,4408}=16.06$, $p<0.001$), with reduced accuracy during test bout 2 in the sleep deprivation group. However, even in the latter case, accuracy remained high (mean $\pm$ SE: 0.95 ± 0.01). While knowledge (probe recall) was high, performance (fraction of hits/FAs) across all phases was impaired in the sleep deprivation group during test bout 2. Thus, as with the TCR task, this suggests that an additional process other than knowledge acquisition (e.g., related to utilization of knowledge) is also necessary for good decision making task performance.

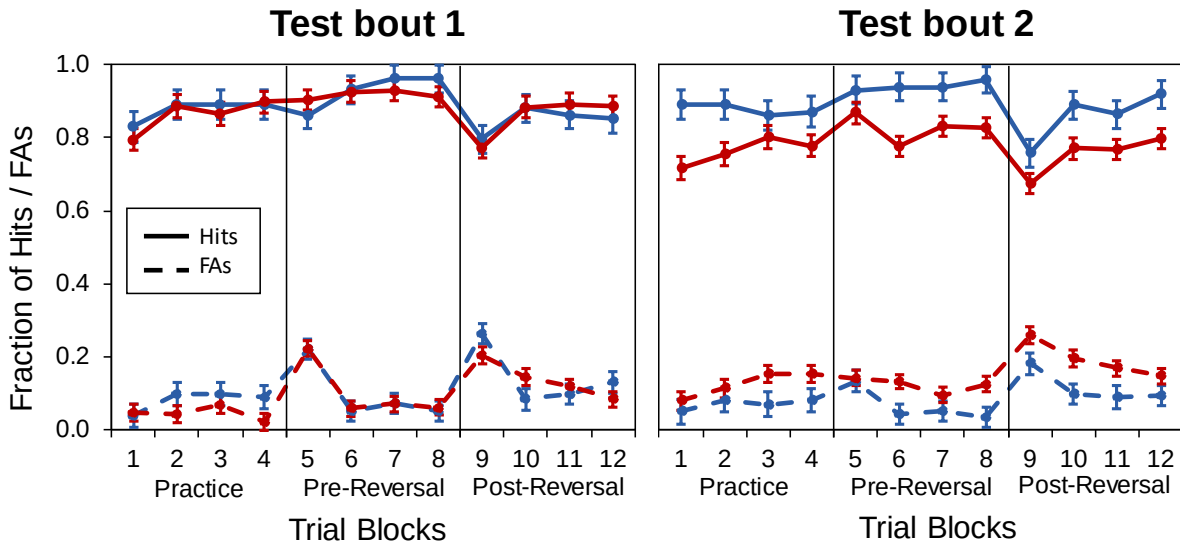


Figure 7: Means ($\pm$ SE) for hits (responses to go stimuli) and false alarms (FAs; responses to no-go stimuli) on a simplified go/no-go reversal learning task at baseline (test bout 1) and after sleep deprivation or well-rested control (test bout 2), in sleep-deprived individuals (red) and well-rested controls (blue).

Advantages and costs of expectation-driven processing during sleep deprivation

We posit that good decisions must be driven by informative expectations (e.g., from experience-based knowledge) regarding the relationship between choices and outcomes. Without developing these expectations, people are unlikely to use choice outcome feedback to 1) develop good decision making patterns based on experience, and 2) adapt to changing circumstances. Expectation-driven decision making has been studied in a variety of contexts using the continuous performance task with switch (AX-version; AX-CPTs), and we have previously implemented this task (Whitney et al., 2017). The AX-CPTs requires that subjects make speeded responses to probe letters that are preceded by a cue. In the pre-switch phase, subjects are instructed to respond with a left mouse click to the target pair (A-X) and with a right mouse click to all other pairs of letters (e.g., A-Y). The A-X target pair is presented 70% of the time, such that individuals form expectation-driven response patterns based on the expectation that the cue “A” predicts the probe “X”. About half-way through the task, the subjects are instructed to respond with a left mouse click to a new target pair (B-Y) and with a right mouse click to all other pairs (including the old target pair). Distractor trials are

presented throughout the task to measure the ability to resist interference on non-target trials that contain the cue “A” or the probe “X”.

For the purposes of the present project, we developed novel indices of attentional control, vigilant attention, and adaptive decision making. Accuracy on pre-switch A-X trials is used as an index of vigilant attention, and all other indices are accuracy on other trial types normalized to pre-switch A-X accuracy because this index of vigilant attention reflects the upper threshold of performance (as declines in attention have downstream consequences for all trial types in this task). Pre-switch accuracy on trials with a target cue and a non-target probe, and with a non-target cue and a target probe, measure resistance to cue interference and resistance to probe interference, respectively. Post-switch accuracy on the new-target trials (B-X) measures cognitive flexibility. Accuracy on A-X trials post-switch is a measure of the ability to switch response patterns. Accuracy on post-switch A-Y trials is a measure of resistance to interference from the old cue, and accuracy on post-switch B-X trials is a measure of resistance to interference from the old probe. In the present study, the AX-CPTs was administered at baseline (test bout 1), after 25.5 hours of sleep deprivation (n=55) or well-rested control (n=30) (test bout 2), and again after 30 hours of sleep deprivation or well-rested control (test bout 3).

The performance of individuals who employ expectation-driven decision making on the AX-CPTs is characterized by lesser resistance to cue interference versus probe interference, meaning that subjects have formed the expectation that a cue “A” will be followed by a probe “X”. We observed this pattern in both well-rested and sleep-deprived subjects during all three of the test bouts; see Figure 8. There were no significant between-group differences in test bout 1, before any subjects were sleep deprived. However, several between-group differences emerged during sleep deprivation (test bouts 2 and 3). Planned contrasts between the sleep deprivation and control groups revealed that the sleep deprivation group exhibited reduced vigilant attention during sleep deprivation (test bout 2: $F_{1,165}=33.85$, $p<0.001$; test bout 3: $F_{1,165}=22.21$, $p<0.001$), as expected. Furthermore, sleep deprivation resulted in

impaired ability to resist probe interference pre-switch (test bout 2: $F_{1,165}=26.99$, $p<0.001$; test bout 3: $F_{1,165}=18.51$, $p<0.001$).

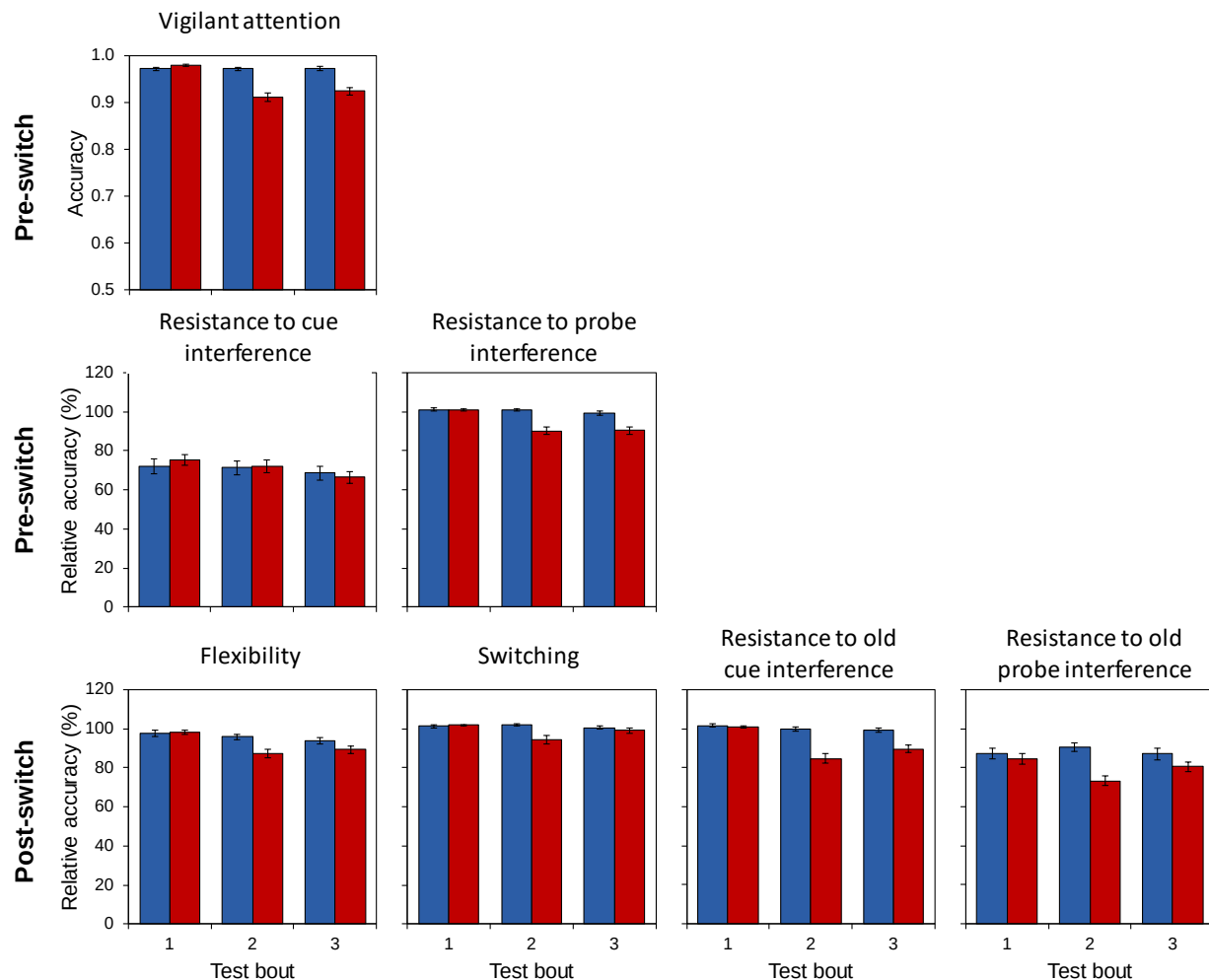


Figure 8: AX-CPTs performance (means $\pm$ SE), by index of attentional control or resistance to interference, over 3 test bouts (baseline, sleep deprivation or well-rested control bout 1, and sleep deprivation or well-rested control bout 2), in the sleep deprivation group (red) and the control group (blue).

Post-switch, we observed diminished cognitive flexibility in the sleep-deprived subjects (test bout 2: $F_{1,165}=11.33$, $p=0.001$; test bout 3: $F_{1,165}=3.19$, $p=0.076$), as compared to well-rested controls. Similarly, the sleep-deprived subjects exhibited worsened ability to switch response patterns, although this was only seen during test bout 2 ($F_{1,165}=13.23$, $p<0.001$). Furthermore, sleep-deprived subjects displayed diminished ability to resist interference from the old cue (test bout 2: $F_{1,165}=33.17$, $p<0.001$; test bout 3:

$F_{1,165}=13.59$, $p<0.001$). A similar pattern was observed for the ability to resist interference from the old probe (test bout 2: $F_{1,165}=19.63$, $p<0.001$; test bout 3: $F_{1,165}=2.80$, $p=0.096$).

These results indicate that sleep-deprived individuals can develop expectations regarding choice outcomes; however, this is at the expense of increased vulnerability to interference. Furthermore, sleep-deprived individuals have difficulty adjusting their expectations to accommodate a change in task contingencies, as we have shown previously (Whitney et al., 2017).

In the laboratory study, we also implemented another task that requires subjects to form expectations based on the pairing of a cue and a probe. In the novel Vigilance and Attentional Control (VAC) task, subjects are instructed to respond differently (with left or right mouse clicks) to images of a “friend” (e.g., a smiley face) and a “foe” (e.g., a mean face), and responses must be made within a 500 ms window. In the first 80 trials, 64 trials begin with a hint regarding the upcoming probe stimulus (the word “friend” or “foe” shown on screen before the presentation of the stimulus; the other 16 trials show “no hint” before the trial stimulus is presented). In this phase, the hints are 75% reliable, most often reflecting the upcoming probe. In the second phase of the task, which includes 48 “hint” trials and 16 “no hint” trials, the hints are 66% unreliable, most often not reflecting the upcoming probe. Due to the short response window, the formation of expectations based on the cue being valid is advantageous to responding quickly and accurately in the first phase of the task. However, in the second phase, reliance on the cues is disadvantageous to accuracy, so expectations should be updated to reflect a low cue-validity. The VAC was administered twice: once at baseline and once 24 hours later after 31 hours of wakefulness ($n=44$) or well-rested control ($n=27$).

Overall performance on the VAC is measured by accuracy in responding to the probe, and accuracy on specific trial types can reveal the functioning of specific components of attention and attentional control. Vigilant attention is measured as accuracy on no-cue trial types. Expectation-driven control may be broken up into two distinct measures; an

advantage of control and a cost of control. Specifically, the use of the cue to form an expectation regarding the probe describes a top-down decision making strategy. In the VAC, the use of a top-down strategy should result in good performance when a cue accurately predicts a probe (i.e., when the cue and probe are matched) – the most frequent trial type in the first phase. Therefore, our index for advantage of control was derived from the difference in accuracy between the matched trial type and the no-cue trial type. Furthermore, if an individual is relying on a top-down decision making strategy, this should result in poor performance when a cue does not accurately predict a probe (i.e., when the cue and probe are mismatched). Thus, our index of cost of control was calculated from the difference between the mismatched trial type and the no-cue trial type.

Figure 9 displays our observations for the VAC. As expected, sleep-deprived individuals exhibited reduced vigilant attention, as compared to well-rested controls, during test bout 2 (vigilant attention accuracy analyzed with a mixed-effects ANOVA by session, reversal, and condition: test bout by task phase by group interaction: $F_{1,69}=11.21$, $p=0.001$). However, there was no effect on the advantage index of control (Test bout by task phase by group interaction: $p=0.21$). Two possible sources may contribute to this: 1) expectation-driven top-down processing, and 2) automatic response priming. If subjects used a strong, expectation-driven top-down control strategy, we would expect there to be large costs to performance on mismatched trials (as calculated by the index of cost). However, we found no effect on the cost index (Test bout by task phase by group interaction: $p=0.11$).

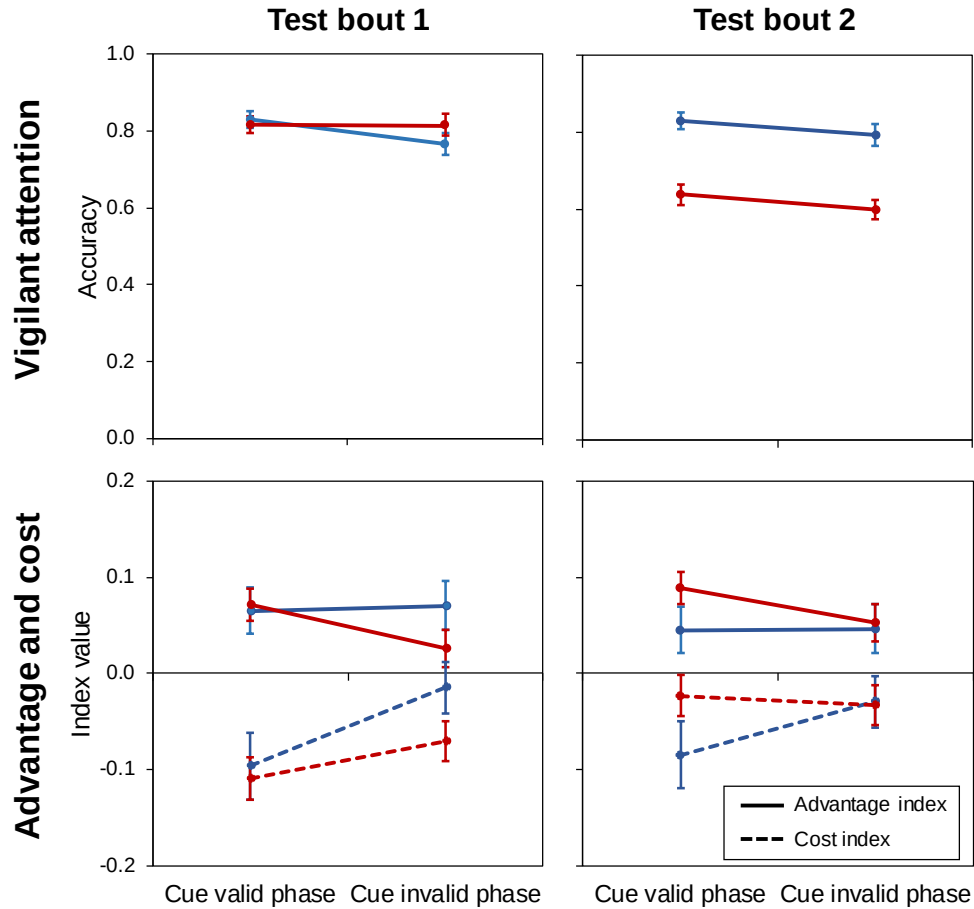


Figure 9: Indices (means $\pm$ SE) of vigilant attention (top panels), expectation-driven control advantage (bottom panels, solid lines), and expectation-driven control cost (bottom panels, dashed lines) in the first (primarily cue valid) phase and the second (primarily cue invalid) phase of the VAC, during test bout 1 (baseline) and test bout 2 (sleep deprivation or well-rested control) in the sleep deprivation group (red) and the control group (blue).

In the AX-CPTs and VAC, we gained converging evidence that deterioration of vigilant attention during sleep deprivation impacts decision making performance on some trial types. However, we obtained different results regarding the use of experience-based expectations. On the AX-CPTs, sleep-deprived subjects exhibited decision making patterns consistent with top-down expectation-driven processing. However, they also exhibited decreased ability to resist interference, which suggests that the use of expectation-driven processing while sleep-deprived may increase the risk of making errors when there is conflicting information. On the VAC, on the other hand, we did not observe these effects. This suggests that subjects did not employ strong expectation-

driven processing on the VAC, as compared to the AX-CPTs. This could be due to a difference in the salience of cues or stimuli, frequency of predictive cues, or task demands.

The results of a recently completed, different sleep deprivation study, in which we employed a version of the attention network test (ANT), may shed light on this issue. The ANT measures the ability to use an alerting cue to detect a stimulus (alerting effect), to use a spatial cue to shift the location of visual attention (orienting effect), and to manage response conflict (conflict effect) (Weaver et al., 2013). In this in-laboratory study with 14 healthy adult subjects (Salih et al., 2019), the task was administered twice: once during baseline, once 24 hours later after 26 hours of wakefulness, and once another 24 hours later after recovery sleep.

Consistent with earlier findings (Jugovac & Cavallero, 2011; Martella et al., 2011; Whitney et al., 2017), sleep deprivation did not significantly degrade the alerting effect on the ANT. In this study, sleep deprivation also did not significantly reduce the orienting effect. However, there was marked impairment in the conflict effect during sleep deprivation ($F_{2,26}=4.74$, $p=0.018$). Thus, sleep deprivation did not reduce subjects' ability to detect a stimulus and shift visual attention in response to cues. However, subjects experienced considerable difficulty managing response conflict while deprived of sleep. This finding is consistent with recent evidence from our group (Whitney et al., 2017) that sleep deprivation causes profound deficits in cognitive flexibility.

Taken together, these findings reveal that sleep deprivation impacts attentional control and resistance to interference to different degrees in different task paradigms. We observed poor cognitive flexibility and a strong interference effect on the AX-CPTs, whereas the VAC displayed relatively small effects of sleep deprivation. On the ANT, we found that interference from conflicting information caused marked performance impairment in sleep-deprived individuals, but this effect was not observed in earlier work from our group and others on a Sternberg working memory task (Habeck et al., 2004; Tucker et al., 2010). While the deterioration of vigilant attention due to sleep deprivation causes substantial performance deficits on a variety of tasks (Lim & Dinges, 2010;

Hudson et al., 2019), the consequences of sleep deprivation for cognitive flexibility and resistance of interference appear to be driven by distinct mechanisms of attentional control (Whitney et al., 2017; Whitney et al., 2019) and the extent to which individuals use expectation-driven processing during task performance.

Implications for operationally more complex settings

To examine the effects of sleep deprivation on task performance and the underlying cognitive processes in operationally more complex contexts, we developed the Situational Awareness of Risk Dynamics (SARD) task. In the SARD, subjects are presented with treasure chests from three different zones of an island (see Figure 10). On each trial, the subject is given the option to open the treasure chest (play) or to pass on the treasure chest. Opening a chest costs \$100 of hypothetical money, but if it has treasure, a sum of \$600 is awarded. If the chest has poison, \$500 is lost. Through feedback, subjects must determine which zone is more advantageous to play (the “good” zone), which zone is more advantageous to avoid and should be passed (the “bad” zone), and which zone offers no advantage either way (the “neutral” zone). Partway through the task, the zones are switched unannounced and subjects must update their representations of these zones and their associated risks. The SARD consists of 5 blocks of 30 trials. In the laboratory study of the present project, the SARD was administered twice: once at baseline and once 24 hours later after 26 hours of wakefulness (n=55) or well-rested control (n=31).

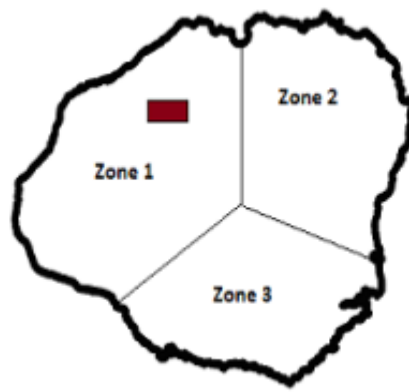


Figure 10: Situational Awareness of Risk Dynamics (SARD) task. Treasure chests containing either treasure or poison appear in three different zones of an island. The three zones are

associated with different levels of risk: in one zone it is advantageous to “play,” in another it is advantageous to “pass,” and in the last it is equally advantageous to play or pass. The locations of these different risk levels switch partway the task.

As expected, subjects’ performance improved over blocks of trials. With practice, subjects played more from the good zone (“hits”, repeated-measures ANOVA, effect of blocks, $F_{1,84}=32.70$, $p<0.001$) and less from the bad zone (“false alarms”, effect of blocks, $F_{1,84}=139.80$, $p<0.001$). The unannounced switching of the zones had a significant effect on performance, with subjects showing an immediate decrease in good choices as evidenced by a decrease in hits ($F_{1,84}=53.41$, $p<0.001$) and increase in false alarms ($F_{1,84}=92.21$, $p<0.001$). Importantly, sleep deprivation had a significant impact on hits (group by test bout interaction, $F_{1,84}=4.94$, $p=0.029$) and false alarms ($F_{1,84}=9.79$, $p=0.002$). In test bout 1, the groups chose to play from the good zones and avoid the bad zones at similar rates. However, in test bout 2, sleep-deprived subjects played less often from the good zones ($p<0.001$) and played more often from the bad zones ($p=0.003$) compared to well-rested controls. See Figure 11.

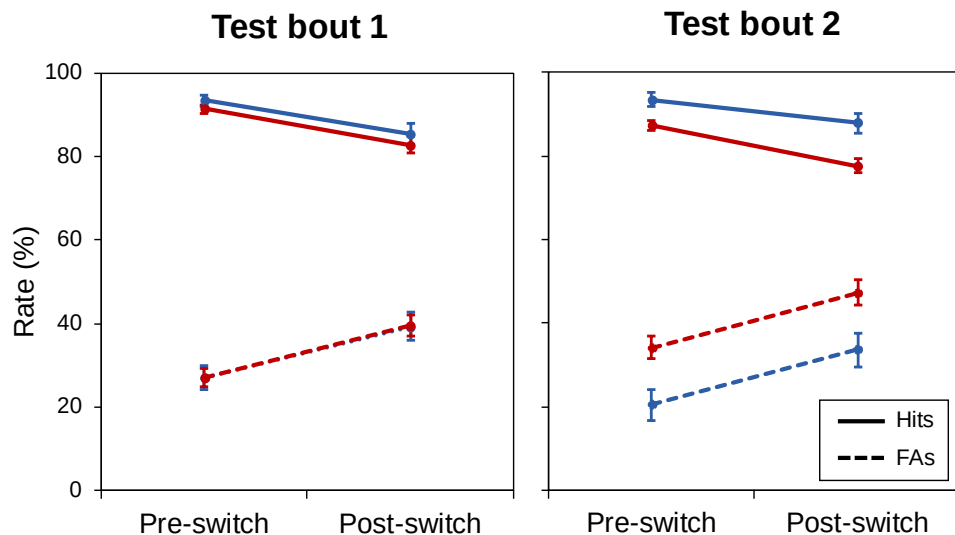


Figure 11: Means ($\pm$ SE) for hits (playing from the good zone) and false alarms (FAs; playing from the bad zone) in the pre- and post-switch phases of the SARD, at baseline (test bout 1) and after sleep deprivation or well-rested control (test bout 2), in sleep-deprived individuals (red) and well-rested controls (blue).

There were no significant effects of condition, test bout, or their interaction on subjects' propensity to play the neutral zone. In both test bouts, sleep-deprived subjects and well-rested controls played the neutral zone slightly less than 50% of the time, indicating they had some awareness of the probabilities associated with the neutral zone. As such, the poorer overall task performance, both pre- and post-switch, in the sleep-deprived subjects was not attributable to a generic increase in risk-taking behavior. These findings suggest that, in operationally more complex environments, sleep-deprived subjects continue to show an impaired ability to effectively acquire and update situational awareness when risks change dynamically.

To investigate the effectiveness of a potential countermeasure against such impairments, we developed a performance task called Robot Blast, in which subjects move through a simulated environment in which they must shoot "enemy" robots and not shoot "friendly" robot. The subject moves past a continuous row of crates. Each crate is either a tall metal crate or a short wooden crate. The subject approaches each crate, turns to face it, and the door opens to reveal either a friendly robot or an enemy robot. If an enemy robot appears and the subject does not shoot the robot within 500 ms, the robot shoots back and the subject sees feedback of losing 1 point; but if the subject shoots the enemy robot, the subject sees feedback of gaining 1 point. Similarly, if a friendly robot appears and the subject incorrectly shoots the robot, the subject loses 1 point; but if the subject withholds, the subject gains 1 point.

Prior to the task, subjects are shown images of the enemy and friendly robots and given a hint (e.g., "We suspect that the enemies are hiding in tall metal crates. Use this tip to your advantage!"). They are then presented with a one-question quiz asking where the hint suggested the enemy robots would be hiding; an incorrect response results in a prompt to try again and subjects must correctly respond in order to begin the task. In the first 20 trials (practice phase), the type of crate predicts the type of robot inside 100% of the time. In the next 120 trials (phase 1), the type of crate predicts the type of robot inside 80% of the time. Then there is a reversal, and during the next 40 trials (phase 2), the type of crate incorrectly predicts the type of robot inside 80% of the time.

Subsequently, subjects enter a new simulated environment and are instructed that the

enemy and friendly robots have switched, and they should now shoot the robots they previously were not to shoot, and vice versa. During the final 60 trials (phase), all crates are the same, so that the prior hint is no longer relevant.

We administered the Robot Blast task once, after 32 hours of sleep deprivation or equivalent well-rested control. On average, the sleep-deprived subjects made over twice as many errors as the well-rested controls (one-way ANOVA, $F_{1,66}=23.26$, $p<0.001$). Whereas there was no significant difference between the sleep-deprived and well-rested groups in the practice phase ($p=0.22$), subjects in the sleep deprivation condition performed significantly worse than subjects in the control condition in phases 1, 2 and 3 – see Figure 12.

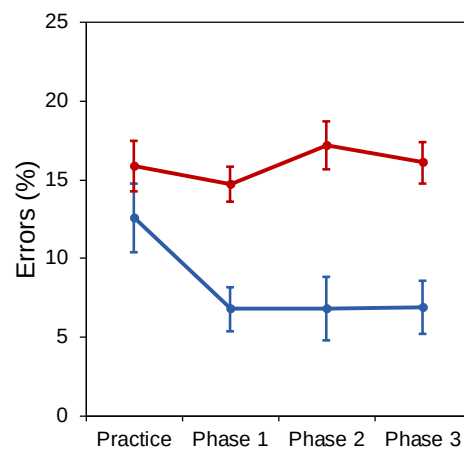


Figure 12: Percent of errors during each phase of the Robot Blast task in sleep-deprived individuals (red) and well-rested controls (blue).

Prior to the task (at the beginning of test bout B2, see figure 1), half the subjects in the sleep deprivation condition received cognitive flexibility training. This included four stories that subjects read through and answered questions related to decision-making (for example, in the first story, you are an emergency room doctor treating a patient for anxiety). In each story, an expectation is established (e.g., symptoms suggest an anxiety attack), a decision is made according to the expectation (e.g., you decide to administer the appropriate medication, leading to symptoms improving), and then something unexpected happens (e.g., the patient presents a different set of symptoms). You are then asked what to do next (e.g., continue the same medication as before or

change course, with the correct response including a change of course from the original expectation). The stories each end with a description of how the expectation was created and what signaled a change needing to be made. At the end of the series of stories, subjects are told to consider how to use feedback to support their decisions and to guide when to change decisions in their upcoming computer tasks. Subjects who did not receive the cognitive flexibility training were shown a similar series of stories with reading comprehension questions (rather than anticipate a decision questions) and no unexpected change in the events of the stories.

Within the sleep deprivation group, subjects who had received cognitive flexibility training performed no better or worse than those who had not received the training during the practice phase ($p=0.66$), phase 1 ($p=0.88$), and phase 2 ($p = 0.82$), although there was a trend of better performance following cognitive flexibility training in phase 3 ($p=0.076$). In phase 2, in which good performance may require cognitive flexibility to recognize the changing pattern and reverse cue expectations, sleep-deprived subjects who had received the prior cognitive flexibility training did not have a smaller proportion of errors related to cue reliance (i.e., responding according to an invalid cue rather than to the robot target) ($p=0.92$). These results indicate that cognitive flexibility training did not yield a robust improvement in sleep-deprived task performance.

The cognitive flexibility training was also followed by the AX-CPTs (test bout 3, as described above). We found a few differences in AX-CPTs performance between sleep-deprived subjects who completed the cognitive flexibility training and sleep-deprived subjects who completed no training. Those who completed the training had a trend for poorer performance on the index of vigilant attention ($t_{52}=1.71$, $p=0.093$), exhibited better switching ability (by 6%, $t_{52}=-2.18$, $p=0.034$), and showed worsened ability to resist interference from the old probe ($t_{52}=2.82$, $p=0.007$). Although assignment to training or no training was random, it cannot be ruled out that these differences may reflect between-subgroup differences apart from the training.

Our novel, dynamic attentional control framework (Figure 2) and the new experimental findings presented here cast doubt on the utility of cognitive flexibility training to

overcome the deficits produced by sleep deprivation in performance tasks that require acquisition and updating of situational awareness. Indeed, based on the effects of cognitive flexibility training on performance of the Robot Blast task and the AX-CPTs, there is no strong support for implementation of cognitive flexibility training as a countermeasure to the impact of sleep deprivation.

What opportunities for training and professional development has the project provided?

The project provided significant opportunities for graduate education and professional development:

- A postdoctoral researcher in the Department of Psychology at Washington State University, Courtney Kurinec, is developing a new line of research based in part on the present project. Her work focuses on the binding of information into memory and factors that perturb this process. The study we conducted and the cognitive tasks we embedded provided a unique opportunity to investigate a reversible perturbation (i.e., sleep deprivation) and its impact on memory and decision making.
- A Ph.D. student in the Neuroscience program at Washington State University, Darian Lawrence-Sidebottom, was involved in dissertation research integrated with the project. This included training in the management and processing of biosamples for subject screening and (ultimately) biomarker assessment; recording and scoring of sleep (polysomnography); recording and processing of galvanic skin conductance; programming of cognitive performance tasks in E-Prime software; data reduction and statistical analysis; and writing manuscripts. The graduate student was involved in the project under the direct mentorship of the PI and Co-PIs of the project, and training and experience was gained on a daily basis and in considerable depth. During all three years of the project, the graduate student presented her work at national conferences on sleep science.

- A Ph.D. student in the Experimental Psychology program (with Quantitative Concentration) at Washington State University, Samantha Riedy, was involved with the project as a sleep specialist and assistant statistician. The project offered unique opportunities to study the cognitive, psychometric, and statistical characteristics of performance outcomes on the various cognitive tests. Shortly after the end of Year 1 of the project, the student earned her M.S. degree on a thesis involving a detailed study of metrics of sustained attention. During all three years of the project, the graduate student presented her work at national conferences on sleep science. She also presented at an international conference on fatigue risk management.
- A Ph.D. student in the Experimental Psychology program at Washington State University, Amanda Hudson, was involved in this project to review the literature on sustained attention and sleep deprivation, on which she published a paper. She also received training in recording of sleep (polysomnography); recording and processing of galvanic skin conductance; programming of cognitive performance tasks in E-Prime software; and data reduction and statistical analysis. The graduate student was involved in the project under the direct mentorship of the PI and one of the co-PIs of the project, and training and experience was gained on a daily basis.
- A Ph.D. student in the Experimental Psychology program at Washington State University, Anthony Stenson, was involved in several of the cognitive performance tests developed for and employed in this project. He received training on the programming of cognitive performance tasks in E-Prime software; data reduction and statistical analysis; cognitive model development; and manuscript writing. The graduate student was involved in the project under the direct mentorship of two Co-PIs of the project, and training and experience was gained in considerable depth.
- Five post-baccalaureate research assistants – Regan Permito, Elizabeth Lewis, Myles Finlay, Lillian Skeiky, and Rachael Muck – were involved in the project during all stages of subject recruitment and screening and laboratory investigation and logistics. They were also each assigned a subset of the data collected in the study for independent processing and analysis under the supervision of the PI and Co-PIs.

This post-baccalaureate training opportunity is offered because the experience gained is widely considered of significant benefit for applications to graduate and medical school – the vast majority of postbaccalaureate trainees in our laboratory go on (after a year or two) to enroll in Ph.D. and M.D. programs across the country. So far, three of the post-baccalaureate research assistants have presented their work at national conferences.

- More than two dozen undergraduate students were involved in the project, providing around-the-clock staffing and constant behavioral monitoring during the 24/7 laboratory experimentation of the project. Records show that the experience gained in the laboratory helps these students significantly with their applications for graduate and medical school (or other endeavors they choose to pursue).

How were the results disseminated to communities of interest?

The results of the project have led to a paradigm shift in our understanding of the effects of sleep deprivation on situational awareness and decision making. This new paradigm has been presented to stakeholders in military and civilian settings at conferences and meetings across the US. In addition, several manuscripts are in development for publication in the scientific literature. The results of the project have also led to the development of a novel, brief performance test for the detection of deficits in both sustained attention and cognitive flexibility, which will be further developed as a diagnostic tool for clinically relevant cognitive impairment in sleep disorders.

4. IMPACT

What was the impact on other disciplines?

The data we collected have resulted in the development of a novel framework for the cognitive mechanisms that underlie errors in dynamic decision making during sleep deprivation (see Figure 2). Furthermore, we developed a suite of novel performance tasks that allow us to differentiate deficits in cognitive processes underlying operationally relevant decision making. In the field of cognitive psychology, our data point to a need to shift away from the dual mechanisms of attentional control view (Braver, 2012), in which discrete modes of control are present or absent in particular task settings, and where comprise of these discrete elements accounts for differences in observed performance. As an alternative, our results indicate that the focus should be on the various cognitive control demands of tasks that will include separable effects of vigilant attention, acquisition, retention and updating of information in working memory, and resistance to interference (Whitney et al., 2019). In the field of sleep science, this work represents a paradigm shift in understanding the effects of sleep deprivation on cognitive performance and brain function (Honn et al., 2019).

What was the impact on technology transfer?

Nothing to Report.

What was the impact on society beyond science and technology?

One of the pervasive – but poorly understood – effects of sleep deprivation on society is its disastrous impact on situational awareness and decision making. Errors in decision making cannot be explained solely by the currently well-known effects of sleep loss such as attentional lapsing. Well-known examples of deterioration of decision-making capabilities include the Space Shuttle Challenger accident and the nuclear meltdown at

Chernobyl; other examples abound. This project revealed basic cognitive mechanisms that underlie this phenomenon, and provided a cohesive framework (Figure 2) for ongoing and future studies to help develop countermeasures and improve safety in 24/7 operational settings.

5. CHANGES/PROBLEMS

Changes in approach and reasons for change

Nothing to Report.

Actual or anticipated problems or delays and actions or plans to resolve them

Nothing to Report.

Changes that had a significant impact on expenditures

Nothing to Report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Nothing to Report.

Significant changes in use or care of human subjects

Nothing to Report.

Significant changes in use or care of vertebrate animals

Nothing to Report. (Not Applicable.)

Significant changes in use of biohazards and/or select agents

Nothing to Report. (Not Applicable.)

6. PRODUCTS

Journal publications

Banks S, Landon LB, Dorrian J, Waggoner LB, Centofanti SA, Roma PG, Van Dongen HPA. Effects of fatigue on teams and their role in 24/7 operations. *Sleep Medicine Reviews*, 2019; 48: 101216. Acknowledgement of federal support: yes. [See Appendix](#).

Hudson AN, Van Dongen HPA, Honn KA. Sleep deprivation, vigilant attention, and brain function: A review. *Neuropsychopharmacology Reviews*, 2019; doi: 10.1038/s41386-019-0432-6 [Epub ahead of print]. Acknowledgement of federal support: yes. [See Appendix](#).

James FO, Waggoner LB, Weiss PM, Patterson PD, Higgins JS, Lang ES, Van Dongen HPA. Does implementation of biomathematical models mitigate fatigue and fatigue-related risks in Emergency Medical Services operations? A systematic review. *Prehospital Emergency Care*, 2018; 22: 69-80. Acknowledgement of federal support: yes. [See Appendix](#).

Ratcliff R, Van Dongen HPA. The effects of sleep deprivation on item and associative recognition memory. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, 2018; 44(2): 193-208. Acknowledgement of federal support: yes. [See Appendix](#).

Satterfield BC, Hinson JM, Whitney P, Schmidt MA, Wisor JP, Van Dongen HPA. Catechol-O-methyltransferase (COMT) genotype affects cognitive control during total sleep deprivation. *Cortex*, 2018; 99: 179-186. Acknowledgement of federal support: yes. [See Appendix](#).

Satterfield BC, Stucky B, Landolt HP, Van Dongen HPA. Unraveling the genetic underpinnings of sleep deprivation-induced impairments in human cognition. *Progress*

in Brain Research, 2019; 246: 127-158. Acknowledgement of federal support: yes. [See Appendix.](#)

Satterfield BC, Wisor JP, Schmidt MA, Van Dongen HPA. Time-on-task effect during sleep deprivation in healthy young adults is modulated by dopamine transporter genotype. Sleep, 2017; 40(12): zsx167. Acknowledgement of federal support: yes. [See Appendix.](#)

Skene DJ, Skorniyakov E, Chowdhury NR, Gajula RP, Middleton B, Satterfield BC, Porter KI, Van Dongen HPA, Gaddameedhi S. Separation of circadian- and behavior-driven metabolite rhythms in humans provides a window on peripheral oscillators and metabolism. Proceedings of the National Academy of Sciences, 2018; 115(3): 7825-7830. Acknowledgement of federal support: yes. [See Appendix.](#)

Skorniyakov E, Gaddameedhi S, Paech GM, Sparrow AR, Satterfield BC, Shattuck NL, Layton ME, Karatsoreos I, Van Dongen HPA. Cardiac autonomic activity during simulated shift work. Industrial Health, 2019; 57: 118-132. Acknowledgement of federal support: yes. [See Appendix.](#)

Vanderheyden WM, Van Dongen HPA, Frank MG, Gerstner JR. Sleep pressure regulates mushroom body neural-glial interactions in Drosophila. Matters Select, 2019; 201903000008. Acknowledgement of federal support: yes. [See Appendix.](#)

Walsh MM, Gunzelmann G, Van Dongen HPA. Computational cognitive modeling of the temporal dynamics of fatigue from sleep loss. Psychonomic Bulletin & Review, 2017; 24: 1785-1807. Acknowledgement of federal support: yes. [See Appendix.](#)

Whitney P, Hinson JM, Nusbaum AT. A dynamic attentional control framework for understanding sleep deprivation effects on cognition. Progress in Brain Research, 2019; 246: 111-126. Acknowledgement of federal support: yes. [See Appendix.](#)

Books or other non-periodical, one-time publications

Ph.D. dissertations:

Satterfield BC. Genetic markers of inter-individual and task-dependent differences in neurobehavioral impairment during total sleep deprivation. Ph.D. dissertation, 2017, Washington State University, accepted. Acknowledgement of federal support: yes.

Skornyakov S. Sleep, autonomic nervous system, and neurobehavioral outcomes. Ph.D. dissertation, 2017, Washington State University, accepted. Acknowledgement of federal support: yes.

Conference abstracts:

Honn KA, Van Dongen H. Paradoxical effect of stimulus density on PVT time-on-task effect during sleep deprivation. *Sleep*, 2018; 41 (Abstract Suppl.): A84. Acknowledgement of federal support: yes. See Appendix.

Satterfield BC, Wisor JP, Schmidt MA, Van Dongen H. DAT1 genotype modulates the time-on-task effect on the PVT during total sleep deprivation. *Sleep*, 2017; 40 (Abstract Suppl.): A1-A2. Acknowledgement of federal support: yes. See Appendix.

Sherazi NA, Riedy SM, Satterfield BC, Schmidt MA, Wisor JP, Van Dongen H. TLR4 genotype is associated with nocturnal sleep duration and consolidation. *Sleep*, 2018; 41 (Abstract Suppl.): A9. Acknowledgement of federal support: yes. See Appendix.

Van Dongen HPA, Gaddameedhi S, Crooks E, Chowdhury NR, Gajula RP, Middleton B, Satterfield BC, Porter K, Skene DJ. Internal desynchrony of central and peripheral circadian rhythms during simulated night shift work. *Sleep Science*, 2019; 12 (Suppl. 3): 71. Acknowledgement of federal support: yes. See Appendix.

Other publications, conference papers, and presentations

Invited lectures:

Honn KA. Fatigue and accident risk: from momentary attentional lapses to prolonged decision-making impairments. Invited lecture at NASA Ames Research Center; Mountain View, California, June 2018.

Van Dongen HPA. Cognitive deficits associated with sleep deprivation. Invited lecture at the Idaho Sleep Professionals Association conference; Boise, Idaho, October 2018.

Van Dongen HPA. Impairments in cognitive performance and emotion regulation due to sleep deprivation. Invited symposium presentation at the SLEEP 2017 conference; Boston, Massachusetts, June 2017.

Van Dongen HPA. Individual differences in the effects of sleep deprivation on performance: Cognitive and genetic differentiation of bottom-up and top-down brain processes. Invited lecture at the University of Helsinki; Helsinki, Finland, September 2018.

Van Dongen HPA. Individual susceptibility to fatigue: impacts for the transportation industry. Invited lecture at the Fatigue in Transportation Forum; Montreal, Canada, June 2018.

Van Dongen HPA. New insights into cognitive impairment due to sleep deficiency in healthy individuals and patients with sleep disorders. Invited lecture at the Woolcock Institute of Medical Research; Sydney, Australia, October 2018.

Van Dongen HPA. Shift work, sleep loss, and managing fatigue risk. Invited lecture at the 2018 Northwest Safety & Health Summit; Anchorage, Alaska, May 2018.

Van Dongen HPA. Sleep deprivation: Effects on health, performance, and safety. Invited lecture at the 2017 Northwest Safety & Health Summit; Spokane, Washington, May 2017.

Van Dongen HPA. Sleep deprivation and the impact on safety. Invited lecture at the Washington Logging Safety Conference; Grand Mound, Washington, January 2019.

Oral presentations at conferences:

Honn KA. More than just nodding off: the relationship between sleepiness and accidents. Oral presentation at the World Sleep 2017 conference; Prague, Czech Republic, October 2017.

Honn KA. Paradoxical effect of stimulus density on PVT time-on-task effect during sleep deprivation. Oral presentation at the SLEEP 2018 conference; Baltimore, Maryland, June 2018.

Lawrence-Sidebottom D. Stability of interindividual differences in top-down attentional control. Oral presentation at the Inland Northwest Research Symposium; Spokane, Washington, April 2019.

Van Dongen HPA. Catechol-O-methyltransferase (COMT) genotype affects dynamic decision making during sleep deprivation. Oral presentation at the Military Health System Research Symposium; Orlando, Florida, August 2018.

Van Dongen HPA. Dealing with multiple dimensions of fitness for duty in biomarker development. Oral presentation at the Sleep DownUnder 2018 conference; Brisbane, Australia, October 2018.

Van Dongen HPA. Impaired cognitive flexibility due to sleep deprivation predicts degraded deadly force decision-making in high-fidelity law enforcement simulations. Oral presentation at the SLEEP 2017 conference; Boston, Massachusetts, June 2017.

Van Dongen HPA. Sleep deprivation and loss of situational awareness: Mechanisms and mitigation strategies. Oral presentation at the SLEEP 2019 conference; San Antonio, Texas, June 2019.

Van Dongen HPA. Toward a common metric for risk assessment across diverse factors in fatigue risk management systems: Quantifying human performance in terms of signal-to-noise ratio. Oral presentation at the 10th International Conference on Managing Fatigue; San Diego, California, March 2017.

Whitney P. Sleep deprivation effects on a novel form of cognitive flexibility. Oral presentation at the 60th Annual Meeting of the Psychonomic Society; Montréal, Québec, Canada, November 2019.

Website(s) or other Internet site(s)

Nothing to Report.

Technologies or techniques

Nothing to Report.

Inventions, patent applications, and/or licenses

Nothing to Report.

Other Products

Nothing to Report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	<i>Hans P.A. Van Dongen, Ph.D.</i>
Project Role:	<i>PI</i>
Researcher Identifier:	<i>ORCID ID: 0000-0002-4678-2971</i>
Contribution to Project:	<i>Dr. Van Dongen oversaw the project and coordinated all personnel activities and tasks.</i>

Name:	<i>Kimberly A. Honn, Ph.D.</i>
Project Role:	<i>Co-PI</i>
Researcher Identifier:	<i>ORCID ID: 0000-0001-8911-6277</i>
Contribution to Project:	<i>Dr. Honn oversaw the laboratory experimentation and the development of the operationally relevant cognitive flexibility task.</i>

Name:	<i>Matthew E. Layton, M.D., Ph.D.</i>
Project Role:	<i>Co-PI</i>
Researcher Identifier:	<i>ORCID ID: 0000-0002-3287-9203</i>
Contribution to Project:	<i>Dr. Layton served as physician of record for the study and oversaw subject health and well-being.</i>

Name:	<i>Paul Whitney, Ph.D.</i>
Project Role:	<i>Co-PI</i>
Researcher Identifier:	<i>ORCID ID: 0000-0003-1973-5261</i>
Contribution to Project:	<i>Dr. Whitney contributed key expertise on the measurement of cognitive flexibility and developed the cognitive flexibility training intervention.</i>

Name:	<i>John M. Hinson, Ph.D.</i>
Project Role:	<i>Co-PI</i>
Researcher Identifier:	<i>ORCID ID: 0000-0002-5012-5974</i>
Contribution to Project:	<i>Dr. Hinson contributed critical expertise on decision making, led the development of performance task, and implemented skin conductance procedures.</i>

Name:	<i>Devon A. Hansen, Ph.D.</i>
Project Role:	<i>Assistant Research Professor</i>
Researcher Identifier:	<i>Washington State University ID: 10064965</i>
Contribution to Project:	<i>Dr. Hansen helped develop study procedures, standing operating procedures, and recruitment and screening protocols.</i>

Name:	<i>Naghmana Sherazi, M.A.</i>
Project Role:	<i>Study Coordinator</i>
Researcher Identifier:	<i>Washington State University ID: 11506109</i>
Contribution to Project:	<i>Ms. Sherazi coordinated staffing and logistics for the study.</i>

Name:	<i>Patricia Grossman</i>
Project Role:	<i>Nurse Practitioner</i>
Researcher Identifier:	<i>Washington State University ID: 11573115</i>
Contribution to Project:	<i>Ms. Grossman assisted the physician of record for the study with the oversight of subject health and well-being.</i>

Name:	<i>Dawn DePriest</i>
Project Role:	<i>Nurse Practitioner</i>
Researcher Identifier:	<i>Washington State University ID: 11458230</i>
Contribution to Project:	<i>Dr. DePriest assisted the physician of record for the study with the oversight of subject health and well-being.</i>

Name:	<i>Sue Weeks</i>
Project Role:	<i>Nurse Practitioner</i>
Researcher Identifier:	<i>Washington State University ID: 10573510</i>
Contribution to Project:	<i>Ms. Weeks assisted the physician of record for the study with the oversight of subject health and well-being.</i>

Name:	<i>Darian Sidebottom</i>
Project Role:	<i>Ph.D. Student</i>
Researcher Identifier:	<i>Washington State University ID: 11357866</i>
Contribution to Project:	<i>Ms. Sidebottom programmed and processed cognitive performance tasks for the study. She also managed biosamples for screening sessions and contributed to the laboratory experimentation.</i>

Name:	<i>Samantha Riedy, M.S., RPSGT</i>
Project Role:	<i>Ph.D. Student</i>
Researcher Identifier:	<i>Washington State University ID: 11365976</i>
Contribution to Project:	<i>Ms. Riedy served as the designated sleep technologist for the study, overseeing recording and scoring of sleep.</i>

Name:	<i>Amanda Hudson, M.S.</i>
Project Role:	<i>Ph.D. Student</i>
Researcher Identifier:	<i>Washington State University ID: 11624214</i>
Contribution to Project:	<i>Ms. Hudson monitored subjects in the laboratory, administered performance tasks, performed physiological recordings, processed data, and published a review paper.</i>

Name:	<i>Julie Erwin, M.S.</i>
Project Role:	<i>Research Associate</i>
Researcher Identifier:	<i>Washington State University ID: 11657249</i>
Contribution to Project:	<i>Ms. Erwin coordinated staffing and logistics for the study, conducted screening sessions, and performed laboratory set-up for the experiment.</i>

Name:	<i>Mark McCauley</i>
Project Role:	<i>Research Operations Engineer</i>
Researcher Identifier:	<i>Washington State University ID: 11331753</i>
Contribution to Project:	<i>Mr. McCauley provided technological support during laboratory experimentation.</i>

Name:	<i>Regan Permito</i>
Project Role:	<i>Postbaccalaureate Research Assistant</i>
Researcher Identifier:	<i>Washington State University ID: 11498976</i>
Contribution to Project:	<i>Ms. Permito conducted screening sessions and performed laboratory set-up for the experiment.</i>

Name:	<i>Elizabeth Lewis</i>
Project Role:	<i>Postbaccalaureate Research Assistant</i>
Researcher Identifier:	<i>Washington State University ID: 11499707</i>
Contribution to Project:	<i>Ms. Lewis monitored subjects in the laboratory, administered performance tasks, and performed physiological recordings.</i>

Name:	<i>Myles Finlay</i>
Project Role:	<i>Postbaccalaureate Research Assistant</i>
Researcher Identifier:	<i>Washington State University ID: 11546225</i>
Contribution to Project:	<i>Mr. Finlay conducted screening sessions, performed laboratory set-up for the experiment, and assisted with polysomnographic recordings.</i>

Name:	<i>Lillian Skeiky</i>
Project Role:	<i>Postbaccalaureate Research Assistant</i>
Researcher Identifier:	<i>Washington State University ID: 11656455</i>
Contribution to Project:	<i>Ms. Skeiky conducted screening sessions and performed laboratory set-up for the experiment.</i>

Name:	<i>Rachael Muck</i>
Project Role:	<i>Postbaccalaureate Research Assistant</i>
Researcher Identifier:	<i>Washington State University ID: 11441657</i>
Contribution to Project:	<i>Ms. Muck conducted screening sessions and performed laboratory set-up for the experiment. She also conducted genotyping analyses.</i>

Name:	<i>Michael Burrows</i>
Project Role:	<i>Research Assistant</i>
Researcher Identifier:	<i>Washington State University ID: 11651609</i>
Contribution to Project:	<i>Mr. Burrows monitored subjects in the laboratory, administered performance tasks, and performed physiological recordings.</i>

Name:	<i>Roxanne Bataller</i>
Project Role:	<i>Undergraduate Research Assistant</i>
Researcher Identifier:	<i>Washington State University ID: 11474968</i>
Contribution to Project:	<i>Ms. Bataller monitored subjects in the laboratory, administered performance tasks, and performed physiological recordings.</i>

Name:	<i>Katie Christanson</i>
Project Role:	<i>Undergraduate Research Assistant</i>
Researcher Identifier:	<i>Washington State University ID: 11583062</i>
Contribution to Project:	<i>Ms. Christanson monitored subjects in the laboratory, administered performance tasks, and performed physiological recordings.</i>

Name:	<i>Sara Delane</i>
Project Role:	<i>Undergraduate Research Assistant</i>
Researcher Identifier:	<i>Washington State University ID: 11622588</i>
Contribution to Project:	<i>Ms. Delane monitored subjects in the laboratory, administered performance tasks, and performed physiological recordings.</i>

Name:	<i>Elizabeth Dotson</i>
Project Role:	<i>Research Assistant</i>
Researcher Identifier:	<i>Washington State University ID: 11094140</i>
Contribution to Project:	<i>Ms. Dotson monitored subjects in the laboratory, administered performance tasks, and performed physiological recordings.</i>

Name:	<i>Karly Dougherty</i>
Project Role:	<i>Undergraduate Research Assistant</i>
Researcher Identifier:	<i>Washington State University ID: 11594060</i>
Contribution to Project:	<i>Ms. Dougherty monitored subjects in the laboratory, administered performance tasks, and performed physiological recordings.</i>

Name:	<i>Rebecca Dunne</i>
Project Role:	<i>Undergraduate Research Assistant</i>
Researcher Identifier:	<i>Washington State University ID: 11622585</i>
Contribution to Project:	<i>Ms. Dunne monitored subjects in the laboratory, administered performance tasks, and performed physiological recordings.</i>

Name:	<i>Nicholas Ensroth</i>
Project Role:	<i>Undergraduate Research Assistant</i>
Researcher Identifier:	<i>Washington State University ID: 11594012</i>
Contribution to Project:	<i>Mr. Ensroth monitored subjects in the laboratory, administered performance tasks, and performed physiological recordings.</i>

Name:	<i>Anna Franzella</i>
Project Role:	<i>Undergraduate Research Assistant</i>
Researcher Identifier:	<i>Washington State University ID: 11656937</i>
Contribution to Project:	<i>Ms. Franzella monitored subjects in the laboratory, administered performance tasks, and performed physiological recordings.</i>

Name:	<i>Adelyn Glock</i>
Project Role:	<i>Undergraduate Research Assistant</i>
Researcher Identifier:	<i>Washington State University ID: 11643865</i>
Contribution to Project:	<i>Ms. Glock monitored subjects in the laboratory, administered performance tasks, and performed physiological recordings.</i>

Name:	<i>Derrik Gratz</i>
Project Role:	<i>Undergraduate Research Assistant</i>
Researcher Identifier:	<i>Washington State University ID: 11599911</i>
Contribution to Project:	<i>Mr. Gratz monitored subjects in the laboratory, administered performance tasks, and performed physiological recordings.</i>

Name:	<i>Cynthia Hernandez</i>
Project Role:	<i>Undergraduate Research Assistant</i>
Researcher Identifier:	<i>Washington State University ID: 11465731</i>
Contribution to Project:	<i>Ms. Hernandez monitored subjects in the laboratory, administered performance tasks, and performed physiological recordings.</i>

Name:	<i>Anna Hubbell</i>
Project Role:	<i>Undergraduate Research Assistant</i>
Researcher Identifier:	<i>Washington State University ID: 11599385</i>
Contribution to Project:	<i>Ms. Hubbell monitored subjects in the laboratory, administered performance tasks, and performed physiological recordings.</i>

Name:	<i>Amanda Kiefer</i>
Project Role:	<i>Undergraduate Research Assistant</i>
Researcher Identifier:	<i>Washington State University ID: 11698233</i>
Contribution to Project:	<i>Ms. Kiefer monitored subjects in the laboratory, administered performance tasks, and performed physiological recordings.</i>

Name:	<i>Sarah Kwate</i>
Project Role:	<i>Undergraduate Research Assistant</i>
Researcher Identifier:	<i>Washington State University ID: 11459552</i>
Contribution to Project:	<i>Ms. Kwate monitored subjects in the laboratory, administered performance tasks, and performed physiological recordings.</i>

Name:	<i>Emily Mathis</i>
Project Role:	<i>Undergraduate Research Assistant</i>
Researcher Identifier:	<i>Washington State University ID: 11698242</i>
Contribution to Project:	<i>Ms. Mathis monitored subjects in the laboratory, administered performance tasks, and performed physiological recordings.</i>

Name:	<i>Madeline McDougal</i>
Project Role:	<i>Undergraduate Research Assistant</i>
Researcher Identifier:	<i>Washington State University ID: 11643204</i>
Contribution to Project:	<i>Ms. McDougal monitored subjects in the laboratory, administered performance tasks, and performed physiological recordings.</i>

Name:	<i>Riley Meister</i>
Project Role:	<i>Undergraduate Research Assistant</i>
Researcher Identifier:	<i>Washington State University ID: 11600345</i>
Contribution to Project:	<i>Mr. Meister monitored subjects in the laboratory, administered performance tasks, and performed physiological recordings.</i>

Name:	<i>Mari Metter</i>
Project Role:	<i>Undergraduate Research Assistant</i>
Researcher Identifier:	<i>Washington State University ID: 11509648</i>
Contribution to Project:	<i>Ms. Metter monitored subjects in the laboratory, administered performance tasks, and performed physiological recordings.</i>

Name:	<i>Amelia Mills</i>
Project Role:	<i>Undergraduate Research Assistant</i>
Researcher Identifier:	<i>Washington State University ID: 11524215</i>
Contribution to Project:	<i>Ms. Mills monitored subjects in the laboratory, administered performance tasks, and performed physiological recordings.</i>

Name:	<i>Cecilia Moeller</i>
Project Role:	<i>Undergraduate Research Assistant</i>
Researcher Identifier:	<i>Washington State University ID: 11582073</i>
Contribution to Project:	<i>Ms. Moeller monitored subjects in the laboratory, administered performance tasks, and performed physiological recordings.</i>

Name:	<i>Amy Morse</i>
Project Role:	<i>Undergraduate Research Assistant</i>
Researcher Identifier:	<i>Washington State University ID: 11652577</i>
Contribution to Project:	<i>Ms. Morse monitored subjects in the laboratory, administered performance tasks, and performed physiological recordings.</i>

Name:	<i>Deena Oubari</i>
Project Role:	<i>Undergraduate Research Assistant</i>
Researcher Identifier:	<i>Washington State University ID: 11698224</i>
Contribution to Project:	<i>Ms. Oubari monitored subjects in the laboratory, administered performance tasks, and performed physiological recordings.</i>

Name:	<i>Dustin Parmiter</i>
Project Role:	<i>Undergraduate Research Assistant</i>
Researcher Identifier:	<i>Washington State University ID: 11698327</i>
Contribution to Project:	<i>Mr. Parmiter monitored subjects in the laboratory, administered performance tasks, and performed physiological recordings.</i>

Name:	<i>Leilani Pendilla</i>
Project Role:	<i>Undergraduate Research Assistant</i>
Researcher Identifier:	<i>Washington State University ID: 11571141</i>
Contribution to Project:	<i>Ms. Pendilla monitored subjects in the laboratory, administered performance tasks, and performed physiological recordings.</i>

Name:	<i>Mary Paterson</i>
Project Role:	<i>Undergraduate Research Assistant</i>
Researcher Identifier:	<i>Washington State University ID: 11695706</i>
Contribution to Project:	<i>Ms. Paterson monitored subjects in the laboratory, administered performance tasks, and performed physiological recordings.</i>

Name:	<i>Samia Quidwai</i>
Project Role:	<i>Undergraduate Research Assistant</i>
Researcher Identifier:	<i>Washington State University ID: 11470835</i>
Contribution to Project:	<i>Ms. Quidwai monitored subjects in the laboratory, administered performance tasks, and performed physiological recordings.</i>

Name:	<i>Nathaniel Rough</i>
Project Role:	<i>Research Assistant</i>
Researcher Identifier:	<i>Washington State University ID: 11621282</i>
Contribution to Project:	<i>Mr. Rough monitored subjects in the laboratory, administered performance tasks, and performed physiological recordings.</i>

Name:	<i>Erika Santacruz</i>
Project Role:	<i>Undergraduate Research Assistant</i>
Researcher Identifier:	<i>Washington State University ID: 11437499</i>
Contribution to Project:	<i>Ms. Santacruz monitored subjects in the laboratory, administered performance tasks, and performed physiological recordings.</i>

Name:	<i>Jonah Scott</i>
Project Role:	<i>Undergraduate Research Assistant</i>
Researcher Identifier:	<i>Washington State University ID: 11698308</i>
Contribution to Project:	<i>Mr. Scott monitored subjects in the laboratory, administered performance tasks, and performed physiological recordings.</i>

Name:	<i>Kelli Singer</i>
Project Role:	<i>Undergraduate Research Assistant</i>
Researcher Identifier:	<i>Washington State University ID: 11584759</i>
Contribution to Project:	<i>Ms. Singer monitored subjects in the laboratory, administered performance tasks, and performed physiological recordings.</i>

Name:	<i>Amanda Sursely</i>
Project Role:	<i>Undergraduate Research Assistant</i>
Researcher Identifier:	<i>Washington State University ID: 11413082</i>
Contribution to Project:	<i>Ms. Sursely monitored subjects in the laboratory, administered performance tasks, and performed physiological recordings.</i>

Name:	<i>Hailey Swearingen</i>
Project Role:	<i>Undergraduate Research Assistant</i>
Researcher Identifier:	<i>Washington State University ID: 11599921</i>
Contribution to Project:	<i>Ms. Swearingen monitored subjects in the laboratory, administered performance tasks, and performed physiological recordings.</i>

Name:	<i>Christopher Thomas</i>
Project Role:	<i>Undergraduate Research Assistant</i>
Researcher Identifier:	<i>Washington State University ID: 115399331</i>
Contribution to Project:	<i>Mr. Thomas monitored subjects in the laboratory, administered performance tasks, and performed physiological recordings.</i>

Name:	<i>Brian T. Ward</i>
Project Role:	<i>Undergraduate Research Assistant</i>
Researcher Identifier:	<i>Washington State University ID: 11593977</i>
Contribution to Project:	<i>Mr. Ward monitored subjects in the laboratory, administered performance tasks, and performed physiological recordings.</i>

Name:	<i>Madelaine R. Wiersma</i>
Project Role:	<i>Undergraduate Research Assistant</i>
Researcher Identifier:	<i>Washington State University ID: 11499681</i>
Contribution to Project:	<i>Ms. Wiersma monitored subjects in the laboratory, administered performance tasks, and performed physiological recordings.</i>

Name:	<i>Austin Yeo</i>
Project Role:	<i>Undergraduate Research Assistant</i>
Researcher Identifier:	<i>Washington State University ID: 11643073</i>
Contribution to Project:	<i>Mr. Yeo monitored subjects in the laboratory, administered performance tasks, and performed physiological recordings.</i>

Name:	<i>Katie O'Brien</i>
Project Role:	<i>Undergraduate Research Intern</i>
Researcher Identifier:	<i>Washington State University ID: 11556260</i>
Contribution to Project:	<i>Ms. O'Brien monitored subjects in the laboratory, administered performance tasks, and performed physiological recordings.</i>

Name:	<i>Senada Karmaj</i>
Project Role:	<i>Undergraduate Research Intern</i>
Researcher Identifier:	<i>Washington State University ID: 11594148</i>
Contribution to Project:	<i>Ms. Karmaj monitored subjects in the laboratory, administered performance tasks, and performed physiological recordings.</i>

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to Report.

What other organizations were involved as partners?

Nothing to Report.

8. SPECIAL REPORTING REQUIREMENTS

Nothing to Report.

9. REFERENCES

- Armbruster DJ, Ueltzhöffer K, Basten U, Fiebach CJ. Prefrontal cortical mechanisms underlying individual differences in cognitive flexibility and stability. *Journal of Cognitive Neuroscience*, 2012; 24(12): 2385-2399.
- Braver TS. The variable nature of cognitive control: A dual mechanisms framework. *Trends in Cognitive Science*, 2012; 16(2): 106-113.
- Braver TS, Paxton JL, Locke HS, Barch DM. Flexible neural mechanisms of cognitive control within human prefrontal cortex. *Proceedings of the National Academy of Sciences*, 2009; 106(18): 7351-7356.
- Brown TI, Carr VA, LaRocque KF, Favila SE, Gordon AM, Bowles B, Bailenson JN, Wagner AD. Prospective representation of navigational goals in the human hippocampus. *Science*, 2016; 352(6291): 1323-1326.
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10. APPENDICES

Conference abstract:

Honn KA, Van Dongen H. Paradoxical effect of stimulus density on PVT time-on-task effect during sleep deprivation. Sleep 41 (Abstract Suppl.): A84.

PARADOXICAL EFFECT OF STIMULUS DENSITY ON PVT TIME-ON-TASK EFFECT DURING SLEEP DEPRIVATION

Honn KA^{1,2}, Van Dongen H^{1,2}

¹Sleep and Performance Research Center, Washington State University, Spokane, WA, ²Elson S. Floyd College of Medicine, Washington State University, Spokane, WA

Introduction: The 10min psychomotor vigilance test (PVT), which requires responding as fast as possible to stimuli presented at random inter-stimulus intervals (ISIs) of 2s-10s, is highly sensitive to vigilant attention deficits due to total sleep deprivation (TSD). The deficits are evident in increased response times (RTs) during task performance, which are amplified by time on task. However, it is not clear what aspect of performing the PVT drives the time-on-task effect. One perspective is that cognitive load associated with the relatively high density of stimuli in the PVT is responsible for its sensitivity to sleep loss and the time-on-task effect. It would thus be expected that increasing the stimulus density should amplify the time-on-task effect. We tested this prediction in a laboratory TSD study comparing the standard task (PVT) to a higher stimulus density version with ISIs of 2s-5s (HD-PVT).

Methods: N=18 subjects (ages 21–37, 14 females) took the HD-PVT at 18:00 after 34h awake, flanked by the standard PVT at 17:00 and 19:00. RTs per 1min bin were analyzed using mixed-effects linear regression to compare the slope of the time-on-task effect between test sessions.

Results: RTs showed significant interaction of test session by slope ($F_{2,6086}=4.16, p=0.016$), with a smaller time-on-task effect in the HD-PVT at 18:00 as compared to the standard PVTs at 17:00 ($t_{6086}=1.73, p=0.083$) and 19:00 ($t_{6086}=2.79, p=0.005$).

Conclusion: Contrary to expectation, increasing the stimulus density in the 10min PVT did not increase the time-on-task effect, but rather reduced it. This suggests that cognitive load associated with responding to stimuli is not what determines the PVT's sensitivity to sleep loss and the magnitude of the time-on-task effect. Instead, the durations of periods between trials, when response inhibition is required, may be the primary contributor to PVT impairment and the time-on-task effect during sleep deprivation.

Support (If Any): CDMRP grant W81XWH-16-1-0319.

Conference abstract:

Satterfield BC, Wisor JP, Schmidt MA, Van Dongen H. DAT1 genotype modulates the time-on-task effect on the PVT during total sleep deprivation. Sleep 40 (Abstract Suppl.): A1-A2.

DAT1 GENOTYPE MODULATES THE TIME-ON-TASK EFFECT ON THE PVT DURING TOTAL SLEEP DEPRIVATION

Satterfield BC, Wisor JP, Schmidt MA, Van Dongen H
Sleep and Performance Research Center, Washington State
University, Spokane, WA

Introduction: Previous research has shown that the magnitude of the time-on-task (TOT) effect, which is the increase in response variability across the duration of a demanding sustained performance task, is affected by a variable number tandem repeat (VNTR) polymorphism in the Dopamine Transporter SL6CA3 gene (DAT1). Sleep deprivation also induces response variability in such tasks, and amplifies the TOT effect, which suggests shared underlying mechanisms. To explore one possible shared mechanism, we investigated whether DAT1 genotype affects the interaction between the TOT effect and total sleep deprivation (TSD).

Methods: 82 healthy adults (27.0 ± 4.7 y; 43 females) participated in one of three laboratory studies. Following a baseline period, subjects underwent at least 38h of TSD. A 10-min psychomotor vigilance test (PVT) was administered 12 times throughout the 38h TSD period. For each test bout and each subject, response times were aggregated into 1-min bins. DAT1 was assayed from blood using PCR and visualized by gel electrophoresis. 79 subjects had the 9- or 10-repeat alleles of DAT1. Another 3 subjects had the rare 8- or 11-repeat variants; they were not used for analysis.

Results: Mixed-effects ANOVA, controlling for study, showed a significant interaction between 1-min bins and DAT1 genotype ($F_{9,87000}=3.07$, $P=0.001$). As observed previously, the TOT effect was reduced in subjects homozygous for the 10-repeat allele. There was also a significant interaction of 1-min bins, time awake, and DAT1 genotype ($F_{99,87000}=1.35$, $P=0.011$). Subjects homozygous for the 10-repeat allele showed less amplification of the TOT effect during TSD than subjects with the 9-repeat allele.

Conclusion: DAT1 genotype modulates the TOT effect on the PVT during TSD. DAT1 is preferentially expressed in the striatum, where genotype affects DAT1 expression and dopamine availability. This suggests a role for striatal dopamine in shaping the impact of TOT and sleep deprivation on performance as measured with the PVT.

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Conference abstract:

Sherazi NA, Riedy SM, Satterfield BC, Schmidt MA, Wisor JP, Van Dongen H. TLR4 genotype is associated with nocturnal sleep duration and consolidation. Sleep 41 (Abstract Suppl.): A9.

TLR4 GENOTYPE IS ASSOCIATED WITH NOCTURNAL SLEEP DURATION AND CONSOLIDATION

Sherazi NA^{1,2}, Riedy SM^{1,2}, Satterfield BC^{1,3}, Schmidt MA^{1,2}, Wisor JP^{1,2}, Van Dongen H^{1,2}

¹Sleep and Performance Research Center, Washington State University, Spokane, WA, ²Elson S. Floyd College of Medicine, Washington State University, Spokane, WA, ³Department of Psychiatry, College of Medicine, University of Arizona, Oro Valley, AZ

Introduction: Toll-like receptor 4 (TLR4) is a cell membrane sensor for the pro-inflammatory membrane component, lipopolysaccharide. TLR4 activation results in synthesis and release of sleep-promoting cytokines known to be upregulated during sleep deprivation. In a rodent genetic model, TLR4 was found to modulate the electroencephalographic response to sleep loss. Thus, TLR4 activation may be involved in sleep regulation. In humans, we investigated whether a rare single nucleotide polymorphism (SNP) of the TLR4 gene, A896G (Asp299Gly), affects sleep duration under laboratory baseline conditions.

Methods: N=49 healthy normal sleepers (27.2 ± 5.2y; 21 females) participated in one of three laboratory studies. Subjects had a 10-hour nocturnal, baseline sleep opportunity (22:00-08:00) recorded polysomnographically. Blood samples obtained prior to the study were assayed for TLR4 genotype using polymerase chain reaction (PCR) with restriction enzyme digestion. 44 subjects were homozygous for the A allele, 5 subjects were heterozygous, and none were homozygous for the G allele. The G allele occurs at a population frequency of just 5%, and the sample was in Hardy-Weinberg equilibrium ($\chi^2=0.14$, $p=0.71$). Genotype effects on total sleep time (TST), wake after sleep onset (WASO), and sleep latency (SL) were analyzed using mixed-effects ANOVA, accounting for study and subjects' age.

Results: Baseline PSG revealed no sleep disorders in any of the subjects. TST was significantly greater ($F_{1,44}=8.49$, $p=0.006$) in heterozygous (A/G) subjects (572.3 ± 18.6min) than in homozygous (A/A) subjects (515.2 ± 6.3min). WASO was significantly less ($F_{1,44}=6.49$, $p=0.014$) in heterozygous subjects (17.6 ± 14.0min) compared to homozygous subjects (55.1 ± 4.8min). There was a trend for smaller SL ($F_{1,44}=3.66$, $p=0.062$) in heterozygous subjects (9.8 ± 9.7min) compared to homozygous subjects (29.4 ± 3.3min).

Conclusion: Subjects with the relatively rare A/G genotype of the TLR4 A896G SNP exhibited longer and more consolidated baseline sleep compared to subjects with the A/A genotype. These data are consistent with the idea that TLR4 is involved in the regulation of sleep.

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Conference abstract:

Van Dongen HPA, Gaddameedhi S, Crooks E, Chowdhury NR, Gajula RP, Middleton B, Satterfield BC, Porter K, Skene DJ. Internal desynchrony of central and peripheral circadian rhythms during simulated night shift work. *Sleep Science*, 2019; 12 (Suppl. 3): 71.

Internal Desynchrony of Central and Peripheral Circadian Rhythms during Simulated Night Shift Work

Hans P.A. Van Dongen^{1,2}, Shobhan Gaddameedhi^{1,5}, Elena Crooks³, Namrata R. Chowdhury⁴, Rajendra P. Gajula⁵, Benita Middleton⁴, Briann C. Satterfield⁶, Kenneth Porter⁵, Debra J. Skene⁴

1. Sleep and Performance Research Center, Washington State University, Spokane, WA, United States.
2. Elson S. Floyd College of Medicine, Washington State University, Spokane, WA, United States.
3. Department of Physical Therapy, Eastern Washington University, Spokane, WA, United States.
4. Faculty of Health and Medical Sciences, University of Surrey, Guildford, United Kingdom.
5. College of Pharmacy and Pharmacological Sciences, Washington State University, Spokane, WA, United States.
6. Department of Psychiatry, College of Medicine, University of Arizona, Tucson, AZ, United States.

Introduction: Shift work causes misalignment between internal circadian rhythmicity and externally imposed behavioral schedules, which has been implicated in elevated risk of metabolic disorders. We investigated the metabolic consequences of misaligned shift schedules using a targeted metabolomics approach. **Methods:** Fourteen healthy adults participated in a 7-day in-laboratory study in dim light. Following a baseline day, subjects were randomized to either a 3-day simulated day shift schedule (sleep: 22:00–06:00) or, after a transition nap (sleep: 14:00–18:00), to a 3-day simulated night shift schedule (sleep: 10:00–18:00). This was followed by a 24-hour constant routine protocol, during which subjects were kept awake under constant conditions, with food intake distributed across hourly, isocaloric snacks, and blood sampling every 3 hours through an intravenous catheter. Plasma was analyzed for markers of the central circadian

pacemaker: melatonin and cortisol. Additionally, 132 metabolites were assayed by means of targeted liquid chromatography/mass spectrometry metabolomics. **Results:** Melatonin and cortisol rhythms maintained approximately the same phase alignment relative to clock time after the day versus night shift schedules. Of the 132 circulating metabolites analyzed, 65 showed significant 24-hour rhythmicity ($p < 0.05$) during constant routine following either or both shift schedules. However, 24 of these metabolites showed a near-12-hour shift following the night shift schedule; 19 metabolites lost rhythmicity following the night shift schedule; and 19 metabolites showed significant rhythmicity following the night shift schedule only. **Conclusions:** After the 3-day simulated night shift schedule, the 24-hour rhythmicity of the majority of circulating metabolites investigated was shifted relative to the central circadian pacemaker, aligning instead with the prior behavioral schedule. This indicates that peripheral circadian clocks in organs involved in metabolism adapt to a shifted behavioral schedule more rapidly than the central circadian clock, suggesting that internal desynchrony between central and peripheral oscillators may underlie the elevated risk of metabolic disorders in shift workers.

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CLINICAL REVIEW

Effects of fatigue on teams and their role in 24/7 operations

Siobhan Banks ^{a,1}, Lauren Blackwell Landon ^{b,1}, Jillian Dorrian ^a, Lauren B. Waggoner ^c,
Stephanie A. Centofanti ^a, Peter G. Roma ^{b,2}, Hans P.A. Van Dongen ^{d,*}

^a Sleep & Chronobiology Laboratory, Behaviour-Brain-Body Research Centre, University of South Australia, Adelaide, SA, Australia

^b Behavioral Health & Performance Laboratory, Biomedical Research and Environmental Sciences Division, Human Health and Performance Directorate, KBR/NASA Johnson Space Center, Houston, TX, USA

^c Flight Operations & Fatigue Research, Delta Air Lines, Inc., Atlanta, GA, USA

^d Sleep and Performance Research Center and Elson S. Floyd College of Medicine, Washington State University, Spokane, WA, USA

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SUMMARY

In 24/7 operations, fatigue from extended work hours and shift work is ubiquitous. Fatigue is a significant threat to performance, productivity, safety, and well-being, and strategies for managing fatigue are an important area of research. At the level of individuals, the effects of fatigue on performance are relatively well understood, and countermeasures are widely available. At the level of organizations, the effects of fatigue are also relatively well understood, and organizational approaches to fatigue risk management are increasingly well documented. However, in most organizational settings, individuals work in teams, and teams are the building blocks of the organizational enterprise. Yet, little is known about the effects of fatigue on team functioning. Here we discuss the effects of fatigue at the levels of individuals, teams, and organizations, and how the consequences of fatigue cross these levels to impact overall productivity and safety. Furthermore, we describe the pivotal role of teams in understanding the adverse organizational effects of fatigue in 24/7 operations and argue that teams may be leveraged to mitigate these effects. Systematic investigation of the effects of fatigue on teams is a promising avenue toward advances in fatigue risk management and provide some ideas for how this may be approached.

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Introduction

The cognitive/psychological and physiological effects of fatigue (defined here as reduced alertness [1]) on individuals are well documented [2] and, despite large inter-individual differences [3], can be relatively well managed with a wide selection of countermeasure approaches [4,5]. The impact of fatigue is also increasingly well understood at the level of organizations [6], and procedures and policies to manage fatigue are a developing research area [7]. In most organizations, individuals work in teams, which together form the organizational enterprise, and team work is central in many 24/7 environments. The field of human factors has examined the influence of fatigue on operations in the context of systems and behaviors that lead to adverse safety and performance outcomes

[8]. However, there is a dearth of research investigating the effects of fatigue in team settings, particularly from a psychological and physiological perspective where the impact of 24/7 operations on individuals have been studied most extensively. This makes it difficult to establish countermeasures, procedures or policies that effectively manage the effects of fatigue on teams, or to leverage teams as a strategy to combat the adverse effects of fatigue on individuals and organizations.

Fatigue may be defined as the “inability to function at one's optimum level, because physical and mental exertion (of all waking activities, not only work) exceeds existing capacity” [9]. Inherent in 24/7 operations, which are common in healthcare, transportation, manufacturing, mining, military settings, and space exploration, fatigue is caused by extended time awake, long and/or intense work, waking hours that cross the biological night, and inadequate opportunities to recuperate through sleep [1]. While fatigue is a state of individuals, it stands to reason that it affects how individuals function within team, and thereby overall team functioning. In the Industrial-Organizational Psychology literature, teams are defined as “1) two or more individuals who 2) socially

* Corresponding author. Sleep and Performance Research Center, Washington State University Health Sciences Spokane, 412 E. Spokane Falls Blvd., Spokane, WA 99202-2131, USA.

E-mail address: hvd@wsu.edu (H.P.A. Van Dongen).

¹ Shared first authorship.

² Shared senior authorship.

interact; 3) possess common goals; 4) are brought together to perform organizationally relevant tasks; 5) exhibit interdependencies with respect to workflow, goals, and outcomes; 6) have different roles and responsibilities; and 7) are together embedded in an encompassing organizational system, with boundaries and linkages to the broader system context, and task environment" [10]. This literature also provides us with frameworks through which the impact of fatigue on teams and team dynamics can be systematically studied.

The primary goals of this paper are to highlight the relevance of teams in fatigue-susceptible, 24/7 operations, to describe the knowledge gaps in how fatigue affects teams, and to highlight the opportunity presented by operationally relevant integration of fatigue and team research. We step through what is known, and unknown, about the effects of fatigue at the individual, team, and organizational levels. We then draw this knowledge together in order to provide structure and clarity to this interdisciplinary issue and outline avenues for further research.

Fatigue at the level of the individual

Impact of fatigue on individual performance

Individuals bring to the workplace a collection of knowledge, skills, and abilities on which they build to perform work tasks. These attributes are often assumed to constitute a stable foundation for individuals' contributions to the organizational mission. However, fatigue can have a dramatic impact on an individual's capacity to wield his/her knowledge, skills, and abilities effectively. In fact, fatigue appears to degrade task performance across a wide range of neurobehavioral functions [2], which can be grouped into three domains that are seen as key to the investigation of team performance (see next section): affect, cognition, and behavior.

Fatigue-related deficits in the domain of affect include reduced empathy, degraded ability to read facial expressions, emotional instability and amplified emotional responsiveness, impaired self-regulation, reduced positive affect and/or increased negative affect, reduced alertness, poor morale, and loss of motivation. Fatigue-related deficits in the domain of cognition include cognitive slowing, attentional failures, difficulties in memory recall, poor decision making, loss of situational awareness, reduced creativity, errors in task performance, and increased risk of accidents. Fatigue-related deficits in the domain of behavior include (physical) inactivity, perseveration (i.e., inflexible repetition of actions that are no longer responsive to the situation), poorly calibrated risk taking (overly risk seeking or overly risk averse), overreacting to provocations, distractibility, degraded quantity and quality of communication, and increased probability of falling asleep unintentionally. These and many additional effects have been extensively documented and discussed in the literature, and there are multiple reviews of the topic (e.g., [2,11–13]).

The effects of fatigue on neurobehavioral performance are relatively well understood, but people do not all suffer the exact same neurobehavioral consequences of fatigue. For one, there is considerable variability among persons in the magnitude of performance impairment due to fatigue [14]. This variability constitutes a trait [3,15], which does not appear to be predicted by other individual differences such as gender, intelligence, or personality, although genetic background may be modestly predictive [16]. Counterintuitively, whereas aging reduces tolerance to working in 24/7 operations overall [17], older age has been found to be moderately protective of performance impairment due to fatigue [18].

While it would seem reasonable to assume that individuals with high vulnerability to fatigue may self-select out of fatigue-inducing

work conditions, this does not appear to be the case, even among highly select work forces such as jet fighter pilots [14]. Reasons for this may include domestic, educational, financial, social and/or lifestyle drivers of job and workplace selection, or the presence of punitive work policies that discourage workers from reporting fatigue. Another reason may be that there is considerable discrepancy between individuals' subjective estimates of fatigue or sleepiness and their objectively assessed level of neurobehavioral performance impairment [19]. Thus, workers may not be able to recognize their vulnerability and may think that they are functioning well despite being fatigued.

Another individual characteristic that determines the impact of fatigue, albeit indirectly, is morningness/eveningness or "chronotype" [20]. That is, some individuals prefer to get up early in the morning and go to bed early in the evening (i.e., morning-types), and some prefer to get up and go to bed later (i.e., evening-types) – a characteristic that is driven by individual differences in the timing of the biological clock [21]. As misalignment between sleep/wake and work schedules on the one hand, and the timing of the biological clock on the other hand, is a major driver of fatigue, it follows that different shift work schedules may have different fatiguing effects for morning-types as compared to evening-types [22]. Conversely, aligning work schedules with the timing of the biological clock improves sleep [23] and, by extension, may help to mitigate fatigue and associated performance deficits.

Task framework and operational context

Importantly, the level of vulnerability to fatigue that each individual brings to the workplace depends on the task at hand [14]. A distinction can be made between tasks that predominantly 1) involve bottom-up processing of information generated by the task environment, as is the case in tasks that require continuous monitoring of systems and acutely detecting anomalies; versus 2) engage top-down attentional control to stay focused and facilitate decision making. Job tasks that depend substantially on bottom-up processing of inflowing information are common in operational settings with a high degree of automation. Laboratory analogs of these kinds of tasks have been studied extensively in the context of fatigue [24,25]. Chief among them is the psychomotor vigilance test (PVT), which has revealed that natural variability in cognitive processing speed is much increased under conditions of fatigue from sleep loss and/or circadian misalignment [26]. This performance "instability," which is commonly described as an increase in "lapses of attention," has been theorized to be caused by transient unresponsiveness of neuronal networks due to excessive prior use [27]. It has been hypothesized that the extent to which an individual is susceptible to this phenomenon depends on the capacity (or level of redundancy) in the neuronal networks underlying cognitive processing in the task at hand [28].

The transient unresponsiveness of neuronal networks associated with fatigue leads to brief disruptions in task performance, of which the moment-to-moment timing during a task is unpredictable [26]. Reason's "Swiss Cheese Model" of accident causation posits that errors and accidents happen when multiple potentiating factors come together in space and time [8]. Lapses of attention due to fatigue represent one such factor, but due to their unpredictable timing they rarely coincide with other factors, which implies a false sense of resilience and safety. Yet, because lapses of attention may occur at any moment, a fatigue-related accident can happen any time regardless of past performance and safety. This is particularly problematic in operational settings that rely heavily on reliable systems monitoring [1] and leads to rare but catastrophic accidents in safety-sensitive settings (e.g., the Chernobyl reactor meltdown and the Space Shuttle Challenger launch accident) [29].

Whereas performance instability is a potent aspect of performance impairment, it fails to account for various important other consequences of fatigue, such as poor decision making, loss of situational awareness, and perseveration. It has recently been shown that another, distinct aspect of performance impairment due to fatigue is involved, i.e., a profound deficit in cognitive flexibility [30]. This may be seen as an inability to flexibly shift between proactive attentional control, when there are clear expectations of what steps are needed to perform a task efficiently; and reactive attentional control, when appropriate actions are to be shaped by new information that needs to be evaluated first. Thus, fatigued individuals are able to maintain information in the focus of attention and anticipate actions that are likely to be effective to perform a task, but they are less able to prevent errors caused by competing information and, especially, adapt to suddenly changing circumstances [31]. These deficits lead to problems in situational decision making under time pressure, and may be especially detrimental during crisis intervention and other dynamic, rapidly evolving scenarios.

There may be yet another, potentially dissociable aspect of individual vulnerability to fatigue, involving deficits in self-regulation of affect and social interaction. Fatigue from sleep deprivation dampens emotional expressiveness [32], reduces emotional empathy [33] and humor appreciation [34], hampers charismatic leadership [35], and confounds socially interactive decisions [36]. Individual differences in these effects of fatigue have not been studied systematically, and would not be readily explainable in terms of lapses of attention or cognitive flexibility. Impaired self-regulation due to fatigue may have especially serious implications in team settings, and is therefore worthy of consideration despite this knowledge gap.

Temporal dynamics of fatigue effects

A significant complication in considering fatigue in workplace settings is that the level of fatigue – and thus a worker's capacity to apply his/her knowledge, skills, and abilities effectively – changes dynamically over time. Principal drivers of this change are time of day and time awake, such that fatigue is greater during nighttime hours and after extended wakefulness (i.e., sleep deprivation), and less during daytime hours and after sleep [37]. An exception to this is a brief period immediately after awakening, which is characterized by a transient cognitive impairment known as “sleep inertia” that characterizes the brain's transition from sleep to waking function [38].

There is also a build-up of fatigue across consecutive days with sleep restriction [39], from which it may take multiple days without sleep restriction to recover [40]. Sleeping less than 6 h per night for 14 d leads to an accumulation of fatigue that is equivalent to a night without any sleep [39]. Interestingly, while objectively measured neurobehavioral performance deficits accumulate across days of sleep restriction, subjective ratings of fatigue and sleepiness do not show such a trend [39]. As a consequence, people may underestimate the impact of fatigue built up across consecutive days of sleep restriction, and may overestimate their readiness to perform in the workplace.

In addition to systematic temporal changes in fatigue related to time of day and time awake/asleep, there are numerous other drivers of fatigue that are predominantly transient in nature [41]. These include environmental conditions such as light exposure, ambient temperature, and background noise, and behavioral conditions such as consumption of caffeine or engagement in exercise (e.g., [1]). While a more detailed discussion of these factors is beyond the scope of this paper, it is important to keep in mind that fatigue is a dynamically changing property of an individual, which

may change substantially even within the time span of a single work shift.

Teams and fatigue in an operational context

Theoretical framework

There are well-established models of team systems, which provide frameworks to consider the potential influences of fatigue. We anchor our discussion of teams in the comprehensive Input-Mediator-Outputs-Input (IMOI) model from the field of Industrial-Organizational Psychology, which considers the components and processes of team systems over time [42]. This model is complementary to human factors frameworks applied to operational fatigue [43], as it focuses greater attention to the psychological environment at the individual, team, and organizational levels, considering work experience in addition to performance and safety. For example, in the IMOI model, mediators such as team cohesion are explicitly considered as predictors of both behavioral well-being and performance. See Fig. 1 and the sections below for model definitions and discussion.

Drawing from general systems theory, the IMOI model is a framework of how teams operate and change over time. The model is conceptualized as a flow from inputs to mediators to outputs, which may then become inputs for subsequent team performance cycles. Inputs can be categorized by context: individual, team, or organization (Fig. 1). Individual-level inputs include such factors as the team members' respective personalities, knowledge, skills, and abilities, including underlying biological systems and trait-like vulnerability to fatigue. Team inputs include size, composition, roles, and leadership structure. Organizational inputs include the setting (e.g., corporate, military, athletic), operational context (e.g., office, virtual, field site), and environmental factors (weather, time of day, natural risks) within which the team works. These inputs contribute to, and interact with, multiple mediating phenomena that affect team task performance and social functioning outputs. Mediators, which are described in more detail below, are conceptualized as affective states, behavioral processes, and cognitive processes; see [10]. Team outputs, similar to team inputs, occur at the individual, team, and organizational levels, affecting individual performance and well-being, team performance and functioning,

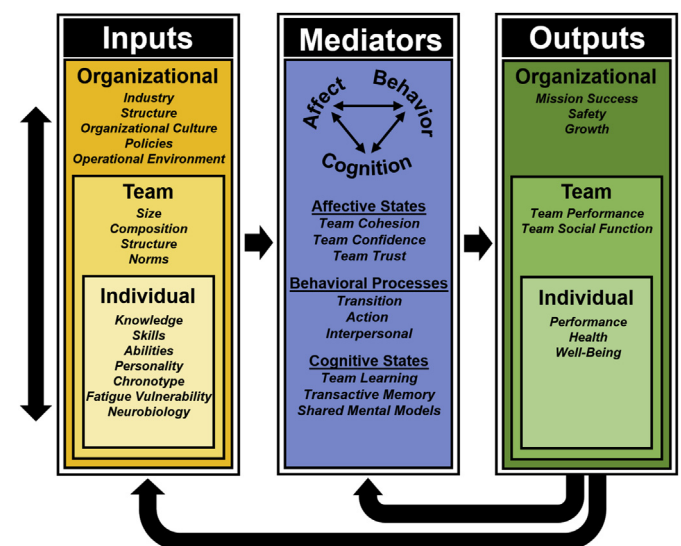


Fig. 1. The Input-Mediator-Output-Input (IMOI) model of team systems with identified fatigue-related inputs (adapted from [42,44]).

and mission success and safety, respectively. As a mission continues over time, a team repeats these IMOI cycles, with the outcome of each episode feeding back to shape the team's mediating processes and states while becoming a contextual input for the next team performance episode.

Potential impacts of fatigue on teams

It is assumed that the effects of fatigue on the team originate with an individual. Within the IMOI model, fatigue can be seen as an input variable that may influence mediators which contribute to the team's outputs. For simplicity in this discussion, fatigue will be considered in the context of established teams operating at a steady state of task performance capacity and social functioning. In so doing, it is assumed that the team possesses the necessary knowledge, skills, and abilities to be effective; is cohesive, confident, and trusting of each other; has established norms and shared understanding related to executing tasks and interacting with each other; and has performed effectively in previous task cycles. Later, how fatigue might affect teams at different points in their lifecycle will also be considered.

Team inputs

Within the IMOI framework, fatigue can impact the team at both the individual input and team input levels. At the individual input level, a team member's compromised ability to develop, retain, or apply the knowledge, skills, and abilities required for effective performance could adversely affect team processes and outputs. For example, fatigued individuals' reduced propensity to communicate contributes to errors in team-based operations [45].

At the team input level, the inclusion or introduction of a fatigued individual may change the team composition. If one or more team members experience a significant reduction in neuro-behavioral capacity due to fatigue, then the team size is effectively reduced, which reduces the available pool of knowledge, skills, and abilities needed to complete the tasks as designed for the team as originally sized. A redistribution of effort and/or increased workload across the remaining team members may be less detrimental in relatively large and/or less interdependent teams, but could critically compromise performance in demanding, time-pressured, safety-critical, and interdependent tasks in small, high-performing teams, for example in emergency response to an onboard fire in a submarine or space vehicle. For less time-pressured tasks, the team may show resilience to critical failure from degraded performance of a fatigued team member by slowing down, but this may create delays. Chronic fatigue in one or more team members may reduce schedule flexibility over time, as the team continues to be functionally understaffed, potentially resulting in failure to complete some mission tasks and longer-term goals.

Fatigue may also have functional effects on team structure, specifically role assignments and leadership positions. If a team, especially a small, high-performing team, has clearly delineated roles and expertise with limited redundancy, then the diminished capacity or functional loss of a team member due to fatigue could be devastating. Effective leadership and structured roles support performance of team processes and team cohesion [46], and a fatigued leader may partially or totally abdicate the leadership position (e.g., [47]) as fatigue negatively affects self-regulation, motivation, communication, and other characteristics needed for effective leadership. Studies of fatigued leaders have revealed that they are more impatient, irritable, and hostile, with these negative attributes persisting over time [48]. These personal characteristics then impact the rest of the team, reducing trust, motivation, and ultimately performance. Notably, individuals' awareness of the

untoward effects of their fatigue on others is limited [48]. A compromised leader who fully asserts authority under diminished capacity for judgment and decision-making without recognizing his/her impairment and without any countermeasures or safeguarding procedures in place is a risk factor for organizational errors and accidents.

Team mediators (processes and states)

Team mediators fall into three categories: affective states, cognitive states, and behavioral processes ([44]; Fig. 1). Each category includes multiple subcomponents (see below) [49]. The affective and cognitive mediators are considered "emergent states," that is, they are inherently team/social phenomena that develop through dynamic interactions among the team members and tend to stabilize over time [10,42]. Behavioral processes within the team system are also inherently team/social-based, but involve overtly observable actions (e.g., conflict management) that can contribute to team performance outputs in their own right and also serve as objective indicators of emergent affective and cognitive states. The mediator phase in the IMOI model is where the negative effects of individuals' fatigue are expressed and ultimately shape team performance and functioning.

Affective states

In the team context, "affective states" is a broad term encompassing bonding to the team and its task; confidence in team members' knowledge, skills, and abilities; and emotional processes and reactions [10]. Teams in 24/7 operational contexts such as military, spaceflight, transportation, and mining often live and work together over extended periods, increasing the influence of affective factors since team members must often act as coworkers, roommates, friends, and social support [50]. Many studies have found that team cohesion, which can be broken down into task cohesion (i.e., working well together, shared goal commitment) and social cohesion (i.e., living well together, shared attachment and liking) [51,52], is positively related to team performance (e.g., [53,54]). Similarly, team confidence is composed of team efficacy (i.e., shared belief in capability to perform a task) and team potency (i.e., shared belief in a teams' general capability to achieve mission success; [44]). Finally, team trust and team psychological safety allow team members to be vulnerable, open, and challenge each other, and these factors are also positively related to team performance [55].

It is unknown exactly how fatigue may impact these emergent affective states of a team at any point in its lifecycle. However, it is not difficult to imagine their formation, maintenance, or repair may suffer when influenced by a fatigued team member's emotional instability, inattention, poor self-regulation, or outsized emotional responses. If fatigue exerts added pressure to an already stressed system, then it may cause a team to reach dysfunctional levels of reduced team cohesion more easily [56]. Notably, the cohesion and performance relationship strengthens over time [53,54]; thus, a fatigue disruption may cause a downward spiral as mediator and output interact over time.

The limited literature on team affect and fatigue has focused primarily on behavioral indicators of cohesion and trust, such as decreased team effectiveness over time as seen in fewer leadership messages and more puerile communication in one laboratory study of simulated US Navy watch teams restricted to 6.5 h of sleep for four days [57]. In studies using anonymous partners, participants were less likely to place trust in the anonymous partner [36] and more likely to engage in socially influenced deception [58] after total sleep deprivation. However, fatigue studies have not directly

assessed team affective states at the subjective level by using surveys explicitly asking whether an individual or team believes the team is cohesive, has confidence, or is trustworthy. Using observational ratings of behaviors, “big data” analyses of communications, physiological indicators, or monitoring physical movements and interactions, may all be used to provide convergent measures of these affective states in addition to subjective measures [59], but this has received very little attention in the literature examining team functioning under fatigue.

Cognitive states

Team cognitive states may also suffer from individuals' fatigue-related cognitive decrements. As operational teams perform tasks and may even live together, they must problem-solve in both the professional and social arenas. Shared understanding (i.e., a shared mental model) of the team's goals, processes, and norms, and shared situational awareness, support team performance [60]. Other team cognition that supports performance and team functioning (e.g., cohesion) includes transactive memory systems (i.e., knowing who on the team knows what and leveraging the collective team memory) and team learning (i.e., reflecting on past performance to adapt and improve; [44]). As fatigue may cause loss of situational awareness [31] and decreases the cognitive processing of information [61], team members' shared understanding may begin to disintegrate, while the collective memory of the team's expertise and lessons learned from past performance episodes may erode or become less accessible. We are not aware of any empirical research systematically examining these complex team cognitive states under conditions of fatigue.

Behavioral processes

Behavioral processes are influenced by team affective and cognitive states, each team members' individual knowledge, skills, and abilities, and fatigue. Fatigue may cause a team to lose efficiency and effectiveness in executing team behavioral processes due to individual impairments in attention, motivation, working memory, processing speed, risk taking, and/or cognitive flexibility. During a team task, teams progress through a series of behavioral transition and action processes, with interpersonal processes as an ever-present third dynamic [42]. Foundational team-oriented behaviors such as communication are woven throughout these processes. For example, a study of US Army teams during a 36-h artillery fire operation simulation found that after 24 h, teams stopped communication upon receipt of relevant info, and performance was decremented accordingly [62].

Behavioral transition processes include mission analysis formulation and planning, goal specification, and strategy formation, while behavioral action processes include monitoring progress toward goals, systems monitoring, team monitoring and backup/supporting behavior, and general coordination. For behavioral transition processes, fatigue may impair judgment and decision-making and cognitive flexibility, thereby negatively impacting the team as the members synthesize and prioritize information. In high-consequence, dynamic environments that change rapidly over time, impairments in re-planning and strategizing based on new information may have serious safety outcomes [63]. One study of professional football and basketball teams found that travel stressors (e.g., eastward travel, distance traveled, frequency of travel, back-to-back travel) resulted in more risk-taking and poor judgment and decision-making as evidenced by a higher number of team-level penalties [64]. This study also found a partial mediating effect of team concentration and an overall negative effect of travel stressors on team performance (i.e.,

difference in score, difference in performance during the game). However, the team may be able to overcome individual-level fatigue effects on behavioral processes. For example, in a laboratory study of team decision-making, errors and processing time increased at the individual level but these effects were attenuated by team membership [65].

Behavioral action processes follow behavioral transition processes, such that the team begins to implement identified plans and strategies to reach agreed-upon goals. Behavioral action processes require considerable attentional resources as team members monitor progress, systems, and each other. In a well-orchestrated team, members maintain situational awareness and a shared understanding, which allow them to efficiently and effectively coordinate actions in the proper sequence. Once fatigue disrupts this process, errors in coordination and backup behavior may occur. Poor decision-making and reduced situational awareness at the individual level is also particularly critical during behavioral action processes, as team members constantly make decisions regarding what to monitor, what and when to communicate to others, when to step in to provide backup, and how and when to execute interdependent actions. There is little research in this area. A US Air Force study of a 36-h air battle management task showed that teams sought more visual information when fatigued, but that overall performance did not decrease [66]. While little research has examined fatigue on team-level action processes, several studies have considered fatigued team communication, which is required for many coordinating actions. Generally, fatigued teams exhibit less communication [62,67].

For the behavioral interpersonal processes of conflict management, motivation and confidence building, and affect management, fatigue may prevent deployment of team-established strategies of managing relationships, as poor self-regulation and amplified emotional responses cause team members to simply ignore those strategies [68]. The well-documented fatigue effects on motivation, mood, empathy, morale, self-regulation, and other affective and interpersonal factors [2] strongly suggest that a fatigued team will experience an increase in conflict and a reduction in prosocial behaviors. For example, laboratory studies found sleep quantity to be negatively related to unethical behavior, while a field study of organizational employees found that sleep quantity and quality predicted unethical behavior [68]. Other studies found sleep quantity to predict helping and prosocial behaviors directed toward the organization but not toward individuals, while a student sample found that sleep quantity predicted prosocial behaviors directed at both individuals and organizations [69,70]. Reduced prosocial behaviors may also exacerbate fatigue. For example, residential support workers on night shifts reported less sleep when colleagues did not provide backup behavior in the form of assistance in completing tasks [71]. These few studies examining team behavioral processes and fatigue have not examined all potential effects on the process subtypes, and there has not been much replication to support strong conclusions.

Team outputs (and the cyclical nature of teamwork)

Team outputs are grouped into two categories: team performance and team functioning. Team performance may be measured by, depending on the setting, patient mortality rates, military targets hit, space monitoring equipment installed, etc. Team functioning may be gauged by team cohesion and team confidence metrics. These outcomes determine team output, and also affect the individual team members' performance, safety, and well-being. Often the metric of primary interest in operational environments is the ultimate team performance; that is, did the team complete the task and the mission, and did they do it safely? Fatigue may

influence operational outcomes directly (e.g., failure to detect a target resulting in a miss), but in a team setting, fatigue acting on the team processes also drives later team outcomes.

A team that is particularly reliant on each member performing a unique and critical role may suffer significantly if one or more members are unable to fully contribute. However, it is possible that the effects of fatigue on team tasks only impact individual processes (e.g., information gathering) without significant consequences to overall team processes (e.g., information sharing, coordination) or outputs (e.g., task completion) [72]. In other words, a team may be able to overcome the negative effects of fatigue on one or more members to accomplish task and mission objectives. In effect, each member of the team can serve as a potential layer of risk mitigation in Reason's "Swiss Cheese Model" of accident causation. Many team settings have developed informal processes of fatigue proofing to do exactly that [73].

Industry-based studies support the importance of teams for managing safety-critical performance [74] and team-level protection against threats from fatigued team members [75,76]. At the same time, fatigue may erode prosocial behaviors and the ability to be a "good team member" [77]. As such, if a team member is identified as fatigued, other team members may strategically redistribute tasks, add backups and checks, and prompt increases in communication. Training a team in how to perform these mitigation strategies, while also maintaining a cohesive environment in which members are able to expect and accept performance decrements and maintain trust in all team members, is challenging but may have long-lasting, positive consequences.

Indeed, team outputs evolve, flowing naturally into the next episode of team performance and creating a new set of inputs for the next IMOI cycle ([42]; Fig. 1). For example, team performance predicts team cohesion [54], and each task is also an opportunity for the team to practice or learn skills and processes, preparing them for the next application of those skills and processes. Each episode may also influence fatigue (e.g., through the time on task effect [1], or by impacting on subsequent sleep [78]), which may result in a team member or members beginning the next task more fatigued. For example, astronauts have reported worry related to tasks performed inadequately earlier in the day affecting sleep that night [56].

Over time, a team that experiences a pattern of poor performance will also experience a decrease in team cohesion, trust, and confidence, which leads to another decrease in performance and an increased likelihood of accidents, and so on – until ultimately, the overall mission is at risk of failure. In the case of a new or forming team, disruption due to fatigue during an early IMOI episode could prevent the team from ever becoming a well-functioning, high-performing unit. To develop strategies to avoid or reverse such a fatigue-induced downward spiral and mitigate the risks of fatigue on performance and safety in team settings, understanding the nuances of how fatigue influences the components and processes of team systems is critical.

Organizational context

Operational framework for managing fatigue

As represented in the IMOI framework (Fig. 1), the effects of an individual who is fatigued can ripple through an operation. For example, in the commercial aviation environment, an error from a single fatigued air traffic controller can result in process changes for others in the air traffic controller's team. In turn, this can result in delays in landings and take-offs and disruption of the scheduling and flow of an entire airport. This can then have follow-on effects for plane scheduling at destination airports, influencing the flow of

the larger airline system. In any tightly connected organizational system, ripple effects from a single fatigued individual can impact on organizational integrity through changes in productivity, safety, staffing, turnover, recruitment, retention, quality control, and accountability [79,80].

The traditional approach to fatigue management at the organizational level has focused on hours-of-service (HOS) regulations prescribing limits on shift duration, mandatory breaks, and time off [6]. Such regulations seek to structure working time arrangements to prevent excessive time awake and time on task, and to allow sufficient sleep opportunity. However, HOS regulatory approaches have been criticized for failing to sufficiently consider factors such as time of day [6,80,81]. Importantly, HOS regulations prescribe individual behavior, and only consider their behavior at work. Unlike other workplace hazards (e.g., toxic exposure), not all factors that influence fatigue occur within the work environment.

Managing fatigue is therefore increasingly seen as a shared responsibility of both the individual worker and the employer [7,82]. In many parts of the world, Occupational Safety and Health regulations identify this shared duty to manage fatigue by employer and employee [80,82]. Typically, responsibility for fatigue management centers on the regulator, the operator, and the individual worker [82]. The employee's duty to be fit for work is more complicated for fatigue than it is for other sources of impairment (e.g., alcohol or other drugs), as it is often not possible to completely remove fatigue from a workplace (especially in 24/7 operations). Moreover, fatigue is a dynamically changing state (often increasing across the duration of a work shift), and it cannot be easily assessed objectively.

Given these challenges, current best practice in fatigue management in large-scale industrial settings involves the development of a fatigue risk management system (FRMS) [6]. Based on the "Swiss Cheese Model" of accident causation, the FRMS framework acknowledges that no single means to prevent errors or incidents is perfect, and there must be multiple, overlapping, and redundant levels of protection [7,82]. Teams are a natural part of this framework, as team members monitor each other, coordinate schedules and work flow, and support other team members to maintain performance effectiveness and enhance error avoidance. Team members may also need to be understanding toward teammates reducing workload due to fatigue. While it is widely recognized that an effective and mature workplace culture is essential in this context [82], the role of teams and the implications for team behavioral processes have not been given any systematic consideration.

Teams and fatigue management

What is currently missing from the FRMS framework is explicit reference to the way in which team dynamics inform fatigue management and vice versa. There is a need for a conceptual model for the incorporation of teams in FRMS. Current thinking by Le Coze [83] and others suggests building on Normal Accidents Theory [84]. According to Normal Accidents Theory, there are two main characteristics of systems – complexity and coupling – that contribute to incidents and accidents. Complexity denotes the number of components that make up a system, including people, groups, and technologies. Coupling denotes the interconnectivity (in space, time, or otherwise) between the components that make up the system. The theory posits that in systems where catastrophic events are possible, highly complex and tightly coupled systems have a higher, if not inevitable (or "normal"), risk of unintended outcomes or system failures. Highly complex, tightly coupled systems cannot easily withstand the impact of an unexpected occurrence (e.g., due to performance failure of a fatigued individual), because other parts of the system must react immediately. The

effects can snowball and, due to high complexity, results in loss of predictability and manageability in many or all aspects of a system. Furthermore, anticipation of risk is predicated on the ability to predict system behaviors and outcomes. This is a challenge in highly complex, tightly coupling systems, which are thus associated with increased risk exposure for an organization.

Normal Accidents Theory provides a potentially useful way to think about the incorporation of teams in FRMS. The “Swiss Cheese Model” foundation for FRMS emphasizes redundancy. However, from the perspective of Normal Accidents Theory, redundancy may increase coupling and complexity, which may actually increase risk rather than safety [83]. Given the inherent complexity of 24/7 operations, the ideal environment for FRMS would be connected in a way that is neither too loose to be manageable nor too tight to be vulnerable. Teams and their characteristics (size, composition, roles, etc., as described previously) could be considered a means to control the degrees of complexity and coupling of an organization – thereby providing a strategy to manage fatigue risks in addition to, and to some extent orthogonal to, the redundancy of layers of protection called for by the “Swiss Cheese Model” [84]. Organizations could take readily steps to harness this strategy, for example by designing work spaces and the regulatory environment to encourage team work. That said, optimal use of this approach would require new research to better understand the dynamics of teams and organizations as systems.

Pivotal role of teams in understanding and managing the consequences of fatigue

Whereas fatigue can have major consequences for organizational outcomes (productivity, safety, and profitability), efforts to mitigate the effects of fatigue are predominantly aimed at detecting and preventing or mitigating fatigue at the level of individuals, not teams. In part, the focus on individuals is a result of the difficulty in assessing and managing the functioning of a team beyond that of the separate individuals in the team. And in part, it follows from how organizations, and society in general, tend to deal with rewards and accountability. Teams are not commonly the specific target of rewards and accountability. Rather, rewards (such as salary and promotion) are bestowed upon individuals based primarily on their personal contributions to the organization. Accountability is usually assigned to designated individuals in the context of their organizational role and responsibility (e.g., leadership position). Not surprisingly, efforts to understand and manage fatigue have historically focused on individuals as well, with HOS regulations and fatigue countermeasure strategies pertaining to people as independent entities rather than as teams – even though the dynamics of teams and their operational functioning may have greater impact on the organization as a whole.

A systems-level understanding of fatigue and the role of teams with regard to fatigue would provide a novel platform for fatigue management design and decision-making. Research into teams would enable better prediction of the potential flow-on effects of a fatigued individual (or individuals) within a system, as well as the usefulness of fatigue control measures such as sending someone off duty or changing their work tasks. Notably, some people are more integral to the functioning of a team or system than others. The level of influence of each person within the team can be described through factors such as team context (e.g., structure, leadership roles) and team affective states (e.g., cohesion, trust) [10,85]. In a larger system, this can be conceptualized as centrality – certain people will be more centralized, and exert more influence on others. Taking out a highly centralized person could significantly

destabilize a system, but an effective team structure may help to reduce the degree of coupling in the system and thereby mitigate the impact of centrality.

The current absence of team-level considerations in fatigue management is an important gap, especially since many of the necessary conditions for successful fatigue management rely on interactions between people and teams. Changes in behavior at a team level could act as a fatigue countermeasure, but there is also the potential for such changes to increase risk in a highly interdependent team system (e.g., not completing one's own tasks while engaging in backup behavior for a fatigued teammate, not communicating adequately [86]). A better understanding is needed of how these interactions and behaviors change in the context of the team as well as the larger organizational system, especially in highly complex and tightly coupled systems where small changes can have large, widely felt consequences.

In conclusion, fatigue affects individual safety and performance as well as organizational effectiveness. Most organizations encourage if not require team work, yet little is known about how fatigue affects teams and how teams affect fatigue outcomes. There is an urgent need to build the empirical knowledge base regarding the role of teams in fatigue risk management, through multi-disciplinary research using established frameworks in the respective sciences of fatigue and teams. A better understanding of the underlying phenomena will form the basis for recommendations regarding the inclusion of team dynamics as part of comprehensive FRMS. The integration of team science into organizational-level fatigue risk management practices and policies is a formidable challenge, but given the importance of teams and team work in 24/7 operational settings, the importance thereof cannot be overstated.

Practice points

- Teams are in a critical, central position between individuals and organizations, but a largely overlooked component of understanding and mitigating the impact of fatigue on performance and safety outcomes.
- Compared to individuals, teams have greater potential to successfully self-monitor fatigue and provide protection against its adverse consequences.
- Multi-level study designs encompassing individual-, team-, and organizational-level effects that incorporate both qualitative and quantitative measures are needed to move this field forward.
- Established team models, such as the Input-Mediator-Output-Input (IMOI) model (Fig. 1), and applicable theories, such as Normal Accidents Theory, provide useful frameworks for understanding and managing the impact of fatigued individuals on teams and organizations. These frameworks may complement extant perspectives on fatigue risk management such as Reason's “Swiss Cheese Model” and fatigue risk management systems (FRMS).
- Organizations would do well to acknowledge and embrace the role of teams and team processes as part of a FRMS. For example, a FRMS could incorporate a process to facilitate team supporting behavior, such as monitoring teammates, enable non-punitive reporting of teammate impairment, and encouraging team work-arounds to compensate for a teammate's diminished capacity due to fatigue.

Research agenda

Teams could be used to provide additional levers for fatigue prevention and fatigue risk management. Focusing on teams provides an opportunity for better outcomes at the individual level (e.g., fatigue, performance, health, and well-being) as well as at the organizational level (e.g., safety, productivity, and profitability). To take advantage of this opportunity, a number of knowledge gaps need to be addressed:

1. There is inadequate knowledge about how fatigue impacts team-level processes and how the team itself contributes to the fatigue of its constituent members. Well-established team frameworks such as the IMOI model provide a foundation for generating testable hypotheses and building an empirical knowledge base on the effects of fatigue in teams.
2. Even with a focus on teams, the contributions of individuals and their inter-individual differences must be considered. To this end, an evidence-based understanding of individual- and team-level differences in vulnerability and resilience to fatigue and subsequent effects on team and social processes and outcomes is critical.
3. It is not known how fatigue and team effects on performance outcomes affect organizations over repeat team performance cycles, or how regulatory and/or organizational fatigue risk management policies and practices affect team processes and outputs. Consequently, it is also unknown how best to leverage teams to make organizational fatigue management approaches more effective. There is a need for research on how organizations influence teams and how individuals and teams influence organizations in the context of 24/7 operations and the fatigue that is commonly associated with such operations.

Addressing these knowledge gaps calls for the integration of fatigue science with team science and a highly multidisciplinary research approach. Fatigue and team scientists may form partnerships to leverage the best research methodologies of each field. Conducting team research is inherently challenging and resource-intensive, as is fatigue research. Coupling these challenges with the additional need to examine both acute and chronic effects requires careful attention to sound experimental design, but could be exceptionally impactful when done well.

Author contributions

PGR, SB, LBL, and HVD conceived the project. SB, LBL, HVD, JD, LBW, PGR, and SAC wrote the paper.

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NEUROPSYCHOPHARMACOLOGY REVIEWS

Sleep deprivation, vigilant attention, and brain function: a review

Amanda N. Hudson¹, Hans P. A. Van Dongen¹  and Kimberly A. Honn¹

Vigilant attention is a major component of a wide range of cognitive performance tasks. Vigilant attention is impaired by sleep deprivation and restored after rest breaks and (more enduringly) after sleep. The temporal dynamics of vigilant attention deficits across hours and days are driven by physiologic, sleep regulatory processes—a sleep homeostatic process and a circadian process. There is also evidence of a slower, allostatic process, which modulates the sleep homeostatic setpoint across days and weeks and is responsible for cumulative deficits in vigilant attention across consecutive days of sleep restriction. There are large inter-individual differences in vulnerability to sleep loss, and these inter-individual differences constitute a pronounced human phenotype. However, this phenotype is multi-dimensional; vulnerability in terms of vigilant attention impairment can be dissociated from vulnerability in terms of other cognitive processes such as attentional control. The vigilance decrement, or time-on-task effect—a decline in performance across the duration of a vigilant attention task—is characterized by progressively increasing response variability, which is exacerbated by sleep loss. This variability, while crucial to understanding the impact of sleep deprivation on performance in safety-critical tasks, is not well explained by top-down regulatory mechanisms, such as the homeostatic and circadian processes. A bottom-up, neuronal pathway-dependent mechanism involving use-dependent, local sleep may be the main driver of response variability. This bottom-up mechanism may also explain the dissociation between cognitive processes with regard to trait vulnerability to sleep loss.

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INTRODUCTION

The study of vigilant attention in the context of sleep deprivation has yielded far-reaching insights into the effects of sleep deprivation on cognition and the brain. The primary focus of this review is to provide an overview of inter-related findings on sleep deprivation and vigilant attention, and review how these findings have shaped our understanding of the neurocognitive effects of sleep deprivation and, by extension, sleep.

Vigilant attention, also called sustained attention, refers to the ability to maintain stable, focused attention across a time interval [1]. Vigilant attention is typically measured with (computerized) performance tasks requiring responses to target signals. In the psychology literature, deficits in vigilant attention have been studied in the context of Signal Detection Theory [2], which provides a “discriminability” measure of an individual’s performance on a stimulus detection task while accounting for the individual’s willingness to respond. The concept of discriminability is directly related to the concept of signal-to-noise ratio [3], which may be seen as a measure of the fidelity of information processing in the brain [4]. Deficits in vigilant attention are also commonly described in terms of the time-on-task effect, or vigilance decrement, which is a decline in timely or correct responses across the duration of a vigilant attention performance task [5].

A variety of task paradigms have been used to measure vigilant attention, including simple reaction time tasks, go/no-go tasks, and two-alternative forced choice tasks, all of which typically

require subjects to make speeded, accurate responses to visual or auditory stimuli. Historically, performance tasks employed to study vigilant attention required responding to relatively infrequently appearing target signals or events (e.g., occurring less than once a minute) across extended periods of time (an hour or more) [6]. High workload—operationalized as a relatively high rate of target signals—can increase the vigilance decrement, so that sensitivity to deficits in vigilant attention can be retained in shorter tasks by increasing the stimulus density (although the vigilance decrement may be reduced again if stimuli are presented as often as every few seconds) [7]. As such, shorter tasks (less than an hour in duration) are currently favored in studies of vigilant attention.

Vigilance deficits have previously been posited to be the result of neural habituation to repeated stimulation [8]. However, studies based on event-related potentials have cast doubt on this idea [9]. It has also been proposed that the vigilance decrement arises from under-stimulation or boredom due to the monotonous nature of stereotypical vigilance tasks [10, 11]. At the level of brain functioning, though, it is not evident why under-stimulation would lead to a vigilance decrement. Even more puzzling, from this perspective, is the pivotal observation that sleep deprivation causes significant impairment in vigilant attention [12–15] and acceleration of the vigilant decrement [16–19]. As we shall see, this phenomenon suggests an alternative explanation for the vigilance decrement (and an alternative view of what constitutes “boredom” at the level of brain function).

¹Sleep and Performance Research Center and Elson S. Floyd College of Medicine, Washington State University, Spokane, WA, USA

Correspondence: Kimberly A. Honn (kimberly.honn@wsu.edu)

Shared senior authorship: Kimberly A. Honn, Hans P. A. Van Dongen.

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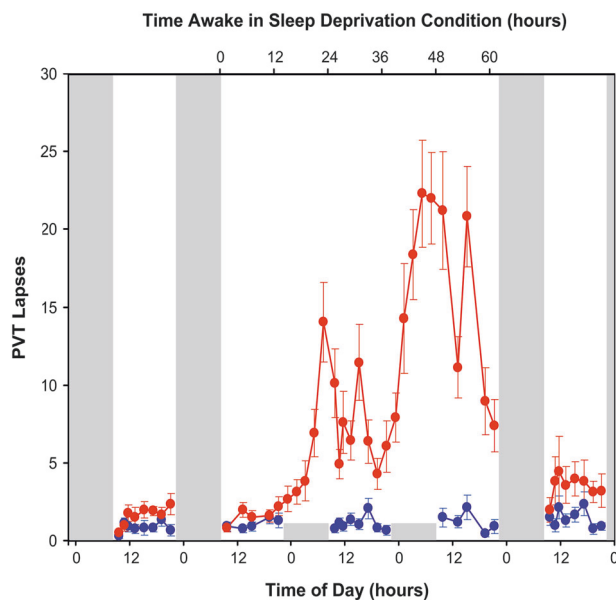


Fig. 1 Effects of acute total sleep deprivation and recovery sleep on vigilant attention. Twenty-six healthy young adults were randomized to a total sleep deprivation condition ($n = 13$) or a control condition ($n = 13$) in a laboratory study. Subjects in the sleep deprivation condition had two baseline days with 10-h sleep opportunities, a 62-h period of total sleep deprivation, and two recovery days with 10-h sleep opportunities. Subjects in the control condition had 10-h sleep opportunities every night. A 10-min PVT was administered repeatedly during scheduled waking periods to measure vigilant attention. Data show the mean ($\pm$ standard error) number of lapses (defined as response times greater than 500 ms) on the PVT. Performance was stable across days in the control group (blue line). In contrast, during the 62-h sleep deprivation period, subjects had significantly impaired performance, with deficits increasing across days of total sleep deprivation—modulated by circadian rhythmicity, such that the number of lapses was highest during the morning hours; and performance was quickly recuperated following recovery sleep (red line). Tall gray bars represent sleep opportunities (22:00–08:00) in both conditions; short gray bars represent sleep opportunities in the control condition only. Figure adapted from Whitney et al. [122] with permission

Central to several of the findings on sleep deprivation and vigilant attention is the psychomotor vigilance test (PVT) [20]. The PVT is a 10-min, one-choice reaction time task that requires responding—as quickly as possible—to a stimulus appearing at random, 2–10 s inter-trial intervals. Performance on the task can be quantified by means of the number of lapses of attention (traditionally defined as the number of response times >500 ms) [21] and a variety of other outcome measures [22] including the time-on-task effect (vigilance decrement) [15, 23]. The high stimulus load and the varying inter-trial intervals require a level of vigilant attention that appears to be near-optimally sensitive to impairment due to sleep deprivation. The task has been characterized in depth [24]. It has no learning curve [25], and baseline aptitude for the task varies little among individuals [21]. As such, it is well suited for use in studies pursuing frequent, repeated measurements to probe the temporal dynamics of vigilant attention.

TEMPORAL DYNAMICS

The timing and duration of periods of sleep and wakefulness are governed by two key physiological processes [26]. A homeostatic process—for which the underlying neurobiology is yet to be elucidated—serves to balance time spent awake with time spent asleep by building up a pressure for sleep across time spent awake

and dissipating that pressure across time spent asleep. Simultaneously, a circadian process—originating in the biological clock in the suprachiasmatic nuclei (SCN) of the hypothalamus—produces a physiological drive for wakefulness during the day and sleep at night (in humans and other diurnal species) by generating a pressure for wakefulness during the afternoon and evening and withdrawing that pressure during the night and early morning.

The difference between the pressure for sleep from the homeostatic process and the pressure for wakefulness from the circadian process is a primary determinant of the level of sleepiness experienced while awake [27]. Although this was first shown on the basis of self-reported fatigue [28], the interplay between the homeostatic and circadian processes also drives the temporal dynamics of vigilant attention, as can be readily observed in performance on the PVT across a period of total sleep deprivation [15]. As shown in Fig. 1, vigilant attention deficits increase across time awake due to the build-up of homeostatic pressure for sleep, with strong modulation over time of day due to the waxing and waning of circadian pressure for wakefulness [29]. As a result of these effects acting in tandem, performance impairment during a period of acute total sleep deprivation is greatest during the early to late morning hours following a night awake, whereas performance is partially restored during the subsequent afternoon in spite of continuing sleep deprivation. While these temporal dynamics can be understood principally as an additive interaction between the homeostatic and circadian processes, there is evidence that the interaction is actually synergistic in nature, with the influence of the circadian process on vigilant attention increasing when homeostatic pressure is high [30, 31].

In comparison with studies of acute total sleep deprivation, studies of sustained sleep restriction (i.e., daily sleep curtailment) have revealed that this two-process understanding of the temporal dynamics of vigilant attention is incomplete. That is, based on the effects of the homeostatic and circadian processes alone (or various other theories of sleep regulation no longer widely considered), it would be predicted that people could adapt to sustained sleep restriction rapidly, reaching a steady state of only mild impairment within a few days and returning to baseline after only one or two nights of extended recovery sleep [32]. Whereas that is indeed what is observed for self-reported sleepiness, data from other performance tasks including the PVT tell a different story [33–36].

Several important observations have stood out. First, there is a steady build-up of vigilant attention deficits (but not self-reported sleepiness) across consecutive days of sleep restriction [35]. Second, this build-up is sleep dose-dependent, such that the balance between wakefulness and prior sleep determines the build-up rate [37, 38] (see Fig. 2). Third, the deficits are expressed primarily in the morning hours, while performance in the afternoon and evening is comparatively little affected (like what is seen during total sleep deprivation, cf. Fig. 1) [39] (see Fig. 3). Fourth, recuperation across consecutive days of recovery sleep following a period of sustained sleep restriction can be slow [34] (see Fig. 4)—compared to recuperation from much greater vigilant attention deficits due to acute total sleep deprivation (cf. Fig. 1). Fifth, the build-up rate of impairment across consecutive days of sleep restriction [40], or across a period of total sleep deprivation [41, 42], and the recuperation rate across subsequent days of recovery sleep [40, 42] depends on prior sleep/wake history (see Fig. 4).

These observations point to the involvement of another key physiological process regulating vigilant attention, for which the temporal dynamics play out more slowly than the homeostatic and circadian processes (i.e., over days and weeks instead of hours and days). Mathematical modeling [37] has indicated that this third process can be seen as an allostatic process [43], which serves to preserve homeostatic and circadian regulation in the

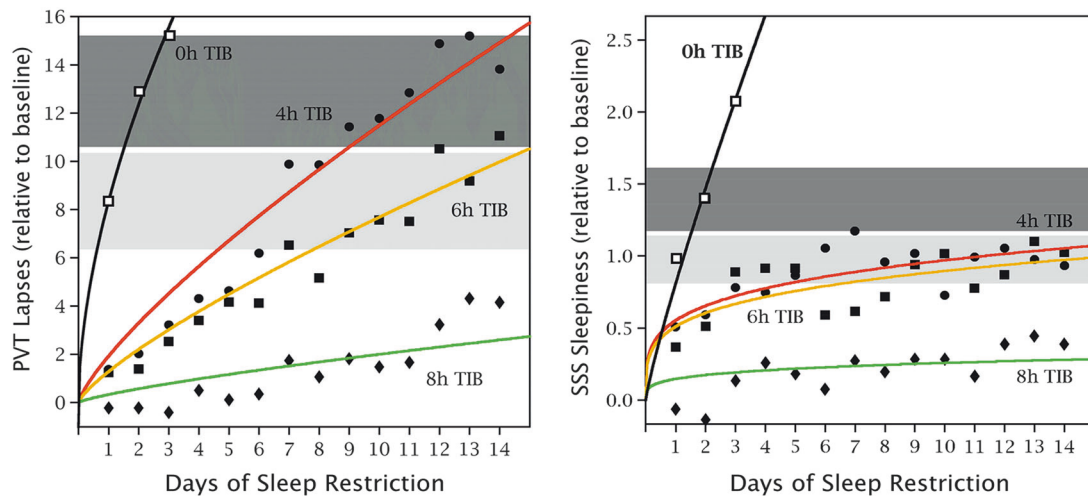


Fig. 2 Vigilant attention and self-reported sleepiness under conditions of sustained sleep restriction. Forty-eight healthy young adults were assigned to 3 days of acute total sleep deprivation (0 h time in bed [TIB]; $n = 13$; black) or 14 days of sustained sleep restriction with randomization to 4 h TIB per day ($n = 13$; red), 6 h TIB per day ($n = 13$; yellow), or 8 h TIB per day ($n = 9$; green), in the laboratory. The 10-min PVT and the Stanford Sleepiness Scale (SSS) [123] were administered repeatedly during scheduled waking periods to measure vigilant attention and subjective sleepiness, respectively. Data show the daily means ($\pm$ standard error) for the number of lapses (defined as response times >500 ms) on the PVT and the self-reported sleepiness score on the SSS, relative to baseline. The horizontal gray bands represent the mean ($\pm$ standard error) in the total sleep deprivation condition following 1 night and 2 nights with 0 h TIB. In the 8-h TIB condition, lapses of attention were relatively rare and subjective sleepiness was stable and low across the study duration. In the 6 and 4-h TIB conditions, there was a steady build-up of vigilant attention deficits on the PVT across the 14 days of sleep restriction, in a sleep dose-response manner—such that impairment in the 4-h TIB condition reached levels equivalent to 2–3 days of acute total sleep deprivation. However, there was no steady build-up of self-reported sleepiness on the SSS, and no systematic dose-response effect—such that subjective sleepiness in the 4 and 6 h TIB conditions stabilized at a much lower level than seen in the total sleep deprivation condition. Figure adapted from Van Dongen et al. [35] with permission

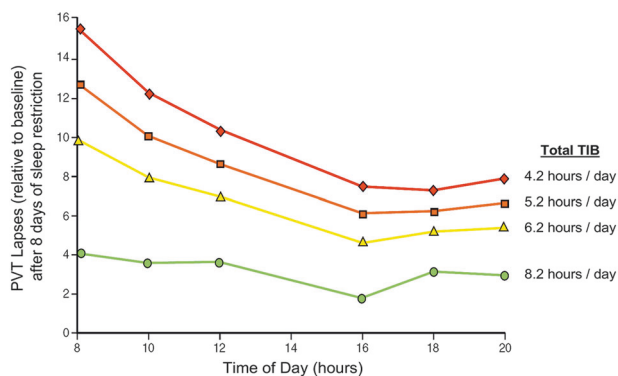


Fig. 3 Vigilant attention deficits after sustained sleep restriction as a function of sleep dose and time of day. In a laboratory study, 90 healthy adults were randomized to one of 18 sustained nocturnal sleep restriction conditions with or without daytime naps of various durations, with the total sleep opportunity ranging from 4.2 to 8.2 h per day. A 10-min PVT was administered repeatedly during scheduled waking periods to measure vigilant attention. Data show the estimated means for the number of PVT lapses (defined as response times >500 ms) after 8 days of sleep restriction, relative to baseline, for daily total time in bed (TIB) of 4.2 h (red), 5.2 h (orange), 6.2 h (yellow), and 8.2 h (green). The data reveal that the dose-response effect of sleep restriction is most pronounced in the morning hours, while the circadian drive for wakefulness provides a degree of protection against vigilant attention deficits in the afternoon (the “wake maintenance zone” [124]). Figure adapted from Mollicone et al. [39] with permission

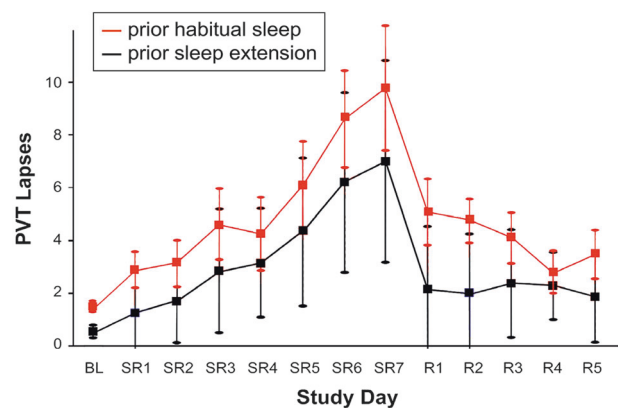


Fig. 4 Effects of sustained sleep restriction and prior wake extension on vigilant attention. In a laboratory study, 24 healthy young adults were assigned to 7 days of sustained sleep restriction to 3 h time in bed (TIB) per day (SR1–7), followed by 5 days of recovery sleep at 8 h TIB per day (R1–5). In the days prior to the laboratory study, they were randomized to a week of sleep extension to 10 h TIB per day ($n = 12$; black) or keeping their habitual sleep schedule ($n = 12$; red). A 5-min PVT was administered repeatedly during scheduled waking periods in the laboratory to measure vigilant attention. Data show the daily means ($\pm$ standard error) for the number of PVT lapses (defined as response times >500 ms). In the prior habitual sleep condition, there was a steady build-up of vigilant attention deficits across days of sleep restriction, and a gradual recuperation across recovery days. In the prior sleep extension condition, however, the build-up of deficits across days of sleep restriction was attenuated, and recuperation across recovery days was accelerated. These results show long-term effects of sleep restriction and extension indicative of an allostatic process modulating the setpoint of the sleep homeostatic process. Figure adapted from Rupp et al. [40] with permission

face of chronic sleep insufficiency. Another, equivalent way to understand the third process is that it shifts the setpoint of the homeostatic process around which the interplay of the pressures for sleep and wakefulness takes place. Thus, sustained sleep

restriction gradually shifts the homeostatic setpoint, while consecutive days of extended recovery sleep gradually shift it back. Interestingly, this means that people's sleep/wake history may enduringly influence their baseline state and, as such, their vulnerability to vigilant attention deficits due to sleep loss [40, 42, 44].

Vigilant attention is affected by a spectrum of other, predominantly transient, factors, including ambient temperature, light exposure, physical activity and posture, hunger, and environmental noise and other distractions [29]. The influences of these and other factors are integrated with homeostatic, circadian, and allostatic processes; recent evidence suggests that this may occur through orexinergic/hypocretinergic neurons in the lateral hypothalamus [45]. Vigilant attention is also significantly affected by sleep inertia, a brief period of disorientation and cognitive impairment immediately after awakening from (deep, non-REM) sleep [46]. The temporal dynamics and underlying mechanisms of these factors are generally poorly understood, and they are outside the scope of this paper. They have considerable practical relevance, though, especially in work settings where managing vigilant attention is critically important for productivity and safety.

INTER-INDIVIDUAL DIFFERENCES

There is wide variability among people in how much vigilant attention performance impairment they exhibit while deprived of sleep [15, 47–50]. The same inter-individual differences in vigilant attention performance impairment are seen under conditions of total sleep deprivation and sustained sleep restriction [51], and they are quite substantial (see Fig. 5). Importantly, these inter-individual differences in vulnerability to sleep loss are highly replicable and stable within individuals [41, 51], indicating that they are a trait, or phenotype. Furthermore, a study in twins demonstrated that vulnerability to sleep loss is heritable [52].

Extensive attempts have been made to find predictors of phenotypic vulnerability to sleep loss. Baseline levels of vigilant attention performance are to some (limited) extent predictive of performance impairment during total sleep deprivation [53]; as are several aspects of brain functioning as characterized through functional neuroimaging [54], which continue to be the subject of investigation [55].

Much attention has been paid to genetic predictors of phenotypic vulnerability to sleep loss, of which several have been discovered—predominantly genetic variants of genes associated with adenosinergic mechanisms that may underlie the homeostatic process [56, 57] and genetic variants of clock genes involved in circadian rhythmicity [58, 59]. Complex biobehavioral traits tend to involve multitudes of genes, generally making it difficult to explain even a small percentage of the observed phenotypic variance [60]. Nonetheless, vigilant attention impairment due to sleep loss is a strongly expressed phenotype [61] (see Fig. 5), and at least one gene has been identified that predicts a relatively substantial portion of inter-individual variability in psychomotor vigilance impairment due to sleep loss. This concerns a single nucleotide polymorphism of the *TNFA* gene, which was found to explain 6.4% of the variance in PVT performance during total sleep deprivation [62]. Moreover, two genetic variants of the dopaminergic system—a variable number tandem repeat polymorphism of the *DAT1* gene and a single nucleotide polymorphism of the *DRD2* gene—together explained 15% of the variance in PVT performance during total sleep deprivation [63].

However, the phenotype of cognitive vulnerability due to sleep deprivation is not a unitary phenomenon. A surprise finding in the study that first established inter-individual differences in vulnerability to sleep loss as a phenotype [41] was the task-dependence of the trait. That is, trait inter-individual differences in vigilant attention deficits as measured on the PVT were not congruent

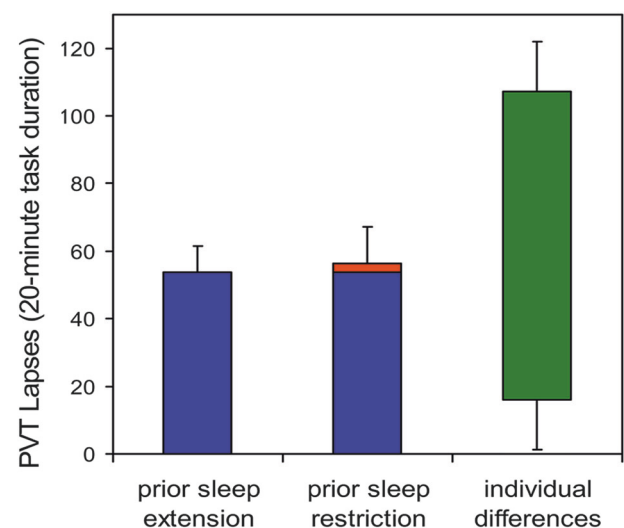


Fig. 5 Inter-individual differences in vigilant attention deficits during periods of total sleep deprivation following two different conditions for prior sleep/wake history. Twenty-one healthy young adults were each exposed to 36 h of acute total sleep deprivation in the laboratory on three separate occasions. In the week prior to each laboratory sleep deprivation session, subjects were randomized to a week of sleep restriction to 6 h time in bed (TIB) per day (one session) or sleep extension to 12 h TIB per day (two sessions). A 20-min PVT was administered repeatedly during scheduled waking periods in the laboratory to measure vigilant attention. Data show mean ($\pm$ standard error) lapses of attention (response times ≥ 500 ms), averaged across the final 24 h of each 36-h sleep deprivation period. While the effect of prior sleep restriction was evident (red), and consistent with the idea of a shifting homeostatic setpoint due to prior sleep/wake history, the effect was small compared to idiosyncratic, trait inter-individual differences in vulnerability to sleep deprivation (green; 95% range). Trait inter-individual differences in vulnerability to vigilant impairment due to sleep deprivation dominated the data set, explaining 67.5% of the variance [41]

with inter-individual differences in performance deficits on a number of other cognitive tasks, and also not with inter-individual differences in self-reported sleepiness. This paradoxical result exposed the issue that overall performance impairment on a cognitive task may be caused by deficits in any of the underlying cognitive processes—a conundrum known as the “task impurity problem” [64]. This highlighted the importance of decomposing task performance into the constituent cognitive processes and examining the effects of sleep deprivation on these processes separately [65, 66].

Efforts to explore this issue further revealed that various cognitive processes, such as working memory scanning, resisting proactive interference, semantic encoding, and motor action planning, may be resilient to degradation caused by sleep deprivation [67–70]—suggesting that performance impairment from sleep loss on a range of cognitive tasks may be driven primarily by underlying deficits in vigilant attention [71]. Interestingly, a recent study of human gene expression during total sleep deprivation suggested a distinction between a large number of genes for which the expression profiles were non-specifically influenced by time awake, and a smaller group of genes for which the expression profiles appeared to be more closely related to the level of performance impairment on the PVT in particular [72]. It is currently unknown whether similar gene expression patterns would emerge with respect to other performance tasks for which performance impairment reflects deficits in vigilant attention.

These intriguing results aside, at least one other cognitive process is also greatly affected by sleep deprivation,

independently from vigilant attention: top-down attentional control [73]. Sleep deprivation-induced impairments in this process are believed to underlie deficits in cognitive flexibility, which are not linked to deficits in vigilant attention and not predicted by the same genes [74, 75]. More research is underway to better understand what is unique about attentional control and the impact of sleep deprivation thereon [76]. At the same time, though, the question may be asked: what is unique about vigilant attention?

TOP-DOWN AND BOTTOM-UP REGULATION

Crucial for a deeper understanding of the effects of sleep deprivation on vigilant attention, and on the brain mechanisms that subserve vigilant attention performance, is the observation that sleep loss-induced deficits in performance on vigilant attention tasks, such as the PVT, are characterized by increased moment-to-moment variability. This was first recognized as an increase in exceptionally slow responses (of, say, more than twice the mean response time) interspersed among otherwise normal, fast responses on reaction time tasks performed during sleep deprivation. This observation led to the “lapse hypothesis,” which posited that performance during sleep deprivation is disrupted by brief moments of reduced arousal that prevent timely responding to the task [77]. The lapse hypothesis provides a simple heuristic for how sleep deprivation leads to increased errors and accidents in real-world settings [78]. This useful feature notwithstanding, careful inspection of the distribution of response times on the PVT (and other vigilant attention tasks) shows a more nuanced picture. That is, during sleep deprivation the whole response time

distribution skews to the right (see Fig. 6). As such, all response times are affected by sleep deprivation, with the right tail of the distribution showing the greatest change [14].

This finding gave rise to the “state instability hypothesis,” which purported that sleep deprivation makes cognitive performance progressively more variable due to the interaction of escalating homeostatic pressure for sleep with the waxing and waning of circadian pressure for wakefulness and a person’s compensatory effort to continue to perform [15]. This hypothesis is consistent with the documented neurobiology of global, top-down sleep/wake regulation. Notable components of this neurobiology include the ascending arousal system, which mediates the brain’s arousal and, as such, reflects the homeostatic sleep drive and the prevailing amount of compensatory effort; the SCN, which orchestrates circadian rhythmicity and the associated wake drive; and the ventrolateral preoptic (VLPO) nucleus or “sleep switch,” which blocks arousal from the ascending arousal system to initiate sleep [79]. When homeostatic sleep drive is high due to sleep deprivation, the interaction of these components may result in rapid fluctuations between wake and sleep states (i.e., state instability) [80], which could explain the observed skewing of response time distributions.

Results of neuroimaging studies of the effects of sleep deprivation on PVT performance support a global (albeit regionally distributed), top-down perspective on state instability and the skewing of response time distributions in vigilant attention performance [54, 81–86]. The restorative effects of wake-promoting drugs (stimulants) that target neurotransmitter systems in the ascending arousal system, such as modafinil and amphetamine [87], are also consistent with this view. However, the well-known restorative effect of caffeine [88], which at typical doses (in the 100–200 mg range) acts predominantly as an adenosine antagonist, is not readily explained in terms of global, top-down sleep/wake regulation.

Moreover, if the effects of sleep deprivation are solely globally mediated, the impact of sleep deprivation would not be expected to differ fundamentally between cognitive processes, nor should there be any profound task-dependence of inter-individual differences in vulnerability to sleep loss. A global, top-down perspective on vigilant attention also does not provide a parsimonious explanation for one of the most prominent features of impaired vigilant attention, i.e., the vigilance decrement or time-on-task effect. The key to understanding these issues may lie in a more detailed investigation of the time-on-task effect during sleep deprivation and adapting a bottom-up perspective on vigilant attention.

VIGILANCE DECREMENT AND LOCAL, USE-DEPENDENT SLEEP

The vigilance decrement involves a gradual degradation of performance across the duration of a vigilant attention performance task [5]. The homeostatic and circadian processes that drive the temporal dynamics of vigilant attention interact with the time-on-task effect, amplifying the time-on-task effect when the homeostatic drive for sleep is high and the circadian drive for wakefulness is low [15, 16, 18, 89, 90] and as a function of consecutive days of sleep restriction [19] (see Fig. 7). Rest breaks provide recuperation from the time-on-task effect [91, 92], as do brief periods of engagement in a different task [92, 93]. The temporal dynamics of such breaks have not been well characterized—e.g., it is unclear how much time is needed to reset the time-on-task effect—but even relatively short breaks can be quite effective. The underlying mechanisms are a topic of debate [94, 95].

Although often described as a gradual decline in the mean level of performance across the duration of a vigilant attention task, the vigilance decrement actually entails an increase in response variability as a function of time-on-task [96]. Under conditions of

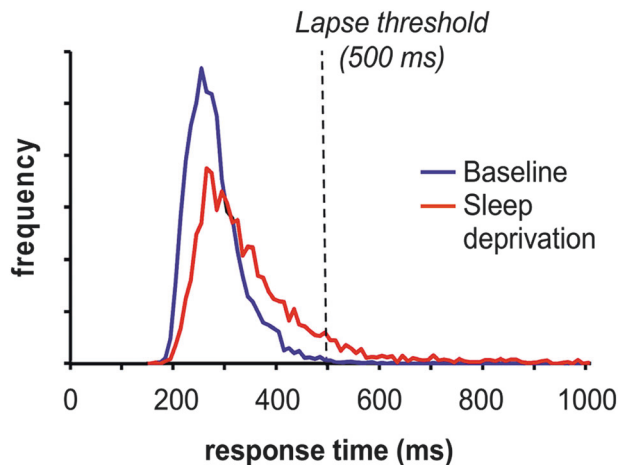


Fig. 6 Effect of sleep deprivation on the PVT response time distribution. Sixteen healthy young adults were each exposed to 38 h of acute total sleep deprivation in the laboratory. A 10-min PVT was administered repeatedly during the sleep deprivation period to measure vigilant attention. A histogram of the response times, in bins of 10 ms each, is shown for daytime performance test times at baseline (blue) and for the same daytime performance test times 24 h later during sleep deprivation (red). The data show that the main effect of sleep deprivation is a skewing of the response time distribution to the right, such that many more response times end up in the right tail of the distribution. The dashed line denotes the commonly used threshold defining lapses of attention (i.e., response times >500 ms). The graph illustrates that the skewing of the distribution due to sleep deprivation lengthens the slowest response times and increases the number of lapses considerably. In contrast, the effects of sleep deprivation on the peak of the distribution and the fastest response times is much more modest, and the majority of responses remains in the baseline range (~200–300 ms for well-rested, healthy young adults). Figure adapted from Grant et al. [90] with permission

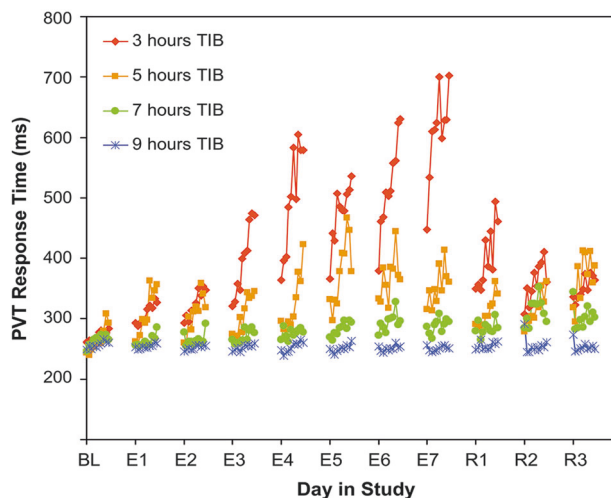


Fig. 7 Effect of sustained sleep restriction on the time-on-task effect. Following a baseline period, 66 healthy young adults were assigned to 7 days of sustained sleep restriction or extension, with daily time in bed (TIB) randomized to 3 h ($n = 18$; red), 5 h ($n = 16$; orange), 7 h ($n = 16$; green), or 9 h ($n = 16$; blue), which was followed by 3 days of recovery sleep at 8 h TIB daily. A 10-min PVT was administered repeatedly during scheduled waking periods to measure vigilant attention. Data show average response times per 1-min bin (not drawn to scale on the time axis) during a baseline day (BL), during the 7 days of experimental sleep restriction or extension (E1–E7), and during the 3 recovery days (R1–R3). In each of the conditions, there was a general increase of the 1-min average response time across the 10-min task duration, which was reset by the rest breaks between the test bouts. This time-on-task effect was exacerbated as a function of consecutive days of sleep restriction, with shorter sleep durations corresponding to greater time-on-task effects in a dose-response manner. The time-on-task effect was diminished across consecutive recovery days. Figure adapted from Van Dongen et al. [19] with permission

sleep deprivation, the increase in response variability over time-on-task is accelerated [15]. The effects of sleep deprivation and time-on-task on response variability are thus similar and interacting—and also involve overlapping brain areas as seen in functional neuroimaging experiments [97]—which has been interpreted as evidence that these effects may essentially be the same [19]. However, whereas the time-on-task effect can be overcome by a mere rest break, the effect of sleep deprivation can only be undone by a period of sleep.

This paradox may be resolved by considering “local sleep theory,” which posits that sleep may be expressed locally in the brain—at the level of neuronal/glial assemblies, such as cortical columns—in a bottom-up, use-dependent manner [98]. In the local sleep state, neuronal/glial assemblies show synchronized firing patterns typical of the sleeping brain, with short bursts of high activity followed by brief periods of inactivity that are characteristic of slow wave sleep [99–101]. Furthermore, they show altered neuronal input-output relationships resulting in high-amplitude evoked responses typical of the sleeping brain [102], which are reversible and show homeostatic and use-dependent properties that are also typical of the sleeping brain [102–104]. However, they can do so independent of the states of neighboring neuronal/glial assemblies and independent of the global brain state [102]. For a review of local sleep theory, see ref. [98].

Local sleep theory’s relevance for vigilant attention has been illustrated in a whisker-twitching experiment in rats, in which specific whisker barrels (i.e., cortical columns) exhibited evoked responses characteristic of sleep, while other whisker barrels simultaneously exhibited evoked responses characteristic of

wakefulness and while the whole organism was functionally awake. The probability of a whisker barrel entering the local sleep state increased with time spent in the wake state and the intensity of stimulation of the associated whisker, indicating a homeostatic, use-dependent process [102]. Notably, rats trained to monitor and respond to stimulation of a specific whisker showed greater performance impairment (more failures to respond) when the corresponding whisker barrel had been driven into the local sleep state [103]. Similarly, in humans implanted with intracranial electrodes to record single neurons, local changes in neuronal activity were observed immediately prior to lapses of attention on the PVT [105]. Collectively, these results suggest that repeated stimulation of the same neuronal circuitry produces local sleep in that circuitry, which results in degraded information processing and increased variability in task performance [19].

This bottom-up perspective on performance impairment in vigilant attention tasks may explain a number of otherwise unexplained phenomena at the intersection of human vigilant attention and sleep deprivation [106]. Although task performance in humans is unlikely to rely critically on information processing by only a single cortical column, there are components of cognitive pathways with relatively sparse circuitry—such as visuospatial mental operations in the precuneus and posterior cingulate cortex [107]—which represent a potential bottleneck for cognitive processing. Extended and/or intensive use of such circuitry through sleep deprivation and/or task performance may result in expression of local sleep and consequent degradation of information processing, leading to a steady increase in performance instability [19]. This would explain the pervasive link between the vigilance decrement and monotony (i.e., persistent use of the same brain circuitry) [108, 109], and suggests that what is commonly experienced as “boredom” during monotonous tasks may actually be an epiphenomenon of the occurrence of local sleep.

During a rest break (or after switching to another task not critically affected by the same bottleneck for cognitive processing), the specific circuitry involved in the prior task can recover through local sleep (without any overt impact, since that circuitry is no longer being relied upon). Thus, a rest break may be conceptualized as an opportunity for local sleep to overcome the time-on-task effect, functionally equivalent to how global sleep overcomes the overall effect of sleep deprivation on cognitive performance.

People may vary in the degree of sparsity of circuits that are potential bottlenecks for cognitive processing. That is, they may differ from each other in how much or how little redundancy there is in the capacity to process information—and this level of redundancy (or “cognitive capacity”) may be dissimilar across distinct circuits in a given individual’s brain. This would provide a plausible explanation for why different cognitive processes are found to be differentially affected by sleep deprivation [66] and why there is considerable task-dependence in the inter-individual differences in vulnerability to sleep deprivation [55]. It has also been suggested as an explanation for developmental changes in vulnerability to vigilant attention performance impairment in adolescents [110].

Furthermore, local sleep theory predicts that the effect of sleep deprivation on cognitive performance is modulated by information processing load (or “task load”). For example, it has been shown that performance deficits on a visual short-term memory task occur especially in individuals who fail to maintain baseline levels of brain activation in the precuneus and posterior cingulate cortex (as observed through functional neuroimaging) while sleep deprived and under high processing load [111]—presumably because these individuals have less redundancy in that task-critical neuronal circuitry and thus suffer the consequences of local sleep induced by sleep deprivation and information processing load more strongly [55].

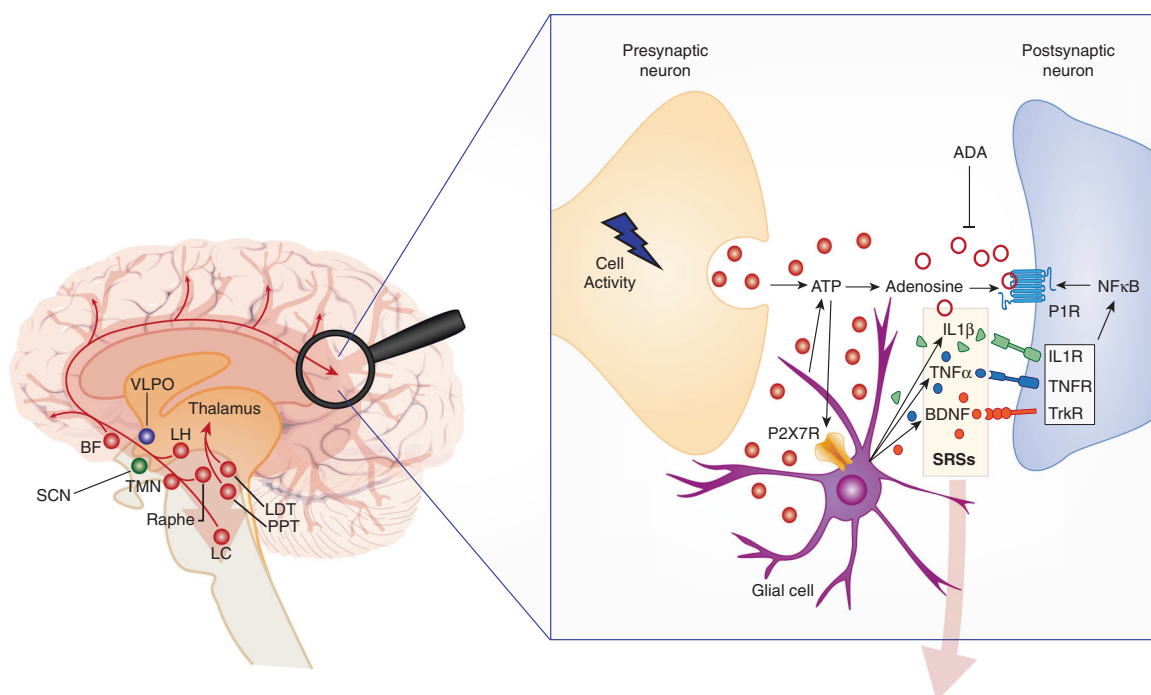


Fig. 8 Conceptual model pertaining to the effects of sleep deprivation on vigilant attention. *Left:* The ascending arousal system (AAS) promotes global arousal throughout the cortex by means of wide-ranging projections (red pathways). These projections originate from cholinergic structures in the brainstem (PPT, pedunculo-pontine tegmental nucleus; LDT, laterodorsal tegmental nucleus) and basal forebrain (BF), monoaminergic structures in the BF and hypothalamus (e.g., LC locus coeruleus; TMN tuberomammillary nucleus; raphe nuclei), and orexinergic/hypocretinergic neurons in the lateral hypothalamus (LH), modulated by circadian rhythmicity generated in the suprachiasmatic nucleus (SCN). The strength of arousal from these projections, through interaction between cortical glutamatergic excitatory neurons, and GABAergic inhibitory neurons in the cortex (not shown), instantiates the homeostatic and circadian processes reflecting prior wakefulness and time of day and mediates the *propensity* for local sleep at the level of neuronal/glia assemblies. This propensity is *manifested* as a consequence of intense neuronal use in support of information processing during vigilant attention task performance, in task-activated cortical areas such as the precuneus (magnifying glass). *Right:* Information processing in a neuronal/glia assembly triggers a series of biochemical processes that induce the local sleep state. Synaptic transmission is associated with increased local metabolic activity and energy transfer and release of adenosine triphosphate (ATP) from presynaptic neurons and glial cells into the extracellular space. Breakdown of extracellular ATP to recover the energy captured in the phosphoryl groups results in use-dependent accumulation of adenosine. Binding of adenosine at postsynaptic adenosine receptors (P1R purine type 1 receptors) promotes local sleep, thereby fundamentally altering the neuronal assembly's synaptic transmission. As a consequence, the fidelity of task-relevant information processing is degraded in a use-dependent manner, modulated by the strength of subcortical arousal from the AAS. This gives rise to the time-on-task effect (vigilance decrement) in interaction with the homeostatic and circadian processes. A rest break (or switching to a task that does not intensively use the same neuronal/glia assemblies) allows adenosine levels to decay (e.g., through the enzymatic action of ADA, adenosine deaminase), thereby resetting the time-on-task effect. Binding of ATP, prior to breakdown, to purine type 2X7 receptors (P2X7R) leads to release of a cascade of sleep regulatory substances (SRSs), such as interleukin-1 β (IL-1 β), tumor necrosis factor α (TNF α), and brain-derived neurotrophic factor (BDNF). Sustained wakefulness allows SRSs to accumulate and, via their receptors and nuclear factor κ B (NF- κ B), causes the density of postsynaptic adenosine receptors to increase. This leads to a build-up of the propensity for use-dependent local sleep across consecutive days of wake extension. Across days of recovery sleep, adenosine receptors downregulate and the baseline propensity for local sleep is gradually restored. *Left and right:* Through mechanisms yet to be elucidated, accumulation of SRSs across the cortex reflecting the collective states of neuronal/glia assemblies is signaled to subcortical circuits (transparent downward arrows), influencing in particular the ventrolateral preoptic nucleus (VLPO). In response, the VLPO blocks the AAS and induces local sleep across the whole cortex (i.e., global sleep), which enables restoration of baseline SRS concentrations and allows recuperation from prior information processing deficits across neuronal/glia assemblies. Figure adapted from a schematic in Van Dongen et al. [19], with visual elements derived from Saper et al. [79] and Davis et al. [125]

This same line of reasoning may provide an explanation for the counterintuitive observation that performance on the relatively brief (i.e., 10-min) PVT is more sensitive to sleep deprivation than performance on classical vigilant attention performance tasks with infrequent critical signals and much longer task duration. Specifically, the PVT has a much higher stimulus density and thus presents a greater information processing load, persistently engaging the same neuronal circuitry [19]. Intriguingly, it would follow that the PVT has been such a useful tool for research on sleep deprivation and vigilant attention [24] because it probes the susceptibility of a key attentional network in the brain to local sleep by very effectively inducing local sleep in that network, with definite, readily interpretable consequences for the response time distribution.

This theoretical account of sleep deprivation and vigilant attention has been supported by research based on cognitive

modeling [112, 113]. Additionally, a (simplified) model for the neurobiological underpinnings, which combines bottom-up and top-down views on vigilant attention, has been proposed (see Fig. 8).

FUTURE RESEARCH DIRECTIONS

The conceptual model shown in Fig. 8 of the neurobiological underpinnings of vigilant attention deficits and the impact of sleep deprivation, time-on-task, rest breaks, and recovery sleep is, of course, an oversimplification of the mechanisms underlying sleep regulation and cognition. Modern experimental techniques such as optogenetics and chemogenetics are sketching an increasingly complex picture of the regulatory mechanisms involved [45, 114]. Nonetheless, evidence has been accumulating

for many of the individual components of the model in Fig. 8, such as the top-down regulation of neuronal activity by the homeostatic and circadian processes [115], the bottom-up, use-dependent drive for local sleep in neuronal/glia assemblies [102], the variability in cognitive processing due to local sleep [103], the binding of extracellular ATP to purine type 2 (X7) receptors [116], key aspects of the signaling mechanisms involving sleep regulatory substances [117, 118], and the upregulation of purine type 1 (A₁) receptors in response to prior sleep loss [119].

Even so, the proposed neurobiological integration of the bottom-up and top-down aspects depicted in Fig. 8 awaits experimental confirmation. This facet of the model could be investigated, for example, by measuring performance on a sequence of alternating cognitive tasks, one being a vigilant attention task, such as the PVT, and another being a task associated with intense use of a different neuronal pathway, during sleep deprivation. By comparing the result with sleep-deprived performance on just the PVT, extended to match for total duration of performance testing, the interaction between bottom-up, use-dependent regulation of the time-on-task effect and top-down, homeostatic regulation of the sleep deprivation effect would be exposed.

The model of Fig. 8 would predict that continued testing on the extended PVT results in progressively worsening performance (per the time-on-task effect), as has been found [120]. However, even if the other task exhibits a time-on-task effect also, the model would *not* predict that performance would continue to worsen across the sequence of alternating tasks. Rather, it would predict that temporarily engaging in the other task allows the neurons specifically used intensively in the PVT to recover so as to reset the time-on-task effect. Thus, the other task would effectively serve as a “rest break” for the PVT. If this prediction does not hold true, then the model needs to be revised.

Several other important implications to the specifics of the interplay between local and global processes remain to be investigated. For example, if performance of a vigilant attention task, such as the PVT, induces the local sleep state, does that then also influence the global homeostatic process, such that repeated performance of the PVT across a period of sleep deprivation would accelerate the build-up of sleep pressure (as compared to not performing the task during sleep deprivation)? And if so, what is the signaling mechanism for this local-to-global interaction? Also, would it work the same way for performance tasks that do not require much vigilant attention, but rather rely critically on, say, attentional control or emotional control? Might this explain why a day full of social interaction can make one feel particularly sleepy? And could addressing these issues shed any light on why sustained sleep restriction leads to cumulative deficits in cognitive performance, but not in homeostatic sleep markers (e.g., delta power in the non-REM EEG or theta power in the waking EEG [32, 35])—suggesting a fundamental distinction between the regulation of sleep and wakefulness versus the regulation of waking alertness and performance?

Sleep deprivation represents a powerful, reversible intervention that allows for the probing of vigilant attention and other aspects of cognition, as well as the underlying mechanisms [61, 73]. Ultimately, research on sleep deprivation, vigilant attention, and brain function may help to determine fixed and/or malleable connections between specific neuronal pathways with specific cognitive processes, which may yield new insights with respect to the elusive mind-body problem [121].

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ADDITIONAL INFORMATION

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DOES IMPLEMENTATION OF BIOMATHEMATICAL MODELS MITIGATE FATIGUE AND FATIGUE-RELATED RISKS IN EMERGENCY MEDICAL SERVICES OPERATIONS? A SYSTEMATIC REVIEW

Francine O. James, PhD, Lauren B. Waggoner, PhD, Patricia M. Weiss, MLIS,
P. Daniel Patterson, PhD, NRP, J. Stephen Higgins, PhD,
Eddy S. Lang, MDCM, CCFP (EM), Hans P. A. Van Dongen, PhD

ABSTRACT

Background: Work schedules like those of Emergency Medical Services (EMS) personnel have been associated with increased risk of fatigue-related impairment. Biomathematical modeling is a means of objectively estimating the potential impacts of fatigue on performance, which may be used in the mitigation of fatigue-related safety risks. In the con-

text of EMS operations, our objective was to assess the evidence in the literature regarding the effectiveness of using biomathematical models to help mitigate fatigue and fatigue-related risks. **Methods:** A systematic review of the evidence evaluating the use of biomathematical models to manage fatigue in EMS personnel or similar shift workers was performed. Procedures proposed by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology were used to summarize and rate the certainty in the evidence. Potential bias attached to retained studies was documented using the Cochrane Collaboration's Risk of Bias tool for experimental studies.

Results: The literature search strategy, which focused on both EMS personnel and non-EMS shift workers, yielded $n = 2,777$ unique records. One paper, which investigated non-EMS shift workers, met inclusion criteria. As part of a larger effort, managers and dispatchers of a trucking operation were provided with monthly biomathematical model analyses of predicted fatigue in the driver workforce, and educated on how they could reduce predicted fatigue by means of schedule adjustments. The intervention showed a significant reduction in the number and cost of vehicular accidents during the period in which biomathematical modeling was used. The overall GRADE assessment of evidence quality was very low due to risk of bias, indirectness, imprecision, and publication bias. **Conclusions:** This systematic review identified no studies that investigated the impact of biomathematical models in EMS operations. Findings from one study of non-EMS shift workers were favorable toward use of biomathematical models as a fatigue mitigation scheduling aid, albeit with very low quality of evidence pertaining to EMS operations. We propose three focus areas of research priorities that, if addressed, could help better elucidate the utility and impact of biomathematical models as a fatigue-mitigation tool in the EMS environment. **Key words:** fatigue risk management; biomathematical models of fatigue and performance; shift work; safety

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Supplemental data for this article can be accessed on the [publisher's website](#).

Address correspondence to P. Daniel Patterson, PhD, NRP, University of Pittsburgh, School of Medicine, Department of Emergency Medicine, Iroquois Bldg., Suite 400A, Pittsburgh, PA 15261, USA. Email: pattersonpd@upmc.edu

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BACKGROUND

Fatigue-related cognitive impairment results from the interaction of multiple factors including sleep history, time awake, and time of day (1, 2). Studies of diverse shift worker groups show that work scheduling practices can create conditions that exacerbate the risk of

fatigue-related cognitive impairment (3). The work schedules of Emergency Medical Services (EMS) personnel are notable for 12-hour and 24-hour shifts (4), which increases the risk of fatigue-related impairment and occupational injuries (5).

Biomathematical modeling is a tool for fatigue risk management in operations that involve shift workers who are at risk of negative safety outcomes. These models are widely used in aviation, rail, maritime, and other high-risk industries to estimate the risk of being impaired by fatigue (6). While a number of different biomathematical models of fatigue have been developed, they all generally take into account the relationships between factors that contribute to fatigue, including sleep history, time awake, and time of day (7). These models produce predictions of alertness, performance, or risk of impairment for given work/rest or wake/sleep schedules. They are therefore useful when making decisions regarding shift scheduling, including the duration and timing of duty periods and rest opportunities.

At their core, biomathematical fatigue models make use of equations capturing the temporal regulation of sleep and sleepiness (8, 9) and perform mathematical calculations on the established relationships between wake/sleep or work/rest schedules and two neurobiological processes that drive fatigue (7). One of these processes is the homeostatic process, which (through brain mechanisms that are yet to be fully elucidated) tracks sleep history and current time awake. The homeostatic process causes sleepiness when sleep and wake amounts are out of balance due to relatively excessive wakefulness (8). The other process is referred to as the circadian process, which (through the biological clock in the suprachiasmatic nuclei of the hypothalamus) drives wakefulness during the day and sleep at night (10). The interaction of the homeostatic and circadian processes, through the effects of sleep history and time awake on the one hand and time of day on the other hand, produces a net level of fatigue (11), which fluctuates over time yet manifests prominently during nighttime wakefulness and after sleep deprivation (9, 12). A key feature of biomathematical models is their ability to provide quantitative predictions of the relative risk of fatigue across hours and days of given wake/sleep or work/rest schedules (7). This is particularly important given that individuals' own ability to estimate their fatigue-related risk is generally poor (13, 14).

High-risk industries have used biomathematical modeling for over 30 years to predict fatigue risk (6, 15). The development of these models was accelerated in the 1990s when the U.S. Army and other groups around the globe increased use of modeling to simulate and investigate changes in human behavior under different sleep conditions (15). While different biomathematical models were developed and tested, all were based on the same fundamental concepts of the homeostatic

and circadian processes and produced nearly identical predictions of fatigue risk (2, 16). Early versions of biomathematical models did not account for the cumulative build-up of fatigue across consecutive days of partial sleep restriction, which is a phenomenon that was discovered in the early 2000s (14, 17). Recent research addressed this issue (15, 18, 19), and modern-day biomathematical models can predict fatigue risk for a wide variety of wake/sleep and work/rest schedules (7). Current versions of these models provide a means of objectively estimating the potential impacts of fatigue on performance and safety, which can be used to help mitigate fatigue-related risks (20).

In shift work settings, the utility of biomathematical fatigue models is realized when making decisions about shift schedules (21). They are often used to adjust planned work schedules to reduce exposure to fatigue risk, especially in 24/7 operations (2, 6). In U.S. military applications and space flight, biomathematical modeling is used as a part of the mission planning process (22). The Federal Railroad Administration (FRA) mandates that modeling is employed in mitigating fatigue risk in passenger rail personnel schedules (23). The Federal Aviation Administration (FAA) recently employed biomathematical modeling in the development of updated duty and flight time regulations, and allows carriers to use biomathematical modeling as a key ingredient in proposals for "alternative methods of compliance" (i.e., operations that are outside the scope of the standard hours of service regulations but are demonstrably safer) (24). Commercial airlines in the U.S. routinely include assessments of fatigue risk produced from biomathematical modeling as part of trip schedule planning in operations (25).

The extent to which biomathematical models have been applied, tested, and evaluated in the EMS setting is unknown. Given significant growth and successful application of biomathematical modeling as part of fatigue risk management in safety-critical operations, a review of the evidence testing biomathematical models with EMS personnel or other shift workers is warranted. We sought to systematically review the evidence for the effectiveness of biomathematical models for fatigue mitigation. Our review was guided by the research question developed *a priori* by a panel of experts assembled to address fatigue risk management in EMS: "In EMS personnel or similar worker groups, does implementation of model-based fatigue risk management mitigate fatigue, fatigue-related risks, and/or improve sleep?" (PROSPERO 2016: CRD42016040112) (26).

METHODS

We used a systematic review study design of 5 databases and one website: PubMed/Medline, the Cumulative Index to Nursing and Allied Health

Literature (CINAHL), Scopus, PsycINFO, the Published International Literature on Traumatic Stress (PILOTS), and the publications section of the National Institute of Justice (NIJ) website. The details of our methodology, study protocol, and procedures for reviewing published and unpublished literature are described in a separate publication (27). In this paper, we describe the components of our protocol unique to this systematic review.

Study Design

We assessed publications that described use of randomized controlled trials, quasi-experimental studies (i.e., before and after designs) (28) and observational study designs. Publications that describe the use of modeling but include no intervention or quantifiable outcome were not considered to have met the inclusion criteria for this review.

Types of Participants

The definition of our target population was developed by a panel of experts and is inclusive of diverse shift worker groups: *“EMS personnel or similar worker groups, defined as shift workers whose job activity requires multiple episodes of intense concentration and attention to detail per shift, with serious adverse consequences potentially resulting from lapses in concentration”* (26). We excluded literature that involved non-shift worker “healthy volunteers” and other non-shift worker populations.

Types of Interventions

We retained studies that reported tests or evaluations of the effectiveness of a biomathematical model in the operational setting to address fatigue and fatigue-related risks. We excluded research if the aim of the study was to calibrate the biomathematical model rather than test the impact of the model on operational outcomes such as personnel performance or safety or patient safety.

Types of Outcome Measures

The outcomes of interest for our research question were selected *a priori* by a panel of experts prior to the execution of the search for literature (26). The panel reached agreement on seven outcome categories: patient safety, personnel safety, personnel performance, acute fatigue, sleep and/or sleep quality, indicators of long term health, and cost to the system. Outcome selection was guided by procedures proposed by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework (27, 29).

Search Methods for Studies

A research librarian (PMW) performed searches of five bibliographic database products and one website. The methods of our search strategies are published in a separate publication (27). In that paper, we identify all sources searched, the search terms incorporated, and the description of search vocabulary. For the systematic review described here, the search incorporated multiple terms covering each of three concepts: emergency medical services and other critical shift-based occupations; fatigue, sleep, and sleep disorders; and models of multiple types and simulations. All searches included literature from January 1980 to September 2016. See Online Supplemental Material for search strategy details specific to this systematic review.

Data Collection and Selection of Studies

Screening

Two investigators (FOJ and LBW) independently screened titles and abstracts to identify potentially relevant publications. Three investigators (FOJ, LBW, and PDP) adjudicated disagreements based on the following inclusion criteria: a) the study describes the population of interest; b) the study describes use of a biomathematical model as the primary intervention of interest; and c) the title and/or abstract describes one or more outcomes of interest. The Kappa statistic was used to determine inter-rater agreement.

Full-Text Review

Two investigators (FOJ and LBW) worked independently to abstract key information from full-text articles. The abstracted information included study design, participant characteristics, intervention characteristics, comparisons, outcome measures, and key findings. The study’s principal investigator (PDP) verified abstractions, and disagreements were handled with discussion. We systematically excluded non-peer reviewed literature including book chapters, conference abstracts, newsletters, and similar publications, dissertations and theses. Two investigators (FOJ and LBW) searched bibliographies to identify potentially relevant research.

Risk of Bias Assessment

Two investigators (FOJ and LBW) documented bias of the retained research across six domains with the Cochrane Collaboration’s risk of bias tool for experimental studies (29). The Cochrane risk of bias tool outlines the assessment of bias across six domains: 1) selection bias (i.e., random sequence generation and allocation concealment); 2) performance bias (i.e., blinding of participants and personnel); 3) detection bias (i.e.,

blinding of outcome assessment); 4) attrition bias (i.e., incomplete outcome data); 5) reporting bias (i.e., selective reporting); and 6) other bias (i.e., other sources of bias not addressed in other domains). We addressed any disagreements with bias assessment by using discussion and consensus.

Statistical Analysis

Three investigators (FOJ, LBW, and PDP) used a system for categorizing the findings from retained research as favorable, unfavorable, mixed/inconclusive, or no impact (30). A description of this categorization methodology is published separately (27). Favorable was assigned when findings favored the intervention (biomathematical modeling). Unfavorable was assigned when findings did not favor the intervention. Mixed/Inconclusive was assigned when findings showed both positive and negative impacts on multiple components of an outcome or when the results reported were insufficient to determine the impact on an outcome (such as lack of adequate description of statistical analyses). No impact was assigned when authors determined the intervention showed no statistical and/or clinically meaningful impact on outcomes.

Quality of Evidence

Three investigators (FOJ, LBW, and PDP) used the GRADE framework to summarize and rate the quality of retained research (evidence) into a standardized evidence profile table (31). The evidence profile table presents the following information: number of studies per outcome; judgments about underlying quality of evidence (e.g., risk of bias, indirectness); statistical results; and a quality rating from very low, low, moderate, to high.

Reporting

We present the findings from this systematic review in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement (32).

RESULTS

The search strategy yielded $n = 2,777$ unique records (Figure 1). Two investigators (FOJ and LBW) independently screened the $n = 2,777$ titles and abstracts. The interrater agreement for inclusion/exclusion of titles and abstracts was substantial (Kappa = 0.80). Fifty-three records were judged potentially eligible based on title and abstract alone. Fifty-four records were reviewed following identification of one manuscript identified during bibliography searches as potentially

relevant. We identified one paper, which involved non-EMS shift workers, and provided limited reporting on outcomes of interest to our systematic review (Table 1) (33). Key findings were abstracted and are reported in the Online Supplemental Material. Fifty-three records were excluded (with 3 duplicates detected), and reasons for exclusion organized in the Population, Intervention, Comparison, Outcome (PICO) format (See Online Supplemental Material).

Given that only one study met inclusion criteria (33), we provide an overview of this study and highlight key findings germane to our outcomes of interest. Moore-Ede et al. (33) briefly described a quasi-experimental study design (before/after design) (28) that used a biomathematical model called the Circadian Alertness Simulator (CAS) in an intervention for a commercial trucking organization. This evaluation was included in a larger investigation of the validity and applicability of the CAS model. In the intervention, truck dispatchers used the model by performing monthly analyses of model-derived fatigue estimates for every driver. The dispatchers used the model's output as a basis for making adjustments to the drivers' schedules in order to reduce predicted fatigue in day-to-day operations. This included adjustments of the start and end times of work for individual drivers, providing rest breaks which allowed two consecutive nights of sleep, minimizing night work, avoiding rapid rotations in the starting time of work, and reducing the number of consecutive shifts worked. Findings relevant to two of our seven outcomes of interest were reported: personnel safety and costs to the system.

Regarding the costs-related outcome, the study's authors reported a comparison of accident rates in the (3-year) period prior to the intervention with accident rates occurring during the intervention year. Findings show a reduction in the frequency and cost of truck accidents, as well as a reduction in CAS fatigue scores. Regarding the personnel safety-related outcome, the authors reported that truck accidents decreased 23.3% from 2.30 per million miles traveled during the 3-year period pre-intervention to 1.76 million miles during the year the intervention was implemented. Severe accidents (defined as those costing over \$20,000) decreased by 55% from 0.20 per million miles prior to the intervention to 0.09 per million miles during the intervention. The mean cost per truck accident decreased 65.8% from \$14,088 (Standard Error of Mean [SEM] \$4,307) during the 3-year pre-intervention period to \$4,820 (SEM \$1,437; t -test, $p < 0.05$) during the intervention year. The reported mean cost of severe accidents decreased by 66.7% from \$152,384 (SEM \$40,841) per accident pre-intervention to \$50,809 (SEM \$6,080) per accident during the intervention (t -test, $p < 0.05$).

We detected serious risks of bias with the Moore-Ede et al. (33) study due to a lack of experimental controls, no indication of concealment of intervention, no indi-

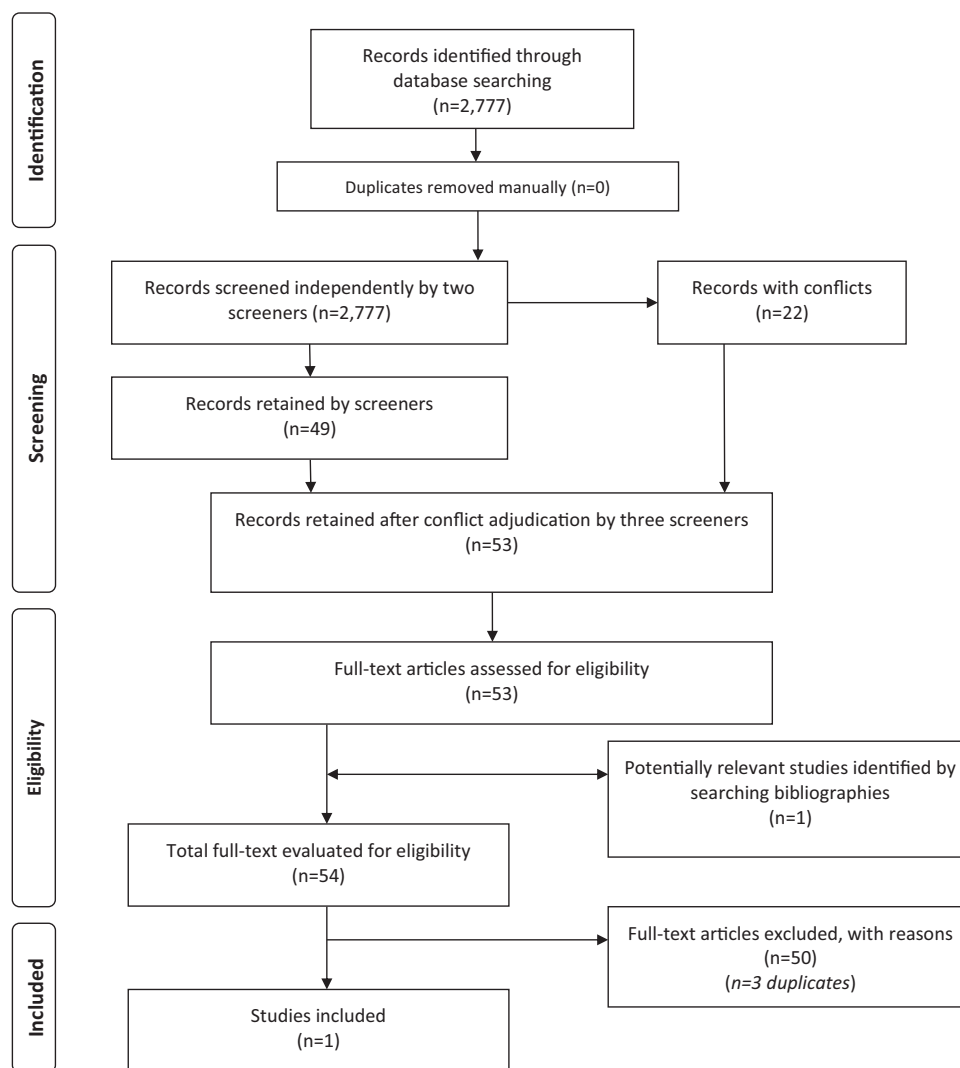


FIGURE 1. PRISMA Flow Diagram for PICO#6 PROSPERO 2016:CRD42016040112.

TABLE 1. Synthesis of individual studies that test implementation of biomathematical models to determine impact on outcomes selected as important to this systematic review

Experimental Study Designs									
			Important Outcomes						
Author, Year	RefID PMID	Study Design	Patient Safety*	Personnel Safety	Personnel Performance [†]	Acute Fatigue [‡]	Sleep and Sleep Quality [§]	Long-Term Health	Cost to System
Moore-Ede, 2004	RefID-1691 PMID-15018271	Quasi-experimental	—	Favorable	—	—	—	—	Favorable

Findings are classified using a system adapted from Bolster and Rourke (2015) where interpretation of findings was classified as favorable if after implementation of the model, improvements in outcomes were observed. Other categories include: unfavorable, mixed/inconclusive, or no impact.

*Includes quality of care.

[†]Includes external subjective ratings of the study subject's performance including perceived satisfaction with the subject's performance.

[‡]Includes acute states of fatigue, sleepiness, and alertness.

[§]Includes sleep latency, total sleep time, recovery, and related measures.

^{||}General wellness or well-being measures included.

cation of blinding participants or investigators, indirectness with EMS personnel, and potential for selective reporting of available outcomes. Our assessment of bias for Moore-Ede et al. (33) appears in Online Supplemental Material. Our quality assessment of this study was very low based on the GRADE elements of risk of bias, inconsistency, indirectness, imprecision, and other considerations (Table 2) (31).

DISCUSSION

Summary of Main Results

The results of this systematic review identified but a single peer-reviewed paper germane to our PICO question and inclusion criteria (33). The paper was judged to have serious risk of bias linked to study design, execution, incomplete reporting, and indirectness with EMS personnel. Findings were limited, yet favorable toward use of biomathematical models as a fatigue mitigation strategy targeting personnel safety and cost to system outcomes. The overall assessment of evidence quality was very low.

Discussion of Systematic Review Findings

To the best of our knowledge, no systematic reviews have been published on the effectiveness of biomathematical modeling-based interventions in reducing the risk or impact of observed fatigue-related impairment. Most of the research describing biomathematical models has reported on the refinement and validation of model mathematics and estimates (34–36) and simulations to estimate fatigue risk across schedules (37, 38).

Several papers retrieved in our search were judged relevant to the PICO question, as they reported on use of biomathematical modeling as a tool in the approach to fatigue mitigation in operational settings (39, 40). After further review, these studies were not retained because the investigators did not report on an evaluation of the effectiveness of the intervention. For example, McCormick et al. (39) and Tvaryanas et al. (40) reported on the use of biomathematical modeling to objectively compare schedule designs. Biomathematical modeling of simulated typical orthopedic surgery schedule rotations and remotely piloted aircraft crew, respectively, was determined useful for the objective comparison of predicted fatigue risk associated with several schedule designs. However, the authors reported no data pertaining to the impact of implementation of model-based interventions on outcomes from the operational environment.

The results of our systematic review show that only one paper, which describes the select findings of one study met our criteria for inclusion. This one paper reported on a limited number of outcomes of interest to

our PICO question as part of a larger effort to validate a specific biomathematical model. The relevant findings are linked to an intervention that assessed the impact of a biomathematical model-based intervention. For this reason, the paper was retained. However, the reported findings were limited.

Minus this one paper describing one study, our review would have been classified as an “empty review.” One of the most important purposes of systematic review methodology is to identify gaps in the scientific literature and to make certain that if important questions are unsupported by published and peer-reviewed science that this state of affairs is rigorously confirmed and that this knowledge is disseminated. The PICO question underlying this systematic review was developed by a panel of multidisciplinary stakeholders and content experts (26). The panel was aware that biomathematical models are in active use in several high-risk operational domains (e.g., the commercial aviation industry) as a means of informing and evaluating scheduling processes and mitigating the risk of fatigue (6, 23–25, 37, 41). It is an established practice in most industries that interventions in active use by multiple organizations undergo some degree of scientific evaluation, but in the area of biomathematical fatigue modeling the published evidence is largely unavailable. Evaluations of biomathematical models may be withheld from the public domain if the model application failed (i.e., biased reporting), for proprietary reasons (e.g., in industry) and security reasons (e.g., in the military), or because they may have yet to be analyzed.

Systematic reviews that fail to identify research to address a well-formulated PICO question, known as “empty reviews,” are commonly reported in the scientific literature (42). In fact, the Cochrane Database of Systematic Reviews contains a growing number of empty reviews with over 100 reported by 2010. They consider empty reviews to be a methodologically sound resource for the advancement of science. Empty systematic reviews serve an important role in clarifying the current state of science for a given question (43). They help to lay the framework for what future directions are required through research. Empty reviews can serve as a call to action and a framework for funding agencies that need to be certain that the research being commissioned or funded in a competitive process will make a unique contribution to our understanding. Practices in healthcare are often supported by widely held beliefs and assumptions related to the scientific evidence supporting it. Empty or minimally sourced systematic reviews in these domains provide a wake-up call that can challenge dogma and call potentially harmful or wasteful practices into question. While an expanded scope to the PICO question posed in this review may have allowed the inclusion of other

TABLE 2. GRADE evidence profile table

Quality assessment									
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Impact / Effect	Quality	Importance
Patient Safety									
0								—	IMPORTANT
Personnel Safety									
1	Experimental study design*	Serious ^{†,‡}	Not serious	Serious [§]	Serious	Relevant data are held private and unpublished. [#]	The number of truck accidents decreased 23.3% from 2.30 per million miles traveled during a three-year pre-intervention period to 1.76 million miles during the intervention year. The number of severe accidents decreased by 55% from 0.20 per million miles prior to the intervention to 0.09 per million miles during the intervention.	⊕○○○ VERY LOW	IMPORTANT
Personnel Performance									
0								—	IMPORTANT
Sleep / Sleep Quality									
0								—	IMPORTANT
Indicators of Long-Term Health									
0								—	IMPORTANT

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biomathematical modeling papers, they would have all lacked that critical element of evaluation of effectiveness. That component was seminal to the spirit of the original PICO question that guided this systematic review and staying the course was essential to remain faithful to the needs of the panel stakeholders even if only one study was ultimately deemed to meet the established inclusion criteria.

Even though this systematic review on the use of biomathematical modeling for mitigation of schedule-related fatigue risk was near-empty, biomathematical modeling is currently employed in a number of regulated operations, including rail and aviation (6), with the list of adopters growing steadily. Despite the increasingly wide-spread use of biomathematical modeling in safety-sensitive, 24/7 operations, however, studies of their effectiveness in controlled pre-post investigations or other scientifically rigorous study designs have not been published. In industries already employing modeling as a fatigue risk management approach, data sets exist that may be informative about the effectiveness of biomathematical model use. Given that such data sets would also include potentially sensitive data on work hours and operational performance, they are often considered proprietary and critical to corporate or organizational strategies and may therefore not be available for analysis and publication. Likewise, modeling efforts conducted by regulators and accident investigators are usually reported directly to individual organizations, and the data contained in these reports are cleaned of all confidential material or marked classified, and thus remain unpublished. As such, it is plausible that biomathematical modeling for managing fatigue risk in high-risk industries is more widely used and more thoroughly characterized than what is depicted in the peer-reviewed literature.

Prospective use of Biomathematical Models of Fatigue in EMS

The main utility of biomathematical models of fatigue is in their ability to include the interaction of factors that contribute to physiological fatigue that would be difficult and inefficient—if not impossible—to fully consider otherwise. Objective metrics estimating predicted fatigue risk allow for the comparison of scheduling solutions, and biomathematical modeling tools may be useful in prospective and retroactive analyses of planned shift schedules (41). This would be analogous to the approach described by the International Civil Aviation Organization, where biomathematical modeling may be used for predictive and reactive hazard identification in duty and flight schedules as part of a comprehensive Fatigue Risk Management System (44). However, biomathematical modeling-based solutions for addressing fatigue risk in EMS operations will require consideration for industry-specific shift work schedules, sleep patterns,

and obstacles to obtain sleep. For example, use of biomathematical models with EMS-specific data may help set boundaries around expected sleep times (e.g., to occur before/after duty times, or during known periods of interim release) (6, 45).

Calibration of sleep estimates and model predictions to the EMS environment is important, given that for many personnel, on-duty sleep opportunities may be driven by task load rather than scheduled break opportunities. Moreover, it is estimated that one half of EMS personnel work 24-hour shifts and that about one third of personnel work multiple EMS jobs (4). Probabilistic estimates of likely sleep times for EMS personnel on typical duty schedules may be used to refine sleep estimates used in model-based analyses (25). Where the biological basis of fatigue risk includes sleep loss, this is a critical consideration for EMS personnel.

We propose 3 focus areas as research priorities that if addressed, could help determine the utility and impact of biomathematical models as a fatigue-mitigation tool in the EMS environment.

Research Priority 1: Which specific outcomes, if any, of the EMS operational environment are predicted by biomathematical modeling estimates? Addressing this research question would help to validate the utility of the modeling approach in EMS operations. Biomathematical models can estimate the physiological likelihood of fatigue related impairment, yet this may not directly relate to negative outcomes in the EMS work environment (7, 41). Planned, natural, or existing safety barriers (e.g., safety alarms, teamwork) may catch many operational errors before they occur or have a measurable impact. The added benefit of biomathematical modeling, or the unique contribution of a model, should be explored. A prospectively designed study could capture reliable sleep data and the occurrence of adverse events. A study that uses a quasi-experimental design (e.g., a before/after study design) would be more feasible and possibly more attractive to the EMS administrator than designs that require randomization to 2 or more conditions (28).

Research Priority 2: How does EMS personnel sleep duration vary by duty period duration, start time, and operation type? Given the known contribution of sleep loss to the risk of fatigue-related impairment, sleep estimates are an essential aspect for any modeling-based analysis and prediction (46). Sleep estimates for EMS must take on-duty sleep into account, especially considering the prevalence of 24-hour duty periods. Data from actigraphy- and/or sleep diary-based, naturalistic studies can inform the development of customized probabilistic distribution of sleep times across EMS duty period types (47), which would improve model based analysis of available schedules.

Research Priority 3: What is the unique contribution of biomathematical modeling to improvements in personnel sleep and organizational outcomes like safety

incidents? Fatigue risk mitigation requires a multifaceted approach or strategy. Seven commonly promoted elements of fatigue mitigation systems include: 1) fatigue management policies; 2) fatigue management with data collection and instillation of controls/countermeasures; 3) a fatigue reporting system for employees; 4) a process for investigation into suspected fatigue-related events; 5) education and training for employees and management; 6) an employer-supported process to diagnose and manage sleep disorders; and 7) a process for internal and external auditing of the fatigue mitigation system/program (48). The combination of these elements may have a positive impact on safety and other outcomes of interest. Carefully designed studies should determine the unique contribution of biomathematical modeling as a key component of a fatigue mitigation system.

LIMITATIONS

The low yield in research related to our PICO question raises a number of questions regarding the limitations of our study. First, our results may be related to the PICO question that guided our literature review. Poorly constructed research questions raise the risk that a team will review literature irrelevant to the prime focus of the systematic review and potentially miss or exclude literature germane to the population, intervention, comparisons, and outcomes of interest. The PICO question that guided this study was carefully constructed and framed in the PICO format (26). The question was judged by a panel of experts to have a high degree of relevance and clarity (27). The panel included individuals with direct involvement in the development, testing, and deployment of biomathematical models. We also reviewed the PROSPERO database of existing and/or previously completed systematic reviews and detected no overlap with our question. For these reasons, we believe that our PICO question was well constructed for purposes of a systematic literature review.

Second, our results may be related to the databases searched. The population, intervention, comparison, and outcomes contained within our PICO question are not isolated to one profession or occupation. Our search was therefore inclusive of multiple databases that may contain literature reporting on use of biomathematical models in diverse populations and settings. The databases searched included PubMed/Medline, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), Scopus, PsycINFO, the Published International Literature on Traumatic Stress (PILOTS), and the publications section of the National Institute of Justice (NIJ) website. We provide a transparent summary of our search strategy in a separate paper (27), and we provide a detail list of key words and search elements used for

each database (see Online Supplemental Material). While a search of other databases and with other search terms may have yielded additional research, we believe the likelihood of discovering additional research that meets our inclusion criteria is very low.

Third, the screening process for this review began with a pooled total of 2,777 from all databases. Per protocol, two screeners with content knowledge and experience with testing and application of biomathematical models evaluated each record independently and delivered a judgment of include or exclude. Their interrater agreement was substantial ($Kappa = 0.80$), and exceeded the initial screening agreement reported in previous systematic reviews on similar topics (49, 50). We also conducted a detailed search of bibliographies of the publications reviewed in full; we searched the grey literature (non-peer-reviewed publications); and we queried experts in the field to validate our findings. While it is possible that research related to our PICO question may have been overlooked, we believe that based on our methodology that the possibility is low.

Finally, we recognize that other investigators conducting the same search may have excluded the one paper retained in this systematic review. The one paper's reported findings may be described as minimal or incomplete, which makes it difficult to provide a comprehensive assessment of the impact that the biomathematical model had on outcomes. We chose to retain this paper because it met our criteria for inclusion: 1) the paper described a shift worker population (our population of interest); 2) the paper described the application of a biomathematical model (our intervention of interest); 3) the paper compared findings pre- and post-introduction of the biomathematical model (our comparison of interest); and 4) the paper reported on outcomes of interest to our search. We retained this paper because it was published in a peer-reviewed journal. Our search of bibliographies, the grey (non-peer-reviewed) literature, and consultation with experts in the field resulted in no additional published papers. We recognize that for the reasons previously outlined, the results and conclusions reached in our paper may differ from what others could have concluded given the available literature.

CONCLUSIONS

In this systematic review, we considered the scientific literature on biomathematical modeling as an intervention designed to mitigate the risk of shift worker fatigue-related impairment and/or to mitigate the likelihood of negative operational outcomes secondary to fatigue-related cognitive impairment. We discovered only one published study of non-EMS shift workers that met our inclusion criteria. While not very fruitful

from the perspective of the evidence it yielded, this systematic review demonstrates convincingly the need for peer-reviewed and publicly available research in an area that has seen widespread commercial interest and investment. This is an important finding. For example, government agencies often expect systematic reviews to be completed on a topic prior to funding large-scale and expensive trials as a means of ensuring that the proposed research is relevant and not redundant. Despite very limited published evidence in real-world applications, biomathematical modeling may be a promising tool for fatigue mitigation (21) with considerable public safety and health implications. It is therefore important to document that the evaluation of this tool has been kept out of the public domain or has fallen short in regard to having been conducted in the first place. The results of this near-empty review thus represent a call to action to fill this important gap in the literature by publishing available studies and conducting new studies of the implementation of biomathematical models to mitigate fatigue and fatigue-related risks.

DISCLOSURES

P. M. Weiss, P. D. Patterson, J. S. Higgins, and E. S. Lang have no financial or commercial interests to disclose. H. Van Dongen is a named inventor on a patent related to individualized fatigue modeling and on 2 patent applications currently pending in this area. Furthermore, H. Van Dongen's laboratory at Washington State University is funded by the National Science Foundation, Office of Naval Research, Federal Express Corporation, and the Institutes for Behavior Resources, to help develop and apply biomathematical and biostatistical fatigue models. H. Van Dongen receives no financial compensation for any patent licenses, and none of the funding, patent, or patent applications are contingent on the outcomes of this systematic review. F. O. James and L. B. Waggoner are employed by the Institutes for Behavior Resources, an independent nonprofit scientific organization that employs the SAFTE-FAST biomathematical modeling software in its fatigue risk management consulting services. The authors have no financial or commercial interests in the SAFTE-FAST product.

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Online Supplement Appendix A – Search strategies

PubMed (National Library of Medicine)

1	Emergency Medical Services [mh] OR Emergency Medical Technicians[mh] OR Emergency Responders[mh] OR Firefighters[mh] OR Police[mh] OR Correctional Officer*[tiab] OR Correctional Officer*[ot] OR Emergency Health Service*[tiab] OR Emergency Health Service*[ot] OR Emergency Medical Service*[tiab] OR Emergency Medical Service*[ot] OR Emergency Medicine Technician*[tiab] OR Emergency Medicine Technician*[ot] OR Emergency Responder*[tiab] OR Emergency Responder*[ot] OR Emergicenter*[tiab] OR Emergicenter*[ot] OR Fire fighter*[tiab] OR Fire fighter*[ot] OR Firefighter*[tiab] OR Firefighter*[ot] OR Fireman[tiab] OR Fireman[ot] OR Firemen[tiab] OR Firemen[ot] OR Firewoman[tiab] OR Firewoman[ot] OR Firewomen[tiab] OR Firewomen[ot] OR First Responder*[tiab] OR First Responder*[ot] OR Law Enforcement [tiab] OR Law Enforcement [ot] OR Medical Emergency Service*[tiab] OR Medical Emergency Service*[ot] OR Paramedic*[tiab] OR Paramedic*[ot] OR Police Force*[tiab] OR Police Force*[ot] OR Police*[tiab] OR Police*[ot] OR Prehospital Emergency[tiab] OR Prehospital Emergency[ot] OR Prehospital Emergency Care[tiab] OR Prehospital Emergency Care[ot] OR public safety[tiab] OR public safety[ot]
2	Aerospace Medicine[mh] OR Air Ambulances[mh] OR Ambulances[mh] OR Automobile Driving[mh] OR Aviation[mh] OR Motor Vehicles[mh] OR Railroads[mh] OR Ships[mh] OR Transportation[mh] OR Transportation of Patients[mh] OR Air Traffic Control*[tiab] OR Air Traffic Control*[ot] OR Ambulance driver*[tiab] OR Ambulance driver*[ot] OR Ambulance*[tiab] OR Ambulance*[ot] OR Aviation[tiab] OR Aviation[ot] OR Boat*[tiab] OR Boat*[ot] OR Bus driver*[tiab] OR Bus driver*[ot] OR Bus[tiab] OR Bus[ot] OR Driver*[tiab] OR Driver*[ot] OR Driving[tiab] OR Driving[ot] OR Navigator*[tiab] OR Navigator*[ot] OR Pilot*[tiab] OR Pilot*[ot] OR Railroad*[tiab] OR Railroad*[ot] OR Ship*[tiab] OR Ship*[ot] OR Subway*[tiab] OR Subway*[ot] OR Train[tiab] OR Train[ot] OR Trains[tiab] OR Trains[ot] OR Truck drivers[tiab] OR Truck drivers[ot] OR Truck driver[tiab] OR Truck driver[ot] OR Truck*[tiab] OR Truck*[ot] OR Trucker*[tiab] OR Trucker*[ot]
3	Nuclear Power Plants[mh] OR Nuclear Power Plant*[tiab] OR Nuclear Power Plant*[ot]
4	Military Personnel[mh] OR Air Force Personnel[tiab] OR Air Force Personnel[ot] OR Armed Forces Personnel[tiab] OR Armed Forces Personnel[ot] OR Army Personnel[tiab] OR Army Personnel[ot] OR Coast Guard[tiab] OR Coast Guard[ot] OR Marine*[tiab] OR Marine*[ot] OR Military[tiab] OR Military[ot] OR Navy Personnel[tiab] OR Navy Personnel[ot] OR Sailor*[tiab] OR Sailor*[ot] OR Soldier*[tiab] OR Soldier*[ot] OR Submariner*[tiab] OR Submariner*[ot]
5	Health Personnel[mh:noexp] OR Nurses[mh] OR Pharmacists[mh] OR Physicians[mh] OR Medical Staff, Hospital[mh] OR Nursing Staff, Hospital[mh] OR Internship and Residency[mh] OR interns[tiab] OR interns[ot] OR residents[tiab] OR residents[ot] OR internship[tiab] OR internship[ot] OR residency[tiab] OR residency[ot] OR house staff[tiab] OR house staff[ot] OR Allied Health Personnel[tiab] OR Allied Health Personnel[ot] OR Doctor*[tiab] OR Doctor*[ot] OR Health Care Provider*[tiab] OR Health Care Provider*[ot] OR Healthcare Provider*[tiab] OR Healthcare Provider*[ot] OR Nurs*[tiab] OR Nurs*[ot] OR Pharmacist*[tiab] OR Pharmacist*[ot] OR Physician*[tiab] OR Physician*[ot]
6	shift work*[tiab] OR shift work*[ot] OR shiftwork*[tiab] OR shiftwork*[ot]
7	1 OR 2 OR 3 OR 4 OR 5 OR 6
8	Fatigue[mh] OR fatigue[tiab] OR fatigue[ot] OR Sleep[mh] OR sleep[tiab] OR sleep[ot]
9	7 AND 8

10	Decision Support Techniques[mh] OR Decision Support Technique[ti] OR Decision Support Technique[ot] OR Decision Support Technic*[ti] OR Decision Support Technic*[ot] OR Decision Aid*[ti] OR Decision Aid*[ot] OR Decision Support Model*[ti] OR Decision Support Model*[ot] OR Decision Analysis[ti] OR Decision Analysis[ot] OR Decision Analyses[ti] OR Decision Analyses[ot] OR Decision Modeling[ti] OR Decision Modeling[ot] OR Clinical Prediction Rule*[ti] OR Clinical Prediction Rule*[ot] OR Models, Biological[mh] OR Biologic Model*[ti] OR Biologic Model*[ot] OR Biological Model*[ti] OR Biological Model*[ot] OR Task Performance and Analysis[mh] OR Task Performance*[ti] OR Task Performance*[ot] OR Critical Incident Technique*[ti] OR Critical Incident Technique*[ot] OR Critical Incident Technic*[ti] OR Critical Incident Technic*[ot] OR Data Interpretation, Statistical[mh] OR Statistical Data Interpretation[ti] OR Statistical Data Interpretation[ot] OR Statistical Data Analysis[ti] OR Statistical Data Analysis[ot] OR Statistical Data Analyses[ti] OR Models, Theoretical[mh] OR Theoretical Model*[ti] OR Theoretical Model*[ot] OR Experimental Model[ti] OR Experimental Model[ot] OR Experimental Models[ti] OR Experimental Models[ot] OR Mathematical Model[ti] OR Mathematical Model[ot] OR Mathematical Models[ti] OR Mathematical Models[ot] OR Theoretical Study[ti] OR Theoretical Study[ot] OR Theoretical Studies[ti] OR Theoretical Studies[ot] OR Models, Statistical[mh] OR Statistical Model*[ti] OR Statistical Model*[ot] OR Probabilistic Model*[ti] OR Probabilistic Model*[ot] OR Polynomial Model*[ti] OR Polynomial Model*[ot] OR Two-Parameter Model*[ti] OR Two-Parameter Model*[ot] OR Two Parameter Model*[ti] OR Two Parameter Model*[ot] OR Binomial Model*[ti] OR Binomial Model*[ot] OR Computer Simulation[mh] OR Computer Simulation[ot] OR simulation[ti] OR simulation[ot] OR biomathematical[ti] OR biomathematical[ot]
11	9 AND 10
12	((patient OR patients) NOT (Sleep Wake Disorders[mh] OR Sleep[mh] OR sleep[tiab] OR sleep[ot] OR Fatigue[mh] OR fatigue[tiab] OR fatigue[ot]))
13	11 NOT 12
14	(("Infant"[Mesh] OR "Child"[Mesh] OR "Adolescent"[Mesh]) NOT "Adult"[Mesh])
15	13 NOT 14
16	(Animals[mh] NOT Humans[mh])
17	15 NOT 16
18	Filters: Publication date from 1980/01/01 to 2017/12/31

Scopus (Elsevier B.V.)

1	INDEXTERMS("Correctional Officer*") OR TITLE-ABS("Correctional Officer*") OR AUTHKEY("Correctional Officer*") OR INDEXTERMS("Emergency Medical Services ") OR TITLE-ABS("Emergency Medical Services ") OR AUTHKEY("Emergency Medical Services ") OR INDEXTERMS("Emergency Medical Technicians") OR TITLE-ABS("Emergency Medical Technicians") OR AUTHKEY("Emergency Medical Technicians") OR INDEXTERMS("Emergency Responders") OR TITLE-ABS("Emergency Responders") OR AUTHKEY("Emergency Responders") OR INDEXTERMS("Firefighters") OR TITLE-ABS("Firefighters") OR AUTHKEY("Firefighters") OR INDEXTERMS("Police") OR TITLE-ABS("Police") OR AUTHKEY("Police") OR INDEXTERMS("Correctional Officer*") OR TITLE-ABS("Correctional Officer*") OR AUTHKEY("Correctional Officer*") OR INDEXTERMS("Emergency Health Service*") OR TITLE-ABS("Emergency Health Service*") OR AUTHKEY("Emergency Health Service*") OR INDEXTERMS("Emergency Medical Service*") OR TITLE-ABS("Emergency Medical Service*") OR AUTHKEY("Emergency Medical Service*") OR INDEXTERMS("Emergency Medicine Technician*") OR TITLE-ABS("Emergency Medicine Technician*") OR AUTHKEY("Emergency Medicine Technician*") OR INDEXTERMS("Emergency Responder*") OR TITLE-ABS("Emergency Responder*") OR AUTHKEY("Emergency Responder*") OR INDEXTERMS("Emergicenter*") OR TITLE-ABS("Emergicenter*") OR AUTHKEY("Emergicenter*") OR INDEXTERMS("Fire fighter*") OR TITLE-ABS("Fire fighter*") OR AUTHKEY("Fire fighter*") OR INDEXTERMS("Firefighter*") OR TITLE-ABS("Firefighter*") OR AUTHKEY("Firefighter*") OR INDEXTERMS("Fireman") OR TITLE-ABS("Fireman")
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	OR AUTHKEY("Fireman") OR INDEXTERMS("Firemen") OR TITLE-ABS("Firemen") OR AUTHKEY("Firemen") OR INDEXTERMS("Firewoman") OR TITLE-ABS("Firewoman") OR AUTHKEY("Firewoman") OR INDEXTERMS("Firewomen") OR TITLE-ABS("Firewomen") OR AUTHKEY("Firewomen") OR INDEXTERMS("First Responder*") OR TITLE-ABS("First Responder*") OR AUTHKEY("First Responder*") OR INDEXTERMS("Law Enforcement ") OR TITLE-ABS("Law Enforcement ") OR AUTHKEY("Law Enforcement ") OR INDEXTERMS("Medical Emergency Service*") OR TITLE-ABS("Medical Emergency Service*") OR AUTHKEY("Medical Emergency Service*") OR INDEXTERMS("Paramedic*") OR TITLE-ABS("Paramedic*") OR AUTHKEY("Paramedic*") OR INDEXTERMS("Police Force*") OR TITLE-ABS("Police Force*") OR AUTHKEY("Police Force*") OR INDEXTERMS("Police*") OR TITLE-ABS("Police*") OR AUTHKEY("Police*") OR INDEXTERMS("Prehospital Emergency") OR TITLE-ABS("Prehospital Emergency") OR AUTHKEY("Prehospital Emergency") OR INDEXTERMS("Prehospital Emergency Care") OR TITLE- ABS("Prehospital Emergency Care") OR AUTHKEY("Prehospital Emergency Care") OR INDEXTERMS("public safety") OR TITLE-ABS("public safety") OR AUTHKEY("public safety")
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	AUTHKEY("Sailor*") OR INDEXTERMS("Soldier*") OR TITLE-ABS("Soldier*") OR AUTHKEY("Soldier*") OR INDEXTERMS("Submariner*") OR TITLE-ABS("Submariner*") OR AUTHKEY("Submariner*")
5	INDEXTERMS("Health Personnel") OR TITLE-ABS("Health Personnel") OR AUTHKEY("Health Personnel") OR INDEXTERMS("Nurses") OR TITLE-ABS("Nurses") OR AUTHKEY("Nurses") OR INDEXTERMS("Pharmacists") OR TITLE-ABS("Pharmacists") OR AUTHKEY("Pharmacists") OR INDEXTERMS("Physicians") OR TITLE-ABS("Physicians") OR AUTHKEY("Physicians") OR INDEXTERMS("hospital medical staff") OR TITLE-ABS("hospital medical staff") OR AUTHKEY("hospital medical staff") OR INDEXTERMS("Internship and Residency") OR TITLE-ABS("Internship and Residency") OR AUTHKEY("Internship and Residency") OR INDEXTERMS("resident*") OR TITLE-ABS("resident*") OR AUTHKEY("resident*") OR INDEXTERMS("interns") OR TITLE-ABS("interns") OR AUTHKEY("interns") OR INDEXTERMS("residents") OR TITLE-ABS("residents") OR AUTHKEY("residents") OR INDEXTERMS("internship") OR TITLE-ABS("internship") OR AUTHKEY("internship") OR INDEXTERMS("residency") OR TITLE-ABS("residency") OR AUTHKEY("residency") OR INDEXTERMS("house staff") OR TITLE-ABS("house staff") OR AUTHKEY("house staff") OR INDEXTERMS("Allied Health Personnel") OR TITLE-ABS("Allied Health Personnel") OR AUTHKEY("Allied Health Personnel") OR INDEXTERMS("Doctor*") OR TITLE-ABS("Doctor*") OR AUTHKEY("Doctor*") OR INDEXTERMS("Health Care Provider*") OR TITLE-ABS("Health Care Provider*") OR AUTHKEY("Health Care Provider*") OR INDEXTERMS("Healthcare Provider*") OR TITLE-ABS("Healthcare Provider*") OR AUTHKEY("Healthcare Provider*") OR INDEXTERMS("Nurs*") OR TITLE-ABS("Nurs*") OR AUTHKEY("Nurs*") OR INDEXTERMS("Pharmacist*") OR TITLE-ABS("Pharmacist*") OR AUTHKEY("Pharmacist*") OR INDEXTERMS("Physician*") OR TITLE-ABS("Physician*") OR AUTHKEY("Physician*")
6	INDEXTERMS("shiftwork") OR TITLE-ABS("shiftwork") OR AUTHKEY("shiftwork") OR INDEXTERMS("shift work") OR TITLE-ABS("shift work") OR AUTHKEY("shift work") OR INDEXTERMS("shift worker") OR TITLE-ABS("shift worker") OR AUTHKEY("shift worker")
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6
8	INDEXTERMS("Fatigue") OR TITLE-ABS("Fatigue") OR AUTHKEY("Fatigue") OR INDEXTERMS("Sleep") OR TITLE-ABS("Sleep") OR AUTHKEY("Sleep")
9	#7 AND #8
10	INDEXTERMS("Decision Support Technique*") OR TITLE("Decision Support Technique*") OR AUTHKEY("Decision Support Technique*") OR INDEXTERMS("Decision Support Model*") OR TITLE("Decision Support Model*") OR AUTHKEY("Decision Support Model*") OR INDEXTERMS("Decision Aid*") OR TITLE("Decision Aid*") OR AUTHKEY("Decision Aid*") OR INDEXTERMS("Decision Analysis") OR TITLE("Decision Analysis") OR AUTHKEY("Decision Analysis") OR INDEXTERMS("Decision Analyses") OR TITLE("Decision Analyses") OR AUTHKEY("Decision Analyses") OR INDEXTERMS("Decision Modeling") OR TITLE("Decision Modeling") OR AUTHKEY("Decision Modeling") OR INDEXTERMS("Clinical Prediction Rule*") OR TITLE("Clinical Prediction Rule*") OR AUTHKEY("Clinical Prediction Rule*") OR INDEXTERMS("Biologic Model*") OR TITLE("Biologic Model*") OR AUTHKEY("Biologic Model*") OR INDEXTERMS("Biological Model*") OR TITLE("Biological Model*") OR AUTHKEY("Biological Model*") OR INDEXTERMS("Task Performance and Analysis") OR TITLE("Task Performance and Analysis") OR AUTHKEY("Task Performance and Analysis") OR INDEXTERMS("Task Performance*") OR TITLE("Task Performance*") OR AUTHKEY("Task Performance*") OR INDEXTERMS("Critical Incident Technique*") OR TITLE("Critical Incident Technique*") OR AUTHKEY("Critical Incident Technique*") OR INDEXTERMS("Theoretical Model*") OR TITLE("Theoretical Model*") OR AUTHKEY("Theoretical Model*") OR INDEXTERMS("Experimental Model*") OR TITLE("Experimental Model*") OR AUTHKEY("Experimental Model*") OR

	INDEXTERMS("Mathematical Model*") OR TITLE("Mathematical Model*") OR AUTHKEY("Mathematical Model*") OR INDEXTERMS("Models, Statistical") OR TITLE("Models, Statistical") OR AUTHKEY("Models, Statistical") OR INDEXTERMS("Statistical Model*") OR TITLE("Statistical Model*") OR AUTHKEY("Statistical Model*") OR INDEXTERMS("Probabilistic Model*") OR TITLE("Probabilistic Model*") OR AUTHKEY("Probabilistic Model*") OR INDEXTERMS("Polynomial Model*") OR TITLE("Polynomial Model*") OR AUTHKEY("Polynomial Model*") OR INDEXTERMS("Two-Parameter Model*") OR TITLE("Two-Parameter Model*") OR AUTHKEY("Two-Parameter Model*") OR INDEXTERMS("Two Parameter Model*") OR TITLE("Two Parameter Model*") OR AUTHKEY("Two Parameter Model*") OR INDEXTERMS("Binomial Model*") OR TITLE("Binomial Model*") OR AUTHKEY("Binomial Model*") OR INDEXTERMS("Biomathematical model*") OR TITLE("Biomathematical model*") OR AUTHKEY("Biomathematical model*") OR INDEXTERMS("Computer Simulation") OR TITLE("Computer Simulation") OR AUTHKEY("Computer Simulation") OR INDEXTERMS("simulation") OR TITLE("simulation") OR AUTHKEY("simulation") OR INDEXTERMS("two process model*") OR TITLE("two process model*") OR AUTHKEY("two process model*") OR INDEXTERMS("two-process model*") OR TITLE("two-process model*") OR AUTHKEY("two-process model*") OR INDEXTERMS("Statistical Data Interpretation") OR TITLE("Statistical Data Interpretation") OR AUTHKEY("Statistical Data Interpretation") OR INDEXTERMS("Statistical Data Analysis") OR TITLE("Statistical Data Analysis") OR AUTHKEY("Statistical Data Analysis") OR INDEXTERMS("Statistical Data Analyses") OR TITLE("Statistical Data Analyses") OR AUTHKEY("Statistical Data Analyses") OR INDEXTERMS("Theoretical Study") OR TITLE("Theoretical Study") OR AUTHKEY("Theoretical Study") OR INDEXTERMS("Theoretical Studies") OR TITLE("Theoretical Studies") OR AUTHKEY("Theoretical Studies")
11	#9 AND #10
12	ALL ("metal*") OR ALL ("iron") OR ALL ("steel ") OR ALL ("aluminum") OR ALL ("titanium") OR ALL ("strut") OR ALL ("blade*") OR ALL ("rotor*") OR ALL ("voltage") OR ALL ("capacitor") OR ALL ("mechanical") OR ALL ("heat") OR ALL ("laser") OR ALL ("welding") OR ALL ("transformer") OR ALL ("beam*") OR ALL ("turbo*") OR ALL ("turbine*") OR ALL ("therm*") OR ALL ("liquid*") OR ALL ("electrical") OR ALL ("water") OR ALL ("magnetic") OR ALL ("fiber*") OR ALL ("optic*") OR ALL ("price") OR ALL ("pricing") OR ALL ("axle*") OR ALL ("crack*") OR ALL ("railroad*") OR ALL ("container*") OR ALL ("road*") OR ALL ("route*") OR ALL ("traffic") OR ALL ("transport") OR ALL ("transportation")
13	#11 AND NOT #12
14	[#13] AND NOT INDEX(medline)
15	[#14] AND PUBYEAR > 1979

PsycINFO (Ovid Technologies)

1	Corrections Officers/ OR correctional officer\$.mp. OR Emergency Services/ OR emergency health service\$.mp. OR emergency medical service\$.mp. OR emergency medicine technician\$.mp. OR Rescue Workers/ OR First Responders/ OR first responder\$.mp. OR emergency responder\$.mp. OR Fire Fighters/ OR fire fighter\$.mp. OR firefighter\$.mp. OR Law Enforcement/ OR law enforcement .mp. OR medical emergency service\$.mp. OR Allied Health Personnel/ OR paramedic\$.mp. OR Police Personnel/ OR police force\$.mp. OR police\$.mp. OR prehospital emergency care.mp. OR public safety.mp.
2	exp Transportation/ OR Aerospace Personnel/ OR Aviation/ OR Aircraft Pilots/ OR pilot\$.mp. OR Air Traffic Control/ OR Air Traffic Control\$.mp. OR Ambulance\$.mp. OR Drivers/ OR driver\$.mp. OR driving.mp. OR Motor Vehicles/ OR (bus or buses).mp. OR truck\$.mp. OR ship\$.mp. OR boat\$.mp. OR Railroad Trains/ OR railroad\$.mp. OR subway\$.mp. OR navigator\$.mp.
3	nuclear power.mp.
4	exp Military Personnel/ OR military.mp. OR air force.mp. OR armed forces.mp. OR army.mp. OR coast guard.mp. OR marine\$.mp. OR navy.mp. OR sailor\$.mp. OR soldier\$.mp. OR submariner\$.mp.

5	Medical Personnel/ OR Health Personnel/ OR Military Medical Personnel/ OR Allied Health Personnel/ OR Nurses/ OR Pharmacists/ OR Physicians/ OR health care provider\$.mp. OR healthcare provider\$.mp. OR Clinicians/ OR doctor\$.mp. OR physician\$.mp. OR nurs\$.mp. OR pharmacist\$.mp. OR Medical Residency/ OR Medical Internship/ OR residents.mp. OR interns.mp. OR internship.mp. OR residency.mp. OR house staff.mp.
6	shiftwork.mp. OR shift work.mp. OR shift worker.mp. OR Workday Shifts/
7	OR/1-6
8	Fatigue/ OR fatigue.mp. OR Sleep/ OR sleep.mp.
9	7 AND 8
10	Binomial Model\$.mp. OR Biologic\$ Model\$.mp. OR Biological Model\$.mp. OR Biomathematical model\$.mp. OR Clinical Prediction Rule\$.mp. OR Critical Incident Technique\$.mp. OR Decision Aid\$.mp. OR Decision Analyses.mp. OR Decision Analysis.mp. OR Decision Modeling.mp. OR Decision Support Model\$.mp. OR Decision Support Technique\$.mp. OR Decision Support Systems/ OR Experimental Model\$.mp. OR Models/ OR Mathematical Modeling/ OR Mathematical Model\$.mp. OR Polynomial Model\$.mp. OR Probabilistic Model\$.mp. OR exp Simulation/ OR simulation.mp. OR Statistical Model\$.mp. OR Task Performance.mp. OR Theoretical Model\$.mp. OR Two Parameter Model\$.mp. OR two-process model\$.mp. OR Computer Simulation/ OR Statistical Data Interpretation.mp. OR Statistical Data Analysis.mp. OR Statistical Data Analyses.mp. OR Statistical Analysis/ OR Theoretical Study.mp. OR Theoretical Studies.mp.
11	9 AND 10
12	limit 11 to yr="1980 -Current"
13	limit 12 to animal
14	limit 12 to human
15	13 NOT 14
16	12 NOT 15
17	limit 16 to (100 childhood <birth to age 12 yrs> or 120 neonatal <birth to age 1 mo> or 140 infancy <2 to 23 mo> or 160 preschool age <age 2 to 5 yrs> or 180 school age <age 6 to 12 yrs> or 200 adolescence <age 13 to 17 yrs>)
18	limit 16 to ("300 adulthood <age 18 yrs and older>" or 320 young adulthood <age 18 to 29 yrs> or 340 thirties <age 30 to 39 yrs> or 360 middle age <age 40 to 64 yrs> or "380 aged <age 65 yrs and older>" or "390 very old <age 85 yrs and older>")
19	17 NOT 18
20	16 NOT 19

CINAHL (EBSCO Industries, Inc.)

S1	(MH "Emergency Medical Services") OR (MH "Emergency Medical Technicians ") OR (MH "Emergicenter*") OR (MH "Paramedic*") OR (MH "Prehospital Care") OR "correctional officer*" OR "emergency health service*" OR "emergency medical service*" OR "emergency medicine technician*" OR "emergency responder*" OR "firefighters" OR "fire fighter*" OR "firefighter*" OR "fireman" OR "firemen" OR "first responder*" OR "law enforcement " OR "medical emergency service*" OR "police" OR "police force*" OR "police*" OR "prehospital care" OR "prehospital emergency" OR "prehospital emergency care" OR "public safety"
S2	(MH "Aerospace Medicine") OR (MH "Ambulances") OR (MH "Automobile Driving") OR (MH "Aviation") OR (MH "Motor Vehicles") OR (MH "Railroads") OR (MH "Ships") OR (MH "Transportation") OR (MH "Transportation of Patients") OR (MH "Aeromedical Transport ") OR (MH "Pilots") OR "ambulance*" OR "railroad*" OR "subway*" OR "train" OR "trains" OR "ship*" OR "boat*" OR "air traffic control*" OR "driver*" OR "driving" OR "navigator*" OR "pilot*" OR "truck"
S3	(MH "Nuclear Power Plants") OR "nuclear power "
S4	(MH "Military Personnel+") OR "air force personnel" OR "armed forces personnel" OR "army personnel" OR "coast guard" OR "marine*" OR "military" OR "navy personnel" OR "sailor*" OR "soldier*" OR "submarine"

S5	(MH "Health Personnel") OR (MH "Internship and Residency") OR (MH "Interns and Residents") OR (MH "Physicians") OR (MH "Physicians, Emergency") OR (MH "Medical Staff, Hospital ") OR (MH "Nurses") OR (MH "Nursing Staff, Hospital ") OR (MH "Pharmacists") OR "health care provider*" OR "healthcare provider*" OR "residen*" OR "intern*" OR "house staff" OR "physician*" OR "doctor*" OR "nurs*" OR "pharmacist"
S6	(MH "Shiftwork") OR "shiftwork" OR "shift work" OR (MH "Shift Workers") OR "shift worker*")
S7	S1 OR S2 OR S3 OR S4 OR S5 OR S6
S8	(MH "Fatigue") OR "fatigue" OR "lassitude" OR "tiredness" OR "exhaustion"
S9	(MH "Sleep") OR "sleep"
S10	"sleep quality" OR "quality of sleep" OR "sleep inertia" OR "sleep latency" OR "sleep homeostasis" OR "sleep health" OR "sleep hygiene" OR "sleep-wake cycle" OR "sleep pressure" OR "sleep time" OR "sleep parameters" OR "sleep pattern"
S11	(MH "Sleep Stages") OR "sleep stage*" OR "sleep phase*" OR "drowsiness" OR "sleepiness" OR (MH "Relaxation") OR (MH "Rejuvenation")
S12	(MH "Sleep, REM") OR "rem sleep" OR "rhombencephalic sleep" OR "fast-wave sleep" OR "fast wave sleep" OR "paradoxical sleep"
S13	(MH "Melatonin") OR (MH "Chronobiology Disorders") OR (MH "Biological Clocks") OR (MH "Light") OR (MH "Lighting") OR (MH "Circadian Rhythm") OR "melatonin" OR "chronobiolog*" OR "biological clock*" OR "biologic clock*" OR "biologic* oscillator*" OR "biologic* pacemaker*" OR "endogenous oscillator*" OR "circadian rhythm*" OR "twenty-four hour rhythm*" OR "twenty four hour rhythm*" OR "ultradian rhythm*" OR "diurnal rhythm*" OR "nyctohemeral rhythm*" OR "24-hour rhythm*"
S14	(MH "Chronotherapy") OR "sleep phase chronotherap*" OR "phase advance chronotherap*" OR "phase delay chronotherap*"
S15	(MH "Wakefulness") OR (MH "Arousal") OR (MH "Attention") OR "wakefulness" OR "arousal" OR "alertness" OR "vigilance"
S16	(MH "Sleep Deprivation") OR "sleep deprivation*" OR "sleep fragmentation*" OR "insufficient sleep syndrome*"
S17	(MH "Sleep Disorders, Circadian Rhythm") OR (MH "Sleep-Wake Transition Disorders") OR "disturbed nyctohemeral rhythm*" OR "circadian rhythm sleep disorder*" OR "sleep wake cycle disorder*" OR "sleep-wake schedule disorder*" OR "sleep wake schedule disorder*" OR "shift-work sleep disorder*" OR "shift work sleep disorder*" OR "non-24 hour sleep-wake disorder*" OR "non 24 hour sleep wake disorder*" OR "non twenty-four hour sleep-wake disorder*" OR "nonorganic sleep wake cycle disorder*" OR "advanced sleep phase syndrome*" OR "delayed sleep phase syndrome*" OR "delayed sleep-phase syndrome*"
S18	(MH "Disorders of Excessive Somnolence") OR (MH "Sleep Disorders\$") OR "excessive somnolence disorder*" OR "hypersomnolence" OR "hypersomnia" OR "sleep wake disorder*" OR "subwakefulness syndrome*" OR "sleep disorder*" OR "sleep related neurogenic tachypnea" OR "sleep-related neurogenic tachypnea" OR "long sleeper syndrome" OR "short sleeper syndrome" OR "short sleep phenotype"
S19	(MH "Insomnia") OR "sleep initiation and maintenance disorders" OR "disorders of initiating and maintaining sleep" OR "dims" OR "early awakening" OR "insomnia*" OR "sleep initiation dysfunction" OR "sleeplessness"
S20	(MH "Sleep Arousal Disorders") OR "sleep arousal disorder" OR "confusional arousal*"
S21	(MH "Sleep Disorders, Intrinsic") OR "intrinsic sleep disorder*" OR "sleep state misperception*" OR "post-traumatic hypersomnia" OR "posttraumatic hypersomnia"
S22	(MH "Dyssomnias") OR "dyssomnia*" OR "environmental sleep disorder*" OR "extrinsic sleep disorder*" OR "limit-setting sleep disorder*" OR "limit setting sleep disorder*" OR "nocturnal eating-drinking syndrome*" OR "nocturnal eating drinking syndrome*" OR "adjustment sleep disorder*" OR "inadequate sleep hygiene"
S23	S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22
S24	S7 AND S23

S25	"Binomial Model*" OR "Biologic* Model*" OR "Biological Model*" OR "Biomathematical model*" OR "Clinical Prediction Rule*" OR "Critical Incident Technique*" OR "Decision Aid*" OR "Decision Analyses" OR "Decision Analysis" OR "Decision Modeling" OR "Decision Support Model*" OR "Decision Support Technique*" OR "Decision Support Systems" OR "Experimental Model*" OR "Goodness of Fit" OR "goodness of fit" OR "Goodness-of-fit" OR "Model*" OR "Mathematical Modeling" OR "Mathematical Model*" OR "Polynomial Model*" OR "Probabilistic Model*" OR "exp Simulation" OR "simulation" OR "Statistical Model*" OR "Task Performance" OR "Theoretical Model*" OR "Two Parameter Model*" OR "two-process model*" OR (MH "Models, Biological") OR (MH "Models, Statistical") OR (MH "Critical Incidents Method") OR (MH "Decision Support Systems, Clinical") OR (MH "Decision Support Techniques") OR (MH "Decision Support Systems, Management") OR (MH "Decision Making, Computer Assisted") OR (MH "Goodness of Fit Chi Square Test") OR (MH "Simulations") OR (MH "Computer Simulation") OR (MH "Task Performance and Analysis")
S26	S24 AND S25
S27	Limiters - Published Date: 19800101-20171231

PILOTS (ProQuest)

((fatigue OR sleep*) AND (model* OR simulation OR biomathematical)) NOT (chronic fatigue OR compassion fatigue)

National Institute of Justice Publications and Multimedia (<https://nij.gov/publications/pages/welcome.aspx>)

((fatigue OR sleep*) AND (model* OR simulation OR biomathematical)) NOT (chronic fatigue OR compassion fatigue)

Online Supplement Appendix B: Key Findings

Moore-Ede, 2004 RefID-1691 PMID-15018271	
Study Setting	A 500 power unit trucking fleet operation
Eligible Participants	Truck drivers
Study Aims	As part of a larger effort to validate a biomathematical model (the Circadian Alertness Simulator, CAS), this paper reported on an intervention and pre-post evaluation of the use of CAS in a trucking operation to help mitigate fatigue risk and reduce accident rates and associated costs.
Study Design & Participants	A quasi-experimental study design comparing accidents and costs associated with accidents during a one-year intervention period to accidents and associated costs three-years prior to initiation of the CAS intervention.
Intervention	The CAS biomathematical model fatigue risk assessment system
Comparison(s)	Number of accidents and associated costs during the one-year intervention phase to three years pre-intervention
Outcome Measure(s)	Trucking accidents and associated costs
Key Finding(s)	The number of truck accidents decreased 23.3% from 2.30 per million miles traveled during a three-year period pre-intervention to 1.76 million miles during the intervention year. The number of severe accidents decreased by 55% from 0.20 per million miles prior to the intervention to 0.09 per million miles during the intervention. The mean cost per truck accident decreased 65.8% from \$14,088 (SEM \$4,307) during a three-year period pre-intervention to \$4,820 (SEM \$1,437; t-test, $p < 0.05$) during the one-year intervention. The mean cost of "severity accidents" (over \$20,000 cost) decreased by 66.7% from \$152,384 (SEM \$40,841) per accident pre-intervention to \$50,809 (SEM \$6,080) per accident during the intervention period (t-test, $p < 0.05$).

Online Supplement Appendix C: Exclusions with reasons

RefID	61
PMID	n/a
Citation/Reference	Åkerstedt T, Axelsson J, Kecklund G (2007) Individual validation of model predictions of sleepiness and sleep hours. Somnologie - Schlafforsch und Schlafmedizin 11: 169–174 Available: http://link.springer.com/10.1007/s11818-007-0315-7 Accessed 8 May 2017.
Exclusion Criteria	Reviewer's Justification
-Population of interest	
-Interventions of interest	No intervention tested
-Comparisons of interest	
-Outcomes of interest	

RefID	62
PMID	7761737
Citation/Reference	Åkerstedt T, Folkard S. Validation of the S and C components of the three-process model of alertness regulation. Sleep. 1995 Jan;18(1):1-6. PubMed PMID: 7761737
Exclusion Criteria	Reviewer's Justification
-Population of interest	
-Interventions of interest	No intervention tested
-Comparisons of interest	
-Outcomes of interest	

RefID	122
PMID	16964748
Citation/Reference	Armentrout JJ, Holland DA, O'Toole KJ, Ercoline WR. Fatigue and related human factors in the near crash of a large military aircraft. Aviat Space Environ Med. 2006 Sep;77(9):963-70. PubMed PMID: 16964748
Exclusion Criteria	Reviewer's Justification
-Population of interest	
-Interventions of interest	No intervention tested
-Comparisons of interest	
-Outcomes of interest	

RefID	218
PMID	15018270
Citation/Reference	Belyavin AJ, Spencer MB. Modeling performance and alertness: the QinetiQ approach. Aviat Space Environ Med. 2004 Mar;75(3 Suppl):A93-103; discussion 104-6. PubMed PMID: 15018270
Exclusion Criteria	Reviewer's Justification
-Population of interest	
-Interventions of interest	No intervention tested
-Comparisons of interest	
-Outcomes of interest	

RefID	264
PMID	17539442
Citation/Reference	Bliese PD, McGurk D, Thomas JL, Balkin TJ, Wesensten N. Discontinuous growth modeling of adaptation to sleep setting changes: individual differences and age. Aviat Space Environ Med. 2007 May;78(5):485-92. PubMed PMID: 17539442
Exclusion Criteria	Reviewer's Justification
-Population of interest	
-Interventions of interest	No intervention tested
-Comparisons of interest	
-Outcomes of interest	

RefID	366
PMID	22239930
Citation/Reference	Cabon P, Deharvengt S, Grau JY, Maille N, Berechet I, Mollard R. Research and guidelines for implementing Fatigue Risk Management Systems for the French regional airlines. Accid Anal Prev. 2012 Mar;45 Suppl:41-4. doi: 10.1016/j.aap.2011.09.024. Epub 2011 Nov 5. PubMed PMID: 22239930
Exclusion Criteria	Reviewer's Justification
-Population of interest	
-Interventions of interest	No intervention tested
-Comparisons of interest	
-Outcomes of interest	

RefID	427
PMID	24024304
Citation/Reference	Chandler JF, Arnold RD, Phillips JB, Turnmire AE. Predicting individual differences in response to sleep loss: application of current techniques. Aviat Space Environ Med. 2013 Sep;84(9):927-37. PubMed PMID: 24024304
Exclusion Criteria	Reviewer's Justification
-Population of interest	
-Interventions of interest	No intervention tested
-Comparisons of interest	
-Outcomes of interest	

RefID	445
PMID	20220612
Citation/Reference	Chen CK, Lin C, Hou TH, Wang SH, Lin HM. A study of operating room scheduling that integrates multiple quantitative and qualitative objectives. J Nurs Res. 2010 Mar;18(1):62-74. doi: 10.1097/JNR.0b013e3181d0365f. PubMed PMID: 20220612
Exclusion Criteria	Reviewer's Justification
-Population of interest	
-Interventions of interest	No intervention tested
-Comparisons of interest	
-Outcomes of interest	

RefID	575
PMID	26026969
Citation/Reference	Darwent D, Dawson D, Paterson JL, Roach GD, Ferguson SA. Managing fatigue: It really is about sleep. Accid Anal Prev. 2015 Sep;82:20-6. doi: 10.1016/j.aap.2015.05.009. Epub 2015 May 27. PubMed PMID: 26026969
Exclusion Criteria	Reviewer's Justification
-Population of interest	
-Interventions of interest	No intervention tested
-Comparisons of interest	
-Outcomes of interest	

RefID	576
PMID	20175402
Citation/Reference	Darwent D, Dawson D, Roach GD. Prediction of probabilistic sleep distributions following travel across multiple time zones. Sleep. 2010 Feb;33(2):185-95. PubMed PMID: 20175402; PubMed Central PMCID: PMC2816963
Exclusion Criteria	Reviewer's Justification
-Population of interest	
-Interventions of interest	No intervention tested
-Comparisons of interest	
-Outcomes of interest	

RefID	577
PMID	22239923
Citation/Reference	Darwent D, Dawson D, Roach GD. A model of shiftworker sleep/wake behaviour. Accid Anal Prev. 2012 Mar;45 Suppl:6-10. doi: 10.1016/j.aap.2011.09.017. Epub 2011 Oct 5. PubMed PMID: 22239923
Exclusion Criteria	Reviewer's Justification
-Population of interest	
-Interventions of interest	No intervention tested
-Comparisons of interest	
-Outcomes of interest	

RefID	593
PMID	11209874
Citation/Reference	Dawson D, Fletcher A. A quantitative model of work-related fatigue: background and definition. Ergonomics. 2001 Feb 10;44(2):144-63. PubMed PMID: 11209874
Exclusion Criteria	Reviewer's Justification
-Population of interest	
-Interventions of interest	No intervention tested
-Comparisons of interest	
-Outcomes of interest	

RefID	613
PMID	17517914
Citation/Reference	Dean DA 2nd, Fletcher A, Hursh SR, Klerman EB. Developing mathematical models of neurobehavioral performance for the "real world". J Biol Rhythms. 2007 Jun;22(3):246-58. Review. PubMed PMID: 17517914
Exclusion Criteria	Reviewer's Justification
-Population of interest	
-Interventions of interest	No intervention tested
-Comparisons of interest	
-Outcomes of interest	

RefID	614
PMID	19543382
Citation/Reference	Dean DA 2nd, Forger DB, Klerman EB. Taking the lag out of jet lag through model-based schedule design. PLoS Comput Biol. 2009 Jun;5(6):e1000418. doi: 10.1371/journal.pcbi.1000418. Epub 2009 Jun 19. PubMed PMID: 19543382; PubMed Central PMCID: PMC2691990
Exclusion Criteria	Reviewer's Justification
-Population of interest	
-Interventions of interest	No intervention tested
-Comparisons of interest	
-Outcomes of interest	

RefID	649
PMID	15018272
Citation/Reference	Dijk DJ, Larkin W. Fatigue and performance models: general background and commentary on the circadian alertness simulator for fatigue risk assessment in transportation. Aviat Space Environ Med. 2004 Mar;75(3 Suppl):A119-21. PubMed PMID: 15018272
Exclusion Criteria	Reviewer's Justification
-Population of interest	
-Interventions of interest	No intervention tested
-Comparisons of interest	
-Outcomes of interest	

RefID	680
PMID	22239925
Citation/Reference	Dorrian J, Darwent D, Dawson D, Roach GD. Predicting pilot's sleep during layovers using their own behaviour or data from colleagues: implications for biomathematical models. <i>Accid Anal Prev.</i> 2012 Mar;45 Suppl:17-21. doi: 10.1016/j.aap.2011.09.019. Epub 2011 Oct 24. PubMed PMID: 22239925
Exclusion Criteria	Reviewer's Justification
-Population of interest	
-Interventions of interest	No intervention tested
-Comparisons of interest	
-Outcomes of interest	

RefID	819
PMID	15018280
Citation/Reference	Folkard S, Åkerstedt T. Trends in the risk of accidents and injuries and their implications for models of fatigue and performance. <i>Aviat Space Environ Med.</i> 2004 Mar;75(3 Suppl):A161-7. Review. PubMed PMID: 15018280
Exclusion Criteria	Reviewer's Justification
-Population of interest	
-Interventions of interest	No intervention tested
-Comparisons of interest	
-Outcomes of interest	

RefID	820
PMID	10643755
Citation/Reference	Folkard S, Åkerstedt T, Macdonald I, Tucker P, Spencer MB. Beyond the three-process model of alertness: estimating phase, time on shift, and successive night effects. <i>J Biol Rhythms.</i> 1999 Dec;14(6):577-87. Review. PubMed PMID: 10643755
Exclusion Criteria	Reviewer's Justification
-Population of interest	
-Interventions of interest	No intervention tested
-Comparisons of interest	
-Outcomes of interest	

RefID	845
PMID	n/a
Citation/Reference	French J. A model to predict fatigue degraded performance. In Human Factors and Power Plants, 2002. Proceedings of the 2002 IEEE 7th Conference on 2002 (pp. 4-4). IEEE.
Exclusion Criteria	Reviewer's Justification
-Population of interest	Conference proceeding
-Interventions of interest	
-Comparisons of interest	
-Outcomes of interest	

RefID	880
PMID	15586782
Citation/Reference	Garbarino S, Mascialino B, Penco MA, Squarcia S, De Carli F, Nobili L, Beelke M, Cuomo G, Ferrillo F. Professional shift-work drivers who adopt prophylactic naps can reduce the risk of car accidents during night work. Sleep. 2004 Nov 1;27(7):1295-302. PubMed PMID: 15586782
Exclusion Criteria	Reviewer's Justification
-Population of interest	No intervention tested
-Interventions of interest	
-Comparisons of interest	
-Outcomes of interest	

RefID	981
PMID	n/a
Citation/Reference	Gundel A, Drescher J, Turowski J. Alertness in airline pilots during night flights: Assessment of alertness using EEG measures. Engineering psychophysiology. Issues and applications Mahwah: LEA. 2000:177-87.
Exclusion Criteria	Reviewer's Justification
-Population of interest	No intervention tested
-Interventions of interest	
-Comparisons of interest	
-Outcomes of interest	

RefID	982
PMID	n/a
Citation/Reference	Gunzelmann G, Veksler BZ, Walsh MM, Gluck KA. Understanding and predicting the cognitive effects of sleep loss through simulation. Translational Issues in Psychological Science. 2015 Mar;1(1):106.
Exclusion Criteria	Reviewer's Justification
-Population of interest	
-Interventions of interest	No intervention tested
-Comparisons of interest	
-Outcomes of interest	

RefID	1163
PMID	25329575
Citation/Reference	Ingre M, Van Leeuwen W, Klemets T, Ullvetter C, Hough S, Kecklund G, Karlsson D, Åkerstedt T. Validating and extending the three process model of alertness in airline operations. PLoS One. 2014 Oct 20;9(10):e108679. doi: 10.1371/journal.pone.0108679. eCollection 2014. PubMed PMID: 25329575; PubMed Central PMCID: PMC4203690
Exclusion Criteria	Reviewer's Justification
-Population of interest	
-Interventions of interest	No intervention tested
-Comparisons of interest	
-Outcomes of interest	

RefID	1199
PMID	10643756
Citation/Reference	Jewett ME, Kronauer RE. Interactive mathematical models of subjective alertness and cognitive throughput in humans. J Biol Rhythms. 1999 Dec;14(6):588-97. Review. PubMed PMID: 10643756
Exclusion Criteria	Reviewer's Justification
-Population of interest	
-Interventions of interest	No intervention tested
-Comparisons of interest	
-Outcomes of interest	

RefID	1235
PMID	17190711
Citation/Reference	Kandelaars KJ, Fletcher A, Dorrian J, Baulk SD, Dawson D. Predicting the timing and duration of sleep in an operational setting using social factors. Chronobiol Int. 2006;23(6):1265-76. PubMed PMID: 17190711.
Exclusion Criteria	Reviewer's Justification
-Population of interest	
-Interventions of interest	No intervention tested
-Comparisons of interest	
-Outcomes of interest	

RefID	1236
PMID	16491583
Citation/Reference	Kandelaars KJ, Fletcher A, Eitzen GE, Roach GD, Dawson D. Layover sleep prediction for cockpit crews during transmeridian flight patterns. Aviat Space Environ Med. 2006 Feb;77(2):145-50. PubMed PMID: 16491583
Exclusion Criteria	Reviewer's Justification
-Population of interest	
-Interventions of interest	No intervention tested
-Comparisons of interest	
-Outcomes of interest	

RefID	1317
PMID	27623842
Citation/Reference	Klerman EB, Beckett SA, Landrigan CP. Applying mathematical models to predict resident physician performance and alertness on traditional and novel work schedules. BMC Med Educ. 2016 Sep 13;16(1):239. doi: 10.1186/s12909-016-0751-9. PubMed PMID: 27623842; PubMed Central PMCID: PMC5022151
Exclusion Criteria	Reviewer's Justification
-Population of interest	
-Interventions of interest	No intervention tested
-Comparisons of interest	
-Outcomes of interest	

RefID	1323
PMID	n/a
Citation/Reference	Kobayashi T. Sleep package model mathematical model for a sleep pattern. Computers & industrial engineering. 1994 Sep 1;27(1-4):385-8.
Exclusion Criteria	Reviewer's Justification
-Population of interest	
-Interventions of interest	No intervention tested
-Comparisons of interest	
-Outcomes of interest	

RefID	1540
PMID	15018262
Citation/Reference	Mallis MM, Mejdal S, Nguyen TT, Dinges DF. Summary of the key features of seven biomathematical models of human fatigue and performance. Aviat Space Environ Med. 2004 Mar;75(3 Suppl):A4-14. PubMed PMID: 15018262
Exclusion Criteria	Reviewer's Justification
-Population of interest	
-Interventions of interest	No intervention tested
-Comparisons of interest	
-Outcomes of interest	

RefID	1612
PMID	24293775
Citation/Reference	McCauley P, Kalachev LV, Mollicone DJ, Banks S, Dinges DF, Van Dongen HPA. Dynamic circadian modulation in a biomathematical model for the effects of sleep and sleep loss on waking neurobehavioral performance. Sleep. 2013 Dec 1;36(12):1987-97. doi: 10.5665/sleep.3246. PubMed PMID: 24293775; PubMed Central PMCID: PMC3825450
Exclusion Criteria	Reviewer's Justification
-Population of interest	
-Interventions of interest	No intervention tested
-Comparisons of interest	
-Outcomes of interest	

RefID	1681
PMID	19194521
Citation/Reference	Mollicone DJ, Van Dongen HPA, Rogers NL, Dinges DF. Response Surface Mapping of Neurobehavioral Performance: Testing the Feasibility of Split Sleep Schedules for Space Operations. Acta Astronaut. 2008;63(7-10):833-840. PubMed PMID: 19194521; PubMed Central PMCID: PMC2633932
Exclusion Criteria	Reviewer's Justification
-Population of interest	
-Interventions of interest	No intervention tested
-Comparisons of interest	
-Outcomes of interest	

RefID	1745
PMID	11669116
Citation/Reference	Nechaev AP. Work and rest planning as a way of crew member error management. Acta Astronaut. 2001 Aug-Nov;49(3-10):271-8. PubMed PMID: 11669116
Exclusion Criteria	Reviewer's Justification
-Population of interest	
-Interventions of interest	No intervention tested
-Comparisons of interest	
-Outcomes of interest	

RefID	2009
PMID	22306977
Citation/Reference	Postnova S, Layden A, Robinson PA, Phillips AJ, Abeyasuriya RG. Exploring sleepiness and entrainment on permanent shift schedules in a physiologically based model. J Biol Rhythms. 2012 Feb;27(1):91-102. doi: 10.1177/0748730411419934. PubMed PMID: 22306977
Exclusion Criteria	Reviewer's Justification
-Population of interest	
-Interventions of interest	No intervention tested
-Comparisons of interest	
-Outcomes of interest	

RefID	2011
PMID	23308206
Citation/Reference	Postnova S, Robinson PA, Postnov DD. Adaptation to shift work: physiologically based modeling of the effects of lighting and shifts' start time. PLoS One. 2013;8(1):e53379. doi: 10.1371/journal.pone.0053379. Epub 2013 Jan 4. PubMed PMID: 23308206; PubMed Central PMCID: PMC3537665
Exclusion Criteria	Reviewer's Justification
-Population of interest	
-Interventions of interest	No intervention tested
-Comparisons of interest	
-Outcomes of interest	

RefID	2016
PMID	25479259
Citation/Reference	Powell DM, Spencer MB, Petrie KJ. Comparison of in-flight measures with predictions of a bio-mathematical fatigue model. Aviat Space Environ Med. 2014 Dec;85(12):1177-84. doi: 10.3357/ASEM.3806.2014. PubMed PMID: 25479259
Exclusion Criteria	Reviewer's Justification
-Population of interest	
-Interventions of interest	No intervention tested
-Comparisons of interest	
-Outcomes of interest	

RefID	2030
PMID	21376901
Citation/Reference	Pruchnicki SA, Wu LJ, Belenky G. An exploration of the utility of mathematical modeling predicting fatigue from sleep/wake history and circadian phase applied in accident analysis and prevention: the crash of Comair Flight 5191. Accid Anal Prev. 2011 May;43(3):1056-61. doi: 10.1016/j.aap.2010.12.010. Epub 2011 Jan 17. PubMed PMID: 21376901
Exclusion Criteria	Reviewer's Justification
-Population of interest	
-Interventions of interest	No intervention tested
-Comparisons of interest	
-Outcomes of interest	

RefID	2045
PMID	19485104
Citation/Reference	Rabinowitz YG, Breitbart JE, Warner CH. Managing aviator fatigue in a deployed environment: the relationship between fatigue and neurocognitive functioning. Mil Med. 2009 Apr;174(4):358-62. PubMed PMID: 19485104
Exclusion Criteria	Reviewer's Justification
-Population of interest	
-Interventions of interest	No intervention tested
-Comparisons of interest	
-Outcomes of interest	

RefID	2053
PMID	15018281
Citation/Reference	Raslear TG, Coplen M. Fatigue models as practical tools: diagnostic accuracy and decision thresholds. Aviat Space Environ Med. 2004 Mar;75(3 Suppl):A168-72. PubMed PMID: 15018281
Exclusion Criteria	Reviewer's Justification
-Population of interest	
-Interventions of interest	No intervention tested
-Comparisons of interest	
-Outcomes of interest	

RefID	2054
PMID	21531251
Citation/Reference	Raslear TG, Hursh SR, Van Dongen HPA. Predicting cognitive impairment and accident risk. Prog Brain Res. 2011;190:155-67. doi: 10.1016/B978-0-444-53817-8.00010-4. Review. PubMed PMID: 21531251
Exclusion Criteria	Reviewer's Justification
-Population of interest	
-Interventions of interest	No intervention tested
-Comparisons of interest	
-Outcomes of interest	

RefID	2071
PMID	15018282
Citation/Reference	Reifman J. Alternative methods for modeling fatigue and performance. Aviat Space Environ Med. 2004 Mar;75(3 Suppl):A173-80. Review. PubMed PMID: 15018282
Exclusion Criteria	Reviewer's Justification
-Population of interest	
-Interventions of interest	No intervention tested
-Comparisons of interest	
-Outcomes of interest	

RefID	2097
PMID	15018266
Citation/Reference	Roach GD, Fletcher A, Dawson D. A model to predict work-related fatigue based on hours of work. Aviat Space Environ Med. 2004 Mar;75(3 Suppl):A61-9; discussion A70-4. PubMed PMID: 15018266
Exclusion Criteria	Reviewer's Justification
-Population of interest	
-Interventions of interest	No intervention tested
-Comparisons of interest	
-Outcomes of interest	

RefID	2110
PMID	20027860
Citation/Reference	Romig E, Klemets T. Fatigue risk management in flight crew scheduling. Aviat Space Environ Med. 2009 Dec;80(12):1073-4. PubMed PMID: 20027860
Exclusion Criteria	Reviewer's Justification
-Population of interest	
-Interventions of interest	No intervention tested
-Comparisons of interest	
-Outcomes of interest	

RefID	2241
PMID	n/a
Citation/Reference	Bakar NB. Review of Workforce Fatigue Models in Workplace. IJCRB. 2011 Jul:693.
Exclusion Criteria	Reviewer's Justification
-Population of interest	
-Interventions of interest	No intervention tested
-Comparisons of interest	
-Outcomes of interest	

RefID	2501
PMID	19456006
Citation/Reference	Tvaryanas AP, MacPherson GD. Fatigue in pilots of remotely piloted aircraft before and after shift work adjustment. Aviat Space Environ Med. 2009 May;80(5):454-61. PubMed PMID: 19456006
Exclusion Criteria	Reviewer's Justification
-Population of interest	
-Interventions of interest	
-Comparisons of interest	No test of biomathematical modelling intervention in operational environment.
-Outcomes of interest	

RefID	2528
PMID	26387894
Citation/Reference	van den Berg MJ, Signal TL, Mulrine HM, Smith AA, Gander PH, Serfontein W. Monitoring and Managing Cabin Crew Sleep and Fatigue During an Ultra-Long Range Trip. Aerosp Med Hum Perform. 2015 Aug;86(8):705-13. doi: 10.3357/AMHP.4268.2015. PubMed PMID: 26387894
Exclusion Criteria	Reviewer's Justification
-Population of interest	
-Interventions of interest	No intervention tested
-Comparisons of interest	
-Outcomes of interest	

RefID	2532
PMID	15018263
Citation/Reference	Van Dongen HPA. Comparison of mathematical model predictions to experimental data of fatigue and performance. Aviat Space Environ Med. 2004 Mar;75(3 Suppl):A15-36. PubMed PMID: 15018263
Exclusion Criteria	Reviewer's Justification
-Population of interest	
-Interventions of interest	No intervention tested
-Comparisons of interest	
-Outcomes of interest	

RefID	2533
PMID	20175396
Citation/Reference	Van Dongen HP. Predicting sleep/wake behavior for model-based fatigue risk management. Sleep. 2010 Feb;33(2):144-5. PubMed PMID: 20175396; PubMed Central PMCID: PMC2817900
Exclusion Criteria	Reviewer's Justification
-Population of interest	
-Interventions of interest	No intervention tested
-Comparisons of interest	
-Outcomes of interest	

RefID	2604
PMID	n/a
Citation/Reference	Walters B, French J, Barnes MJ. Modeling the effects of crew size and crew fatigue on the control of tactical unmanned aerial vehicles (TUAVs). InSimulation Conference, 2000. Proceedings. Winter 2000 (Vol. 1, pp. 920-924). IEEE.
Exclusion Criteria	Reviewer's Justification
-Population of interest	
-Interventions of interest	No intervention tested
-Comparisons of interest	
-Outcomes of interest	

RefID	1149
PMID	n/a
Citation/Reference	(French) Hurdiel R, McCauley P, Van Dongen HPA, Pezé T, Theunynck D. Sommeil et prédiction mathématique de performances cognitives en situation réelle de course au large en solitaire. Science & Sports. 2013 Sep 30;28(4):207-10.
Exclusion Criteria	Reviewer's Justification
-Population of interest	
-Interventions of interest	No intervention tested.
-Comparisons of interest	
-Outcomes of interest	

RefID	n/a
PMID	24404236
Citation/Reference	McCormick F, Kadzielski J, Evans BT, Landrigan CP, Herndon J, Rubash H. Fatigue optimization scheduling in graduate medical education: reducing fatigue and improving patient safety. J Grad Med Educ. 2013 Mar;5(1):107-11. doi: 10.4300/JGME-D-12-00021.1. PubMed PMID: 24404236; PubMed Central PMCID: PMC3613293
Exclusion Criteria	Reviewer's Justification
-Population of interest	
-Interventions of interest	No intervention tested
-Comparisons of interest	
-Outcomes of interest	

Online Supplement Appendix D: Risk of bias table

Moore-Ede, 2004 RefID-1691 PMID-15018271		
Domain	Support for judgment	Review authors' judgment
<i>Selection bias.</i>		
Random sequence generation.	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.	No description of randomization is provided. Intervention and control data were drawn from the same population (trucking operations). Control data were derived from operational data collected prior to the start of the intervention.
Allocation concealment.	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.	No method to conceal allocation sequence is described. Intervention data were derived from operations occurring within intervention year (April 2001 – March 2002). Control data were drawn from operations occurring within a period that preceded intervention (April 1998 – March 2001).
<i>Performance bias.</i>		
Blinding of participants and personnel <i>Assessments should be made for each main outcome (or class of outcomes).</i>	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Intervention is provided (to drivers' fatigue risk from their schedules) via dispatchers. No effort to blind dispatchers to intervention is described. No effort to blind drivers to intervention condition is described.
<i>Detection bias.</i>		
Blinding of outcome assessment <i>Assessments should be made for each main outcome (or class of outcomes).</i>	Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	No efforts to blind outcome assessors from knowledge of condition are described. Assessors were part of the intervention (i.e. provided coaching to dispatchers who implemented the intervention) and were aware of the experimental conditions.
<i>Attrition bias.</i>		
Incomplete outcome data <i>Assessments should be made for each main outcome (or class of outcomes).</i>	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.	Outcome measures of interest were: accident rate/million miles, cost per accident, annual cost for severity accidents. No data are provided on attrition or exclusions. Overall size of intervention group is not reported.
<i>Reporting bias.</i>		
Selective reporting.	State how the possibility of selective outcome reporting was examined by the review authors, and what was found.	Selective outcome reporting bias is not addressed by the authors.
<i>Other bias.</i>		
Other sources of bias.	State any important concerns about bias not addressed in the other domains in the tool. If particular questions/entries were pre-specified in the review's protocol, responses should be provided for each question/entry.	A number of safety/effectiveness-related outcomes would exist in operations. Justification for the specific outcomes selected is not provided. Commercial interests of investigators/authors

The Effects of Sleep Deprivation on Item and Associative Recognition Memory

Roger Ratcliff and Hans P. A. Van Dongen
The Ohio State University and Washington State University

Sleep deprivation adversely affects the ability to perform cognitive tasks, but theories range from predicting an overall decline in cognitive functioning because of reduced stability in attentional networks to specific deficits in various cognitive domains or processes. We measured the effects of sleep deprivation on two memory tasks, item recognition (“was this word in the list studied”) and associative recognition (“were these two words studied in the same pair”). These tasks test memory for information encoded a few minutes earlier and so do not address effects of sleep deprivation on working memory or consolidation after sleep. A diffusion model was used to decompose accuracy and response time distributions to produce parameter estimates of components of cognitive processing. The model assumes that over time, noisy evidence from the task stimulus is accumulated to one of two decision criteria, and parameters governing this process are extracted and interpreted in terms of distinct cognitive processes. Results showed that sleep deprivation reduces drift rate (evidence used in the decision process), with little effect on the other components of the decision process. These results contrast with the effects of aging, which show little decline in item recognition but large declines in associative recognition. The results suggest that sleep deprivation degrades the quality of information stored in memory and that this may occur through degraded attentional processes.

Keywords: diffusion model, reaction time and accuracy, total sleep deprivation, drift rate, recognition memory

Sleep deprivation has profound effects on human brain functioning. For example, sleep deprivation is associated with large-scale changes in the activity of neurotransmitters and neuromodulators, such as dopamine (Volkow et al., 2009) and adenosine (Urry & Landolt, 2014). Sleep deprivation leads to significant shifts in the dominant frequencies in the waking EEG (Torsvall & Akerstedt, 1987). Furthermore, it changes evoked potentials, indicative of altered stimulus processing (Corsi-Cabrera, Arce, Del Río-Portilla, Pérez-García, & Guevara, 1999). Not surprisingly, sleep deprivation also has substantial impact on cognitive performance (Jackson & Van Dongen, 2011). Yet, the effects of sleep deprivation on different cognitive tasks are ostensibly widely different (Lim & Dinges, 2010). Cognitive, pharmacological, neuroimaging, and genetic approaches have been put to use in the search for underlying mechanisms. This search has been hampered, however, by reliance on methods not specifically designed

to test the effects of sleep deprivation and use of global outcome measures (Whitney & Hinson, 2010).

Recently there has been a focus on experimental and modeling studies of component processes of cognitive functioning (Gunzelmann, Gluck, Price, Van Dongen, & Dinges, 2007; Chee & Chuah, 2008; Ratcliff & Van Dongen, 2009; Tucker, Whitney, Belenky, Hinson, & Van Dongen, 2010). This has yielded new insights, indicating that distinct cognitive processes can be differentially affected by sleep deprivation (Jackson et al., 2013). One (qualitative) theory about the underlying mechanism posits that the effects of sleep deprivation are use-dependent, involving degraded information processing in neuronal networks that are most intensively used during performance of the task at hand (Van Dongen, Belenky, & Krueger, 2011). The diffusion decision model (Ratcliff, 1978; Ratcliff & McKoon, 2008; Ratcliff, Smith, Brown, & McKoon, 2016) provides an account of decision making that has been explicitly related to neuroscience measures (Forstmann, Ratcliff, & Wagenmakers, 2016; Gold & Shadlen, 2007; Smith & Ratcliff, 2004) and as such offers measures that can be related to neuronal processing theories.

There has been a long history of the use of item and associative tasks to examine processing and representation in memory. In an item recognition task, words or pictures are presented and the subject is to decide if the test item was in the study list. In associative recognition, pairs of words are presented and the subject is to decide if a test pair was composed of words studied together or whether the words were from different study pairs. Murdock (1974) reviewed and distinguished these as different forms of memory that operated in different ways and required different model-based approaches. Following the early work, a

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Roger Ratcliff and Hans P. A. Van Dongen, Department of Psychology, The Ohio State University, and the Sleep and Performance Research Center, Washington State University.

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Correspondence concerning this article should be addressed to Roger Ratcliff, Department of Psychology, The Ohio State University, Columbus, OH 43210. E-mail: ratcliff.22@osu.edu

number of studies have provided evidence for this distinction (Clark & Shiffrin, 1992; Hockley, 1991, 1994; Hockley & Cristi, 1996; Humphreys, 1976, 1978; Malmberg & Xu, 2007). Theories that attempted to deal with item and associative recognition and recall have produced integrated models that have common representations for all the kinds of information but different retrieval mechanisms (Gillund & Shiffrin, 1984; Murdock, 1982; Shiffrin & Steyvers, 1997). More recently, in research in aging, a sharp distinction has been drawn between item and associative recognition. The general finding is that associative recognition declines with age but item recognition is largely spared (Balota, Dolan, & Duchek, 2000; Craik, 1983, 1986, 1994; Gordon & Clark, 1974; Naveh-Benjamin, 2000; for further discussion see Ratcliff, Thapar, & McKoon, 2011; McKoon & Ratcliff, 2012). The generality of the associative recognition decline relative to item recognition was supported by Old and Naveh-Benjamin (2008) in a meta-analysis of data from 90 studies.

There is an extensive body of literature on sleep deprivation and memory, but most of the research has focused on the role of sleep in memory consolidation after the memories have been acquired. Yet, obtaining sufficient sleep beforehand may also be important, in order to be able to encode memories effectively (Walker & Stickgold, 2006), retain them reliably during task performance (Habeck et al., 2005), and recall them accurately when probed (e.g., Tantawy, Tallawy, Farghaly, Farghaly, & Hussein, 2013; Mograss, Guillem, Brazzini-Poisson, & Godbout, 2009). Vice versa, acute sleep deprivation appears to degrade some or all of these aspects of memory task performance (e.g., Nilsson, Bäckman, & Karlsson, 1989). The underlying mechanisms, however, have not been fully elucidated. At the neuronal level, it remains unknown whether the effects of sleep deprivation are global and nonspecific, or local and specific (Chee & Van Dongen, 2013). Insight into this issue may be gained by considering item recognition and associative recognition tasks, which have clearly defined shared and distinct features and may or may not be affected by sleep deprivation differentially.

If forming associations is more difficult or associations in memory are more fragile (i.e., more easily disrupted), then associative recognition should show more decline during sleep deprivation than item recognition. To date there have been few studies of item or associative recognition memory and sleep deprivation, and no head to head comparison has been made. For item recognition, Harrison and Horne (2000) presented two lists of 12 pictures (at 10 s per picture) and followed this with a test list of 48 pictures, half old and half new. Subjects were asked whether they had seen each test picture before (recognition). If so, they were then asked to specify whether it was included in List A or List B (i.e., list discrimination or in their terms, temporal memory). There was no significant effect of sleep deprivation on recognition (though d' fell from about 2.8 to 2.3) but there was a decline in list discrimination performance. This pattern suggests that item recognition may not decline with sleep deprivation, but tasks that require binding (item to list context as in Harrison and Horne or item to item as in associative recognition) may decline. Other studies using a few lists of pictures have found declines in recognition memory (Mograss, Guillem, Brazzini-Poisson, & Godbout, 2009; Williams, Gieseeking, & Lubin, 1966). But there have not been studies like those in the list-learning memory area with multiple

lists and comparisons other than the Harrison and Horne (2000) study that compare different forms of memory.

Diffusion Model

The diffusion model is designed to explain the cognitive processes involved in making simple two-choice decisions. The model separates the quality of evidence entering a decision from the decision criteria and from nondecision processes. This allows a direct comparison across tasks and across subject groups in components such as the quality of evidence used in the decision process and how much evidence is needed for a decision. The model can be seen as decomposing accuracy and reaction time (RT) data for correct and error responses into distinct cognitive processes. The model has provided successful explanations of performance in many paradigms in cognitive psychology and different subject populations. For example, it has been used to examine processing in children (Ratcliff, Love, Thompson, & Opfer, 2012), sleep-deprived individuals (Ratcliff & Van Dongen, 2009), aphasic individuals (Ratcliff, Perea, Colangelo, & Buchanan, 2004), hypoglycemic individuals (Geddes et al., 2010), individuals with depression (White, Ratcliff, Vasey, & McKoon, 2010), and individual differences (Pe, Vandekerckhove, & Kuppens, 2013; Ratcliff, Thapar, & McKoon, 2010; Schmiedek et al., 2007). It has also been used to examine decision processes in neurophysiology (Forstmann et al., 2016), including single-cell recordings (Hanes & Schall, 1996; Ratcliff, Cherian, & Segraves, 2003), EEG (Philiastides, Ratcliff, & Sajda, 2006), MEG (Wenzlaff, Bauer, Maess, & Hecker, 2011), and fMRI (Hecker, Marrett, & Ungerleider, 2008).

In the decision process of the diffusion model, information about a stimulus is accumulated over time from a starting point z toward one of two response criteria, or boundaries, a and 0 (see Figure 1). A response is executed when the amount of accumulated evidence reaches one of the boundaries. The rate at which information is accumulated is labeled "drift rate" (v) and it is determined by the quality of the information available from the match between a test probe and memory. Within-trial variability (noise) in the accumulation of information from the starting point to the boundaries results in processes with the same mean drift rate terminating at different times (producing RT distributions) and sometimes terminating at the wrong boundary (producing errors).

The total RT for a stimulus is the time taken by this decision process plus other, nondecision, processes (e.g., test probe encoding and accessing memory with it, and response execution). Nondecision processes are combined into one distribution in the model, the time taken by them (mean value T_{er}). Drift rates, boundaries, and nondecision times are the three main components of the model used in understanding differences between tasks, among subject populations, from experimental manipulations such as sleep deprivation, and due to individual differences.

The values of the components of processing are assumed to vary from trial to trial, under the assumption that subjects cannot accurately set the same parameter values from one trial to another (e.g., Laming, 1968; Ratcliff, 1978). Across-trial variability in drift rate is normally distributed with SD η , across-trial variability in starting point is uniformly distributed with range s_z , and across-trial variability in the nondecision component is uniformly distributed with range s_r . This across-trial variability allows the model to

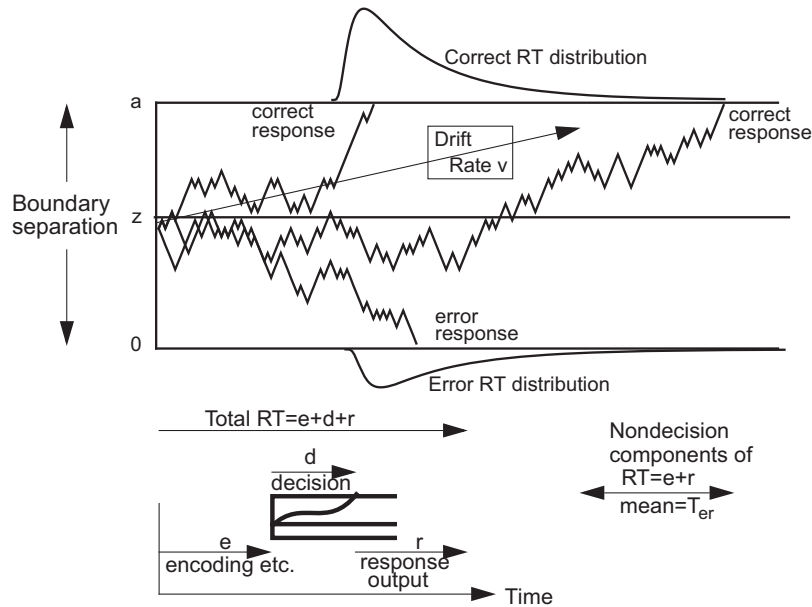


Figure 1. An illustration of the diffusion model.

fit the relative speeds of correct and error responses (Ratcliff, Van Zandt, & McKoon, 1999). In signal detection theory, which deals only with accuracy, all sources of across-trial variability would be collapsed onto one parameter, namely variability in evidence across trials. In contrast, in diffusion model fitting, the separate sources of across-trial variability are identified. If simulated data are fit by the model, then, for example, variability in drift rate is not incorrectly recovered as variability in starting point (Ratcliff & Tuerlinckx, 2002). Partly the success of parameter identifiability comes from the requirement that the model is fit to both the correct and error RT distributions, which provides tight constraints on the model (see Ratcliff, 2002).

In almost all RT studies, some proportion of responses are spurious contaminants (e.g., Ratcliff, 1979, 1993). These have previously been explicitly modeled in applications of the diffusion model (Ratcliff & Tuerlinckx, 2002) as random delays in process-

ing. Thus, predicted RTs are a mixture of pure diffusion model processes and of diffusion model processes with a delay added (usually 0% - 2%), which means that contaminant processes are just as accurate as processes without contaminants. In Ratcliff and Van Dongen (2009) we used a different assumption, and that was that contaminants were random guesses (Vandekerckhove & Tuerlinckx, 2008) that were uniformly randomly distributed over the range from the shortest to the longest RT for each response category. Thus the predicted RT distribution was a probability mixture of diffusion model processes and random guesses. Random guesses can be distinguished from the assumption of an added random delay, because random guesses reduce accuracy in the most accurate conditions, as was seen for some subjects in Ratcliff and Van Dongen's study. Here we fit the model with both contaminant assumptions. In both cases, the proportion of contaminants was estimated to be small. Note that recovery of diffusion

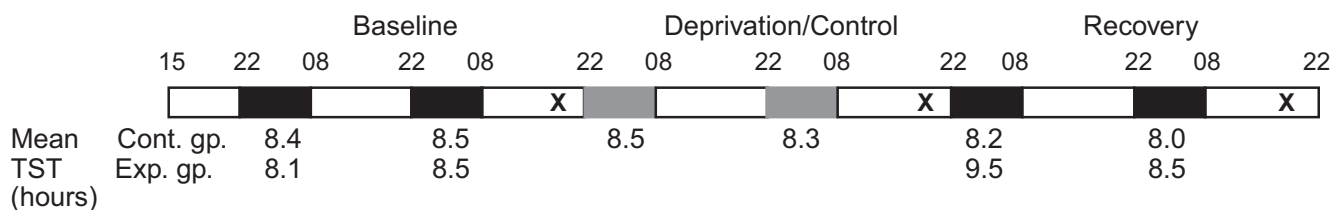


Figure 2. Subjects stayed in the laboratory continuously from 15:00 on Day 1 until 22:00 on Day 7. Black areas represent 10-hr nocturnal periods in bed for sleep (22:00–08:00). Gray areas represent 10-hr nocturnal periods in bed for sleep (22:00–08:00) for the control group only; the sleep deprivation group was kept awake continuously for a total of 62 hours. X's indicate the three administrations of the item and associative memory tasks (at 17:00): after 9 hours of scheduled wakefulness during baseline; after 57 hours of continuous wakefulness in the sleep deprivation group or 9 hours of scheduled wakefulness in the control group; and after 9 hours of scheduled wakefulness following 2 nights of recovery sleep. The top row of numbers represents time of day, the second row is mean total sleep time (TST) for the control group and the bottom row is mean total sleep time for the experimental group (as measured with polysomnography; Butkov, 2002).

Table 1
Accuracy and Mean RT

Task	Condition	“Old” or “Intact” Stimuli			“New” or “Rearranged” Stimuli		
		Pr correct	Mean correct RT (ms)	Mean error RT (ms)	Pr correct	Mean correct RT (ms)	Mean error RT (ms)
Item Recognition	Sleep: baseline	.674	907	1001	.852	943	931
	Sleep: deprived	.608	884	954	.655	941	887
	Sleep: recovery	.654	844	947	.859	855	932
	Control	.734	898	1027	.872	937	959
	Control	.686	860	945	.830	848	961
	Control	.678	834	915	.842	841	892
Associative Recognition	Sleep: baseline	.722	908	975	.719	1004	1015
	Sleep: deprived	.588	939	927	.655	990	941
	Sleep: recovery	.698	870	949	.723	944	920
	Control	.775	898	988	.751	1020	1041
	Control	.730	860	929	.814	943	905
	Control	.717	828	842	.811	888	947

model parameters is reasonably robust to the assumed form of the contaminant distribution - for example, if exponentially distributed contaminants were simulated and the parameter recovery algorithm assumed uniformly distributed contaminants, the model pa-

rameters would be recovered well (Ratcliff, 2008). Results are shown for the random delays assumption.

Method

Subjects

A total of 26 subjects, ages 22–37 years (10 were women) completed the study. Subjects were screened with physical exam, urine and blood chemistry, and questionnaires, to be physically and psychologically healthy and free of traces of drugs. They were good sleepers (getting between 6 and 10 hours a night) and had no sleep or circadian disorder as assessed by history, questionnaires, wrist actigraphy (Ancoli-Israel, 2005), and baseline polysomnogram (Butkov, 2002). They had normal or corrected to normal vision. They had not traveled between time zones and had not been engaged in shift work in the prior 1 month. Subjects were required to maintain their habitual sleep schedule in the week before the study and to avoid napping, as monitored by sleep/wake logs, time-stamped voice recording of bedtimes and rising times, and wrist actigraphy (wrist-worn activity monitoring). They were instructed to abstain from drugs, smoking, alcohol, and caffeine in the week before the study. Compliance was verified with urine and breathalyzer tests on the first day in the laboratory. The study was approved by the Institutional Review Board (IRB) of Washington State University, and all subjects gave written informed consent.

Experimental Design

Subjects were in the laboratory for 6 consecutive nights (7 days). They were randomized to a total sleep deprivation condition (13 subjects) or a control condition (13 subjects). On Days 1 and 2, all subjects had baseline sleep (10 hours in bed each night; 22:00–08:00). On Day 3, subjects in the experimental condition began 62 hours of continuous wakefulness. That day at 17:00, while 9 hours awake, they took their baseline test. Two days later at 17:00, while 57 hours awake (48 hours after Test 1), they took their second test. After the 62 hours of wakefulness, subjects were allowed two recovery nights (10 hours in bed each night). At 17:00 on the last day (48 hours after Test 2), they took their recovery test. Control subjects were tested on the

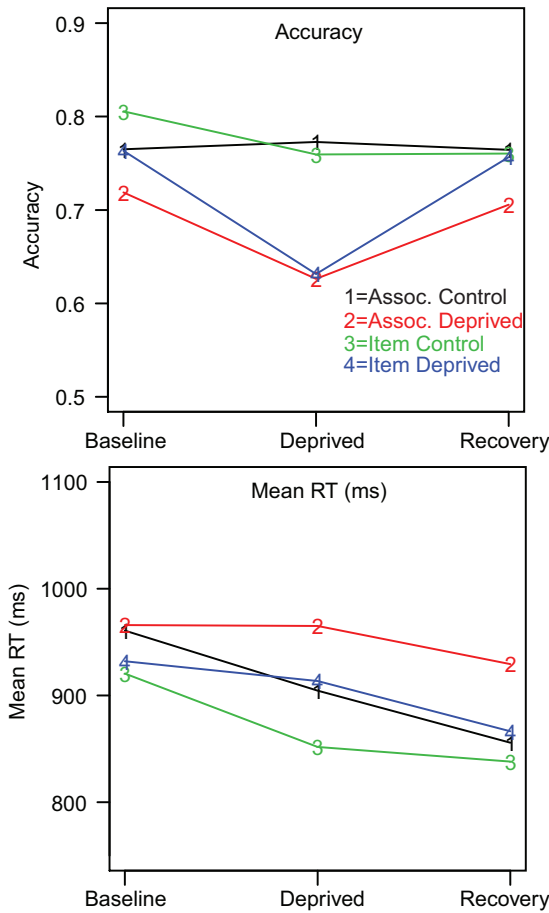


Figure 3. Plots of mean accuracy and mean correct RT in each session for item and associate recognition, for the sleep deprived and control groups. See the online article for the color version of this figure.

Table 2
Diffusion Model Parameters for Item Recognition

Condition	a	T _{er} (sec)	η	s _z	p _o	s _t (sec)	z	v	χ ²
Control 1	.161	.639	.224	.060	.003	.177	.070	.222	61.7
Control 2	.151	.604	.282	.020	.003	.159	.073	.196	65.0
Control 3	.138	.607	.219	.063	.003	.153	.070	.197	66.0
Sleep 1 (baseline)	.171	.615	.229	.077	.003	.173	.077	.195	69.9
Sleep 2 (deprived)	.151	.569	.175	.058	.007	.305	.071	.084	75.5
Sleep 3 (recovery)	.157	.594	.230	.072	.008	.188	.076	.228	51.0

Note. a = boundary separation; z = starting point; T_{er} = nondecision component of response time; η = standard deviation in drift across trials; s_z = range of the distribution of starting point (z); s_t = range of the distribution of nondecision times; p_o = proportion of contaminants; χ² = chi-square; v = the mean of absolute values of drift rates for studied items and new items from Table 3.

same days and at the same time of day, but they had sleep (10 hours in bed; 22:00–08:00) each night throughout the study.

Subjects continually stayed inside the isolated, environmentally controlled laboratory during the study, and were behaviorally monitored at all times by trained research assistants. The laboratory was temperature controlled (21°C) with fixed light levels (<100 lux) during scheduled wakefulness and lights off during scheduled sleep periods. Each person had an isolated room for sleep and performance testing. Meals were provided every 4 waking hours. Between test bouts and meals, subjects were permitted only nonvigorous activities. Subjects were monitored throughout the experiment, and no visitors, phone calls, live TV or radio, or Internet access were allowed. Besides the memory tasks, a number of other performance tests were administered throughout the experiment (Whitney, Hinson, Jackson, & Van Dongen, 2015). Figure 2 shows details of the design, including the mean number of hours of sleep for the two groups as measured with polysomnography (Butkov, 2002).

All sleep periods were recorded with digital polysomnography (Nihon Kohden, Foothill Ranch, CA), and total sleep times were assessed per the criteria of the American Academy of Sleep Medicine (Iber, Ancoli-Israel, Chesson, & Quan, 2007). The data in Figure 2 show that all subjects were well-rested after the two baseline nights, and the sleep deprivation group shows the expected increase in sleep duration in the first recovery night (night 5) following the 62-hr sleep deprivation period. Subjects were kept awake with nonvigorous activities and social interaction. This method has been used many times in previous studies; for a demonstration that the sleep deprivation intervention was successful, see Whitney et al. (2015).

Procedure

Cognitive performance was tested on an item and associative recognition memory task. The design is within subjects for sessions and memory tasks (and variables within tasks) and between subjects for the sleep deprivation and control groups. The task had 15 study-test blocks. For each block, the study list consisted of eight high-frequency and eight low-frequency word pairs, each displayed for 3 s in the upper left corner of an LCD monitor, followed by a 100-ms blank screen and then the next pair. From a viewing distance of 57 cm, the median edge-to-edge width of the word pairs was 6.0 degrees and the height was 0.5 degrees. The words were shown in clearly visible, light characters presented against a dark background. Half of the high-frequency pairs were presented once and half twice; likewise, half of the low-frequency pairs were presented once and half twice.

The pairs were presented in random order. Each study block was immediately followed by one of two types of test blocks: three-item recognition or 12 associative recognition blocks. No word was repeated within a session, but the same pools were used from session to session with completely different randomizations (so a new word in item recognition in one session could be a member of an intact pair in associative recognition in the next session). The test type was cued after the study list so that subjects could not differentially encode the stimulus and the test type was randomized across lists.

Item recognition test blocks consisted of the 32 words from the 16 word pairs plus 32 new words that had not appeared in the study pairs, presented in random order. Subjects were asked to press the ?/ key on the keyboard if the test word had been in any of the immediately preceding study pairs, and the Z key if not. These keys were also labeled “Yes” and “No”, respectively. The test words remained on the screen until a response was made. After each response there was a 500-ms blank screen and then the next item was presented.

Associative recognition test blocks consisted of 16 pairs of words, all of which had appeared in a study pair: four intact low-frequency pairs, four intact high-frequency pairs, four rearranged low-frequency pairs, and four rearranged high-frequency pairs. Subjects were asked to press the ?/ (“Yes”) key if the two words of a test pair had occurred in the same pair in the study list and the Z (“No”) key if the words had occurred in different pairs. The words in the test pairs always occupied the same position as in the study list: If a word was the first of a pair in the study list, it was the first of a test pair, whether the pair was intact or rearranged. For each test pair, the first word was displayed for 300 ms and then the second word was presented immediately below the first. This was done to reduce the variability in RTs that could occur if reading times included both words. Both words remained on the screen until a response was made.

Table 3
Drift Rates for Item Recognition

Condition	v _{HF1}	v _{LF1}	v _{HF2}	v _{LF2}	v _{HFN}	v _{LFN}
Control 1	.082	.154	.143	.292	-.260	-.402
Control 2	.007	.146	.131	.346	-.199	-.349
Control 3	.067	.175	.082	.345	-.180	-.333
Sleep 1 (baseline)	.087	.113	.140	.264	-.205	-.361
Sleep 2 (deprived)	.020	.063	.092	.116	-.070	-.142
Sleep 3 (recovery)	.073	.178	.145	.334	-.239	-.401

Note. HF = High Frequency; LF = Low Frequency; 1 = One Presentation; 2 = Two Presentations; N = New Item.

Table 4
Diffusion Model Parameters for Associative Recognition

Condition	a	T _{er} (sec)	η	s _z	p _o	s _t (sec)	z	v	χ ²
Control 1	.162	.596	.124	.056	.001	.306	.069	.145	86.2
Control 2	.170	.554	.180	.061	.002	.212	.069	.182	67.1
Control 3	.155	.559	.205	.041	.001	.290	.068	.183	68.2
Sleep 1 (baseline)	.171	.594	.197	.067	.001	.310	.075	.141	80.6
Sleep 2 (deprived)	.157	.558	.130	.052	.006	.369	.075	.065	97.8
Sleep 3 (recovery)	.176	.514	.159	.085	.001	.284	.077	.122	87.6

Note. a = boundary separation; z = starting point; T_{er} = nondecision component of response time; η = standard deviation in drift across trials; s_z = range of the distribution of starting point (z); s_t = range of the distribution of nondecision times; p_o = proportion of contaminants; v = the mean of absolute values of drift rates for intact and rearranged items from Table 5.

During both types of test blocks, subjects were instructed to respond as quickly and accurately as possible, but not so quickly that they started hitting the wrong key by mistake. If a response time was under 280 ms, a TOO FAST message was flashed on the screen for 1,500 ms (to discourage fast guessing), followed by a blank screen for 500 ms, then the next item. Subjects were not informed until after the study list about which type of test list they would be given for that block.

Subjects were given practice blocks of each type of test before beginning the experimental trials, and were given reminders of task instructions at the beginning of each test block. They were also informed that they could take a brief break between blocks of trials.

Results

Experimental Data

Summaries of the accuracy and RT data for the experimental and control groups for the three sessions are shown in Table 1 and Figure 3. Responses from the first block of each session, short (<280 ms) and long (>2,500 ms) outlier RTs in all blocks (less than 9.0% of the data in the sleep deprivation session and less than 3.6% of the data in the other sessions), and the first response in each test list were eliminated. For both item and associative recognition, response proportions were very similar for the experimental and control groups in the baseline and recovery sessions, but in the sleep deprivation session, the subjects showed a drop in accuracy relative to the control subjects.

We performed an analysis of variance with control versus sleep deprived subjects as a between-subjects variable (condition) and the three sessions as a within subjects variable (session). The mean accuracy values and mean correct RTs were averaged over old and

new responses for item recognition and over intact and rearranged responses for associative recognition. For item recognition, there was a significant effect on accuracy for session, $F(2, 48) = 19.6, p < .05$ and the interaction between condition and session was significant, $F(2, 48) = 9.5, p < .05$. These showed a drop in accuracy for the sleep deprived session relative to the control and baseline and recovery sessions. There was a significant effect on mean RT across sessions only, $F(2, 48) = 11.8, p < .05$, which showed an overall effect on RTs. This could be interpreted as a practice effect.

For associative recognition, there was a marginally significant effect on accuracy for session, $F(2, 48) = 3.0, p = .058$ and the interaction between condition and session was significant, $F(2, 48) = 4.4, p < .05$. These showed a drop in accuracy for the sleep deprived session relative to the control and baseline and recovery sessions. There was a significant effect on mean RT across sessions only, $F(2, 48) = 7.2, p < .05$, which again could be interpreted as a practice effect.

It is notable that there was no moderate increase in RT for the sleep deprived session relative to the baseline and recovery sessions and the control condition, given the relatively large drop in accuracy. For both item and associative recognition, mean RT for the sleep deprived session was about the same as for the baseline condition, but for the control subjects, the matched condition showed a drop of 60 ms (though the interaction was not significant).

Diffusion Model Fits

The model was fit to the data for each task and every session for each subject by minimizing a chi-square value obtained from observed and predicted frequencies of observations between RT

Table 5
Drift Rates for Associative Recognition

Condition	V _{IHF1}	V _{RHF1}	V _{ILF1}	V _{RLF1}	V _{IHF2}	V _{RHF2}	V _{ILF2}	V _{RLF2}
Control 1	.031	-.154	.133	-.118	.164	-.160	.250	-.150
Control 2	-.025	-.274	.098	-.191	.176	-.238	.283	-.223
Control 3	-.055	-.319	.117	-.193	.148	-.267	.328	-.145
Sleep 1 (baseline)	.030	-.202	.109	-.142	.113	-.193	.252	-.088
Sleep 2 (deprived)	-.018	-.143	-.015	-.075	.067	-.081	.146	-.037
Sleep 3 (recovery)	.032	-.182	.088	-.151	.089	-.142	.174	-.116

Note. I = Intact; R = Rearranged; HF = High Frequency; LF = Low Frequency; 1 = One Presentation; 2 = Two Presentations.

quantiles, using a general simplex minimization routine (Nelder & Mead, 1965). In this procedure, the values of all the parameters, including the variability parameters, are estimated simultaneously, fitting the model to all the data from all the conditions of an experiment. The minimization routine adjusts the parameters of the model until it finds the parameter estimates that give the minimum chi-square value (see Ratcliff & Childers, 2015; Ratcliff & Tuerlinckx, 2002).

With the best-fitting parameter values, the model accounted well for the data, as shown by the chi-square values (averaged over subjects) in Tables 2 and 4. These values are only a little higher than the critical values, namely, 71.0 for item recognition ($df = 53$) and 93.9 for associative recognition ($df = 73$). Ratcliff, Thapar, Gomez, and McKoon (2004) discussed the quality of fits of the

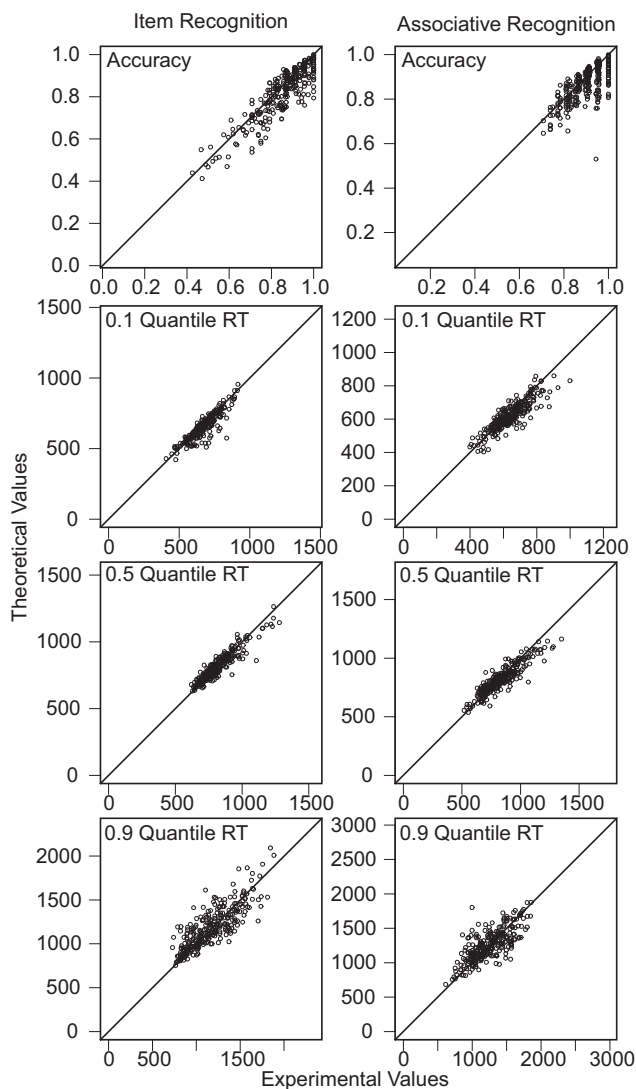


Figure 4. Plots of accuracy and the .1, .5 (median), and .9 RT quantiles for correct responses (x-axis) and predicted values from fits of the diffusion model (y-axis) for item and associative recognition (for RTs, only values from conditions with greater than 15 responses are plotted).

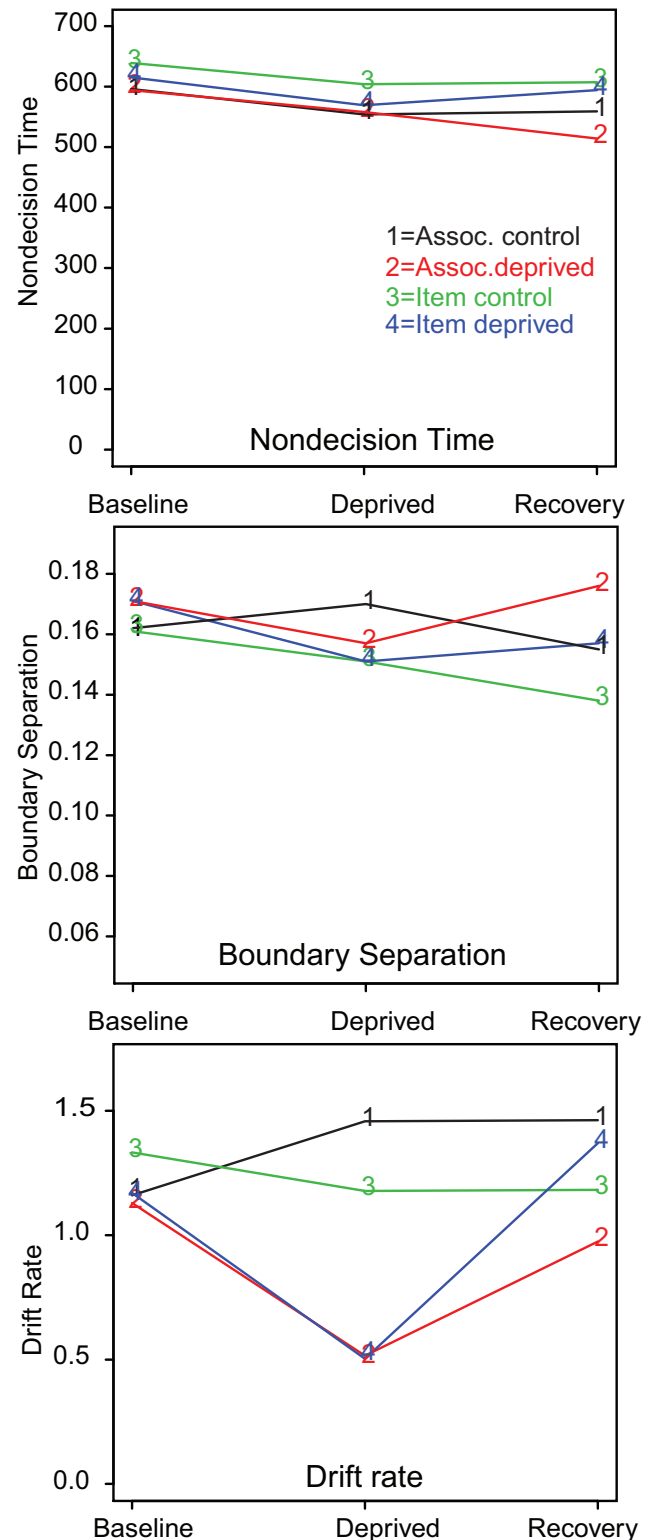


Figure 5. Plots of drift rate, boundary separation, and nondecision time as a function of session for item and associate recognition, for the sleep deprived and control groups. See the online article for the color version of this figure.

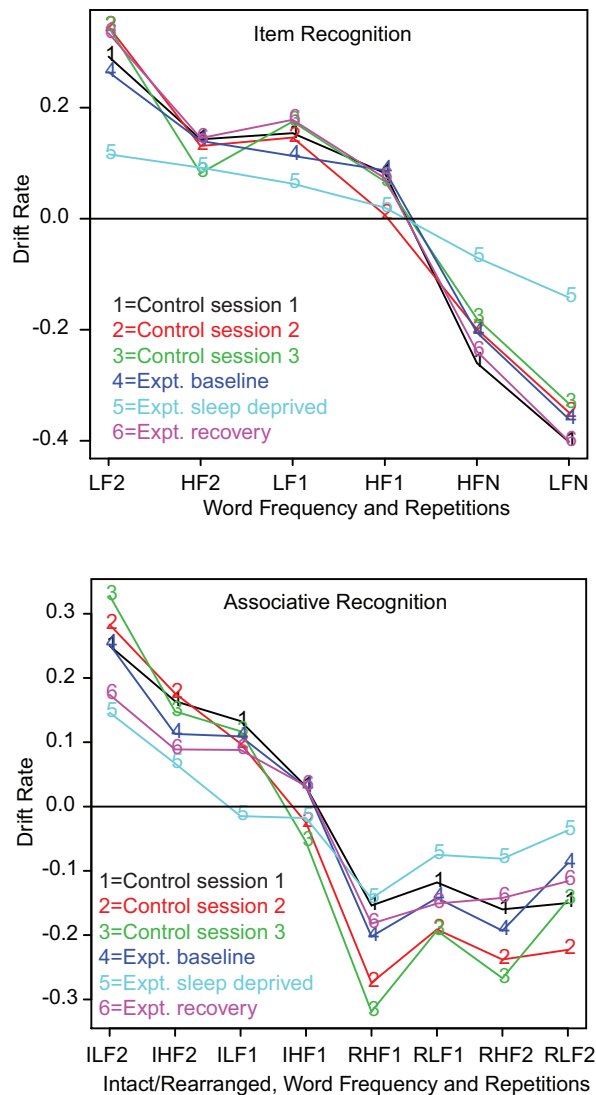


Figure 6. Plots of drift rates for the individual conditions and sessions. For item recognition, LF = low frequency; HF = high frequency; 2 = two presentations; 1 = one presentation, and N = new. For associative recognition, the first letter I = intact; and R = rearranged; LF = low frequency; HF = high frequency; 2 = two presentations; and 1 = one presentation. See the online article for the color version of this figure.

diffusion model to data, as indicated by chi-square values, and showed that small shifts in the proportions of responses between quantiles within a condition or between conditions (for predictions vs. observations) could account for contributions to chi-square as

large as the critical values. Thus, the chi-square values represent reasonable fits of the model to the data. Tables 2-5 show the means for the best-fitting parameters values averaged over subjects.

Goodness of fit is illustrated in Figure 4, with theoretical values for correct responses for accuracy and the .1, .5, and .9 quantile RTs plotted against the empirical values for each subject for item recognition (left column) and associative recognition (right column). Because these experiments had relatively low numbers of observations per condition, only values representing more than 15 observations are plotted (about 270 points in each case). For associative recognition, there was a maximum of 23 observations per condition, which means that only quantile RTs with accuracy greater than .65 are shown and for item recognition, there was a maximum of 24 observations per condition for old items and 48 for new items (the first item in each list was discarded). The choice proportions show 57 deviations between predictions and data (out of 624) greater than 10% for associative recognition and 52 for item recognition (out of 468). Given that the standard deviation in response proportion for .95 accuracy and 23 observations is 0.05 and for .80 accuracy and 23 observations is 0.08, we would expect this many deviations of this size. For the .1 RT quantiles for correct responses, there are only 14 and 12 deviations of more than 100 ms, and for the .5 quantile RTs, only 23 and 7 deviations of more than 100 ms for associative and item recognition, respectively. In general, there are few systematic biases in the predictions given the relatively low numbers of observations per condition (see Ratcliff & Childers, 2015, for examples of variability in parameter estimates and power with as few as 80 total observations per subject).

For mean drift rates (the mean of: the drift rates for old items and minus the drift rates for new items), nondecision time, and boundary separation, Figure 5 shows the best-fitting values, averaged over subjects. In this figure, the drift rates are the absolute values averaged over trial types (see Tables 3 and 5 for separate values). Differences in accuracy and RT over the experimental conditions (old vs. new, intact vs. rearranged, repetitions and word frequency) were accounted for by differences in drift rates (Tables 3 and 5).

Parameter Estimates

For the parameter estimates of the diffusion model, the main results to note are the drop in drift rate for both item and associative recognition in the sleep deprivation session; and little effect on nondecision time or boundary separation, but with a small decrease in both over sessions (a practice effect).

The parameter values represent the behavior of components of cognitive processing in the experiment, and we use their values to interpret the effects of sleep deprivation on performance in the two-choice tasks. Two-way mixed-effects ANOVAs of each of the

Figure 7 (opposite). Scatter plots, histograms, and correlations for drift rates for the control group and the sleep deprived group. The diagonal plots are histograms of the values. The panels above and to the right of the diagonal show the correlations, and the sizes of the digits represent the sizes of the correlation. The panels below and to the left of the diagonal show the scatter plots, with each dot representing an individual subject. The lines are lowess smoothers (from the R function). The identity of the comparison in each off-diagonal plot or correlation is obtained moving vertically and horizontally from the task labels in the corresponding diagonal plots. "B", "S" and "R" represent the baseline, sleep deprived (or control second session) and recovery sessions. "Item" and "Assoc" represent item and associative recognition memory, respectively. See the online article for the color version of this figure.

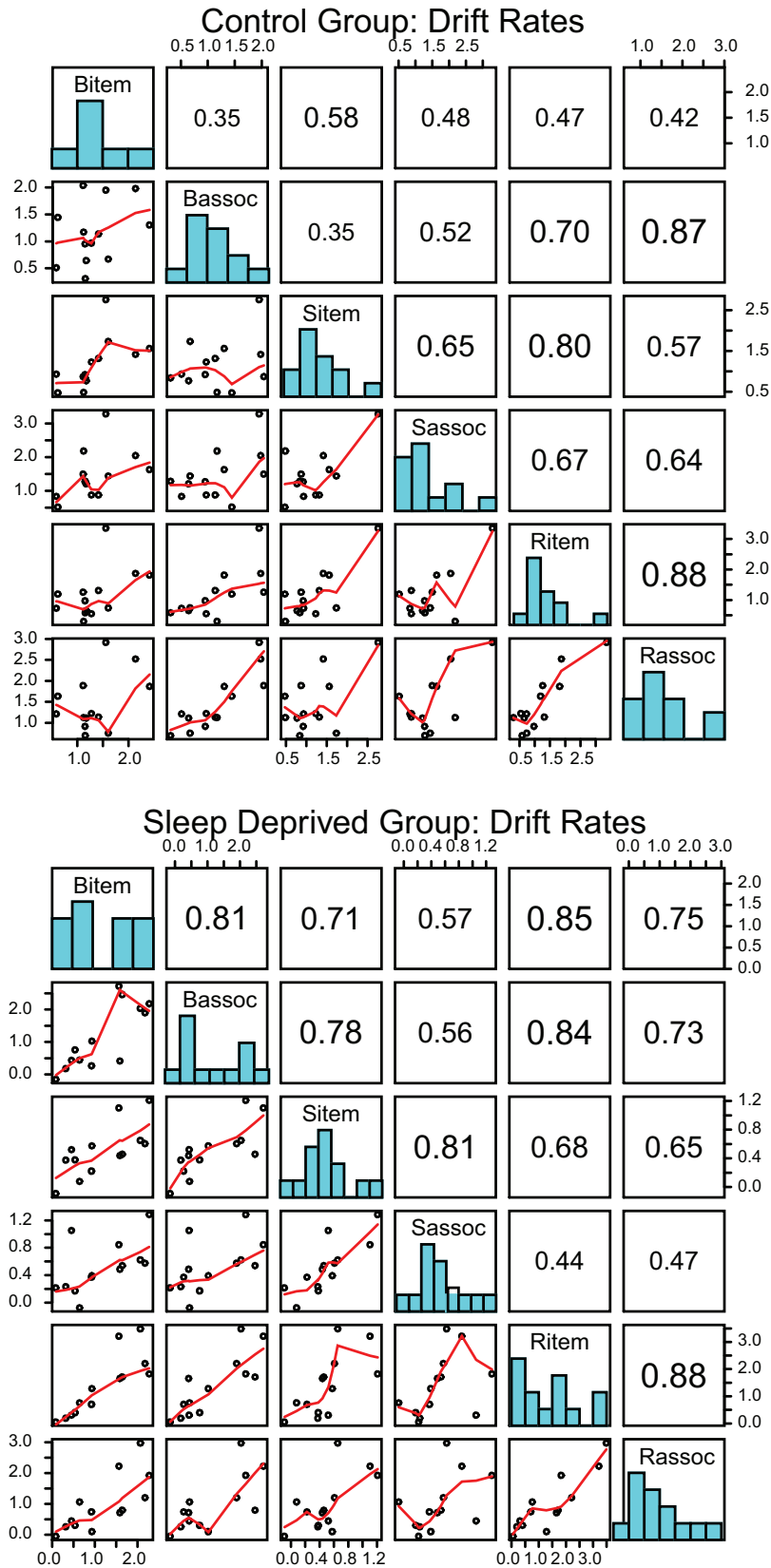


Figure 7 (opposite)

parameters for the three sessions by experimental and control groups were performed. The degrees of freedom for all the F 's are 2 and 48. The mean values of the parameter used in these analyses are shown in Tables 2 and 4.

For drift rate, there was a main effect of session for item recognition ($F = 7.2, p < .05$) but not associative recognition ($F = 1.6$), and for both types of recognition there was an interaction between session and group ($F = 6.8, p < .05$ and $5.9, p < .05$). In both cases, this represented a fall in drift rates for the sleep deprived group. For boundary separation, there was a main effect of session for item recognition ($F = 5.4, p < .05$) and an interaction between group and session for associative recognition ($F = 5.9, p < .05$). These effects can be seen in Figure 5, but the differences are relatively modest in size. There was a difference in nondecision time across sessions, with a significant main effect ($F = 4.6, p < .05$ and $3.7, p < .05$). This represents a practice effect across sessions. The interaction of session with group for across-trial variability in drift rate was significant ($F = 4.1, p < .05$ and $3.9, p < .05$), showing that across-trial variability in drift rate was lower for the sleep deprivation condition (Tables 2 and 4). This could also represent a scaling effect, with mean and SD both being reduced in this condition (Ratcliff, Thapar, & McKoon, 2010). Across-trial variability in starting point showed a main effect across sessions for item recognition ($F = 3.8, p < .05$), but not for associative recognition ($F = 2.2, p > .05$).

It is possible that sleep deprivation might induce a bias to respond "new" or "rearranged" if the subjects become more conservative about making a response about the presence of the item or presence of the intact relationship between the test pair of words. Figure 6 shows plots of the separate drift rates in Tables 3 and 5, and these show that the zero point of drift rate (the drift criterion) does not change with sleep deprivation.

The primary effect of sleep deprivation was a drop in drift rate for both types of recognition. Also, across-trial variability in drift rate was lower in the sleep deprivation session. Furthermore, there were effects on boundary separation and nondecision time, which can be interpreted as practice effects.

Predictions for the effect of the decrease in drift rate in the model for accuracy and mean RT were generated using parameters similar to those in the model fits (Tables 2–5). Using $a = 0.16$, $T_{er} = 0.55$, $\eta = 0.18$, $s_z = 0.06$, $p_o = 0.001$, and $s_r = 0.3$, for drift rate $v = 0.07$, accuracy = 0.63 and mean RT = 967 ms, and for drift rate $v = 0.14$, accuracy = 0.74 and mean RT = 928 ms. Thus an 11% change in accuracy corresponds to about a 39 ms change in mean RT, consistent with the sizes of the effects in Figure 3.

Contaminant Assumptions

In Ratcliff and Van Dongen (2009), the assumption that some proportion of responses were random guesses was needed in fitting the data from the numerosity discrimination task. To check whether this assumption would improve the fits of the model to the data from the two memory tasks in the present study, we refit the data with the random contaminant assumption. The main result was that the estimated proportion of contaminants was small and had a mean of 1% or less for each group and task (in the sleep deprivation session, there was one subject with 6.1% contaminants

in item recognition and one with 3.3% contaminants in associative recognition, but the means were 0.6% and 0.7% respectively). This resulted in parameter estimates for the two sets of fits with the different contaminant assumptions that were almost identical.

Individual Differences

Thirteen subjects in the sleep deprivation group and 13 in the control group is a small number of subjects with which to conduct individual differences studies. But we have a reasonable amount of power if the pairwise correlations between the six conditions replicate (i.e., 15 pairs). We cannot tell if one correlation is larger than another, but we can tell if a parameter correlates across sessions and tasks. Figures 7, 8, and 9 show correlations and scatter plots between pairs of parameter values, and histograms of the parameter values. Drift rates correlated strongly across tasks and across sessions for both groups of subjects with a mean correlation of 0.65 and with the lowest pairwise correlation of 0.35. This implies that someone with good memory in item recognition has good memory in associative recognition in both the control subjects and the experimental subjects (and for those in the sleep deprivation session). Boundary separation showed the same pattern with a mean correlation of 0.54 and with the lowest pairwise correlation of 0.20. Nondecision time showed a weaker pattern with the mean correlation of 0.43 but with this there were some negative correlations with the lowest value -0.26 (this was probably due to one large value of nondecision time shown in Figure 9 - the effect of such a deviant score would be expected because of the low number of observations in each comparison).

Of particular interest is the comparison of the sleep deprivation conditions with the baseline and recovery sessions. If sleep deprivation differentially disrupts memory performance for individuals, the correlations for the sleep deprived sessions with the baseline and recovery sessions should be reduced relative to the correlations between the baseline and recovery sessions. In fact, the mean correlations for drift rates between the sleep deprivation session and the baseline and recovery sessions were 0.63 and 0.63, while the mean correlation between the baseline and recovery sessions was 0.81. Thus the sleep deprivation condition produced correlations with the baseline and recovery sessions that are a little lower than the correlation between the baseline and recovery sessions, but the correlation is still very high, showing little disruption in the relative effect of sleep deprivation across subjects. Generally, all these comparisons show consistent individual differences across tasks and sessions (see also Patanaik, Zagorodnov, Kwoh, & Chee, 2014).

Discussion

The experimental data from this study were fit with the diffusion decision model, which fits accuracy and RT distributions for correct and error responses. In the diffusion model in designs in which difficulty is manipulated within lists, differences in performance between conditions that vary in difficulty (once- vs. twice-presented words, high- vs. low-frequency words) are accounted for by differences in drift rates. Boundary settings cannot change between easy items and difficult items because the settings cannot change as a function of test item type once the accumulation of information has begun. To change the settings before accumulation

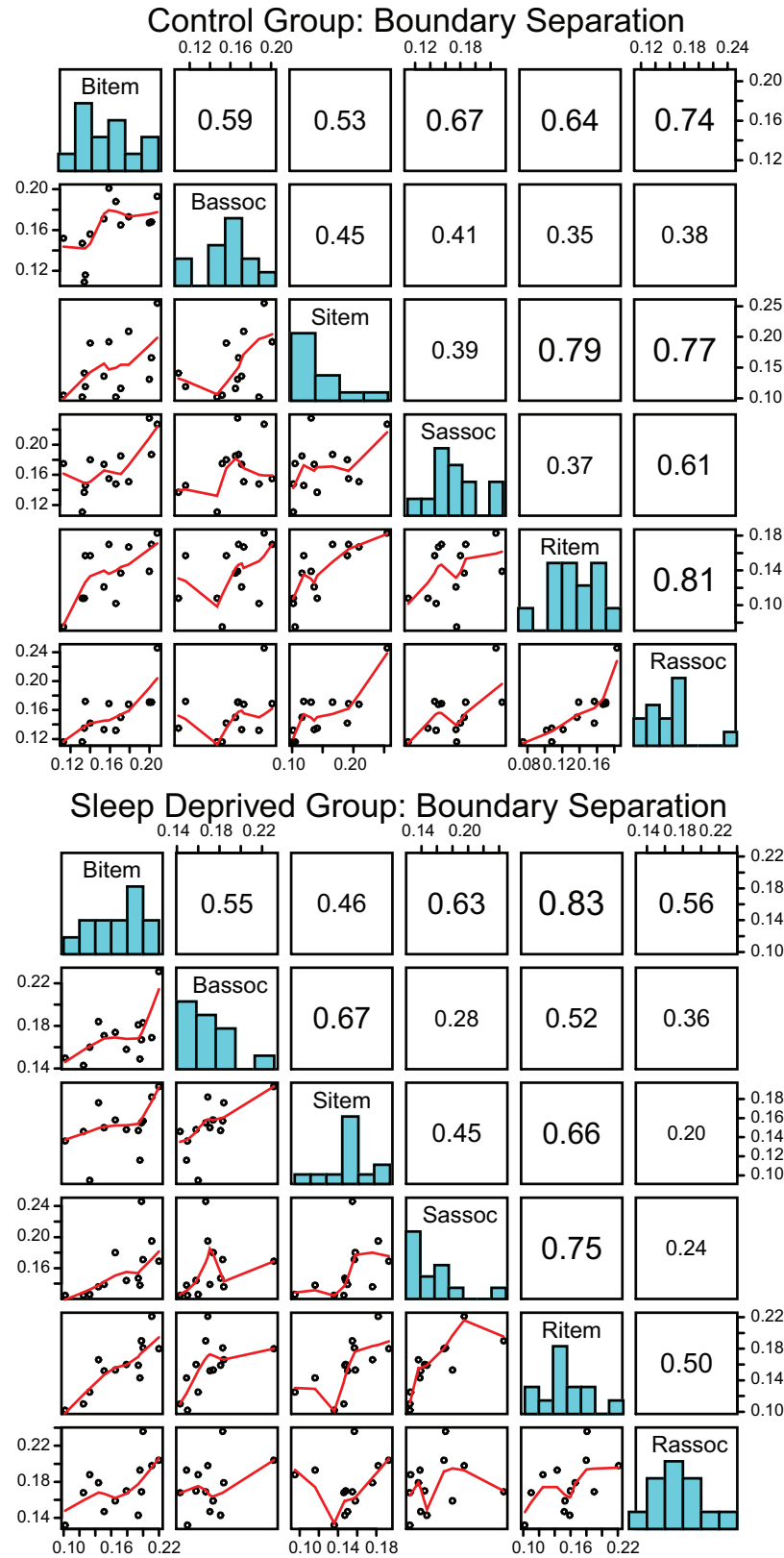


Figure 8. Scatter plots, histograms, and correlations for boundary separation. Details are the same as for Figure 7. See the online article for the color version of this figure.

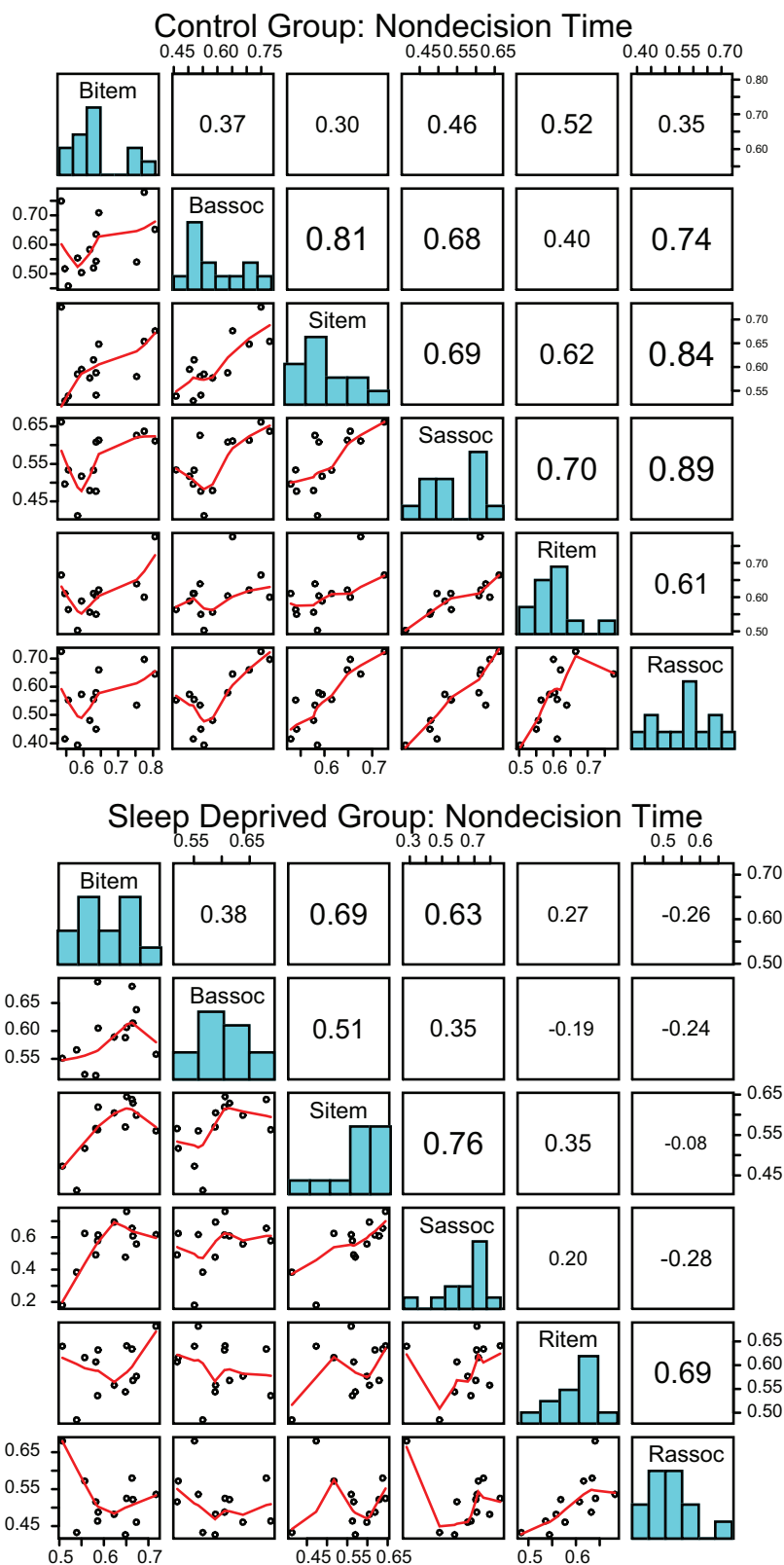


Figure 9. Scatter plots, histograms, and correlations for nondecision time. Details are the same as for Figure 7. See the online article for the color version of this figure.

began would require knowing whether a test item was easy or difficult, something that cannot be known until after information has been accumulated. As expected, differences in accuracy and RT between once- and twice-presented words and high- and low-frequency words were all explained by differences in drift rates. Note that all parameters of the model were allowed to vary between sessions, because practice could alter any of the parameters.

The diffusion model analysis indicates that the quality of stored information in memory that drives the decision process is reduced in the sleep deprivation condition relative to the control group and relative to the baseline and recovery sessions. This implicates reduced quality of encoding during study of the word lists, reduced maintenance (retention) of stored information in memory, or reduced ability to retrieve information from memory (or combinations of these) as the main processes affected by sleep deprivation. Because item and associative information require somewhat different retrieval processes, a deficit in encoding or maintenance is the more plausible.

There were mainly nonsignificant effects of sleep deprivation on boundary separation and nondecision time, and results were most consistent with practice effects on these components of processing (cf. Dutilh, Kryptos, & Wagenmakers, 2011; Dutilh, Vandekerckhove, Tuerlinckx, & Wagenmakers, 2009; Petrov, Van Horn, & Ratcliff, 2011; Ratcliff, Thapar, & McKoon, 2006). The only other systematic effect was a decrease in across-trial variability in drift rate for the sleep deprivation condition in both item and associative recognition. These results suggest that other decision-making processes are not significantly affected by sleep deprivation in these tasks.

Ratcliff and Van Dongen (2009) examined the effects of sleep deprivation on performance in a numerosity discrimination task using a diffusion model analysis. They found a drop in drift rates for the sleep deprived condition along with an increase in the number of contaminants (though there were large individual differences), as well as smaller but significant changes in boundary separation and across-trial variability in both nondecision time and starting point. The present study replicated the drop in drift rates, but the other effects were not obtained. This may be due to smaller numbers of observations - two tasks were presented per 45 min. session, while in Ratcliff and Van Dongen (2009) the one task took the whole session. The effect of sleep deprivation on drift rate has also been observed (Ratcliff & Van Dongen, 2011) on a psychomotor vigilance test (PVT), which is a simple RT task designed to measure sustained attention (Lim & Dinges, 2008). Having found this effect again in our present study of two types of recognition memory tasks, we may see a trend emerging, suggesting that reduced drift rate may be a universal feature of the impact of sleep deprivation on cognitive performance.

Recent studies have suggested that memory task performance deficits during sleep deprivation are due to deficits in attentional processing and memory maintenance, whereas memory encoding and retrieval seem to be relatively unaffected by sleep deprivation (Rakitin, Tucker, Basner, & Stern, 2012; Wee, Asplund, & Chee, 2013). However, evidence to the contrary, namely that the encoding phase is affected by sleep deprivation, has also been reported (Tucker et al., 2011). The present study sheds some light on these issues through a head-to-head comparison of item and associative recognition memory (though the Tucker and Wee studies address

somewhat different working memory processing). We found that the effects of sleep deprivation on diffusion model parameters were similar for the two types of recognition memory, suggesting shared mechanisms underlying the effects of sleep deprivation on the two tasks. This was corroborated by consistency (correlation) of model parameter changes due to sleep deprivation for the two tasks. There is overlap between brain regions activated during memory task performance and brain regions associated with attentional processes, raising the possibility that performance deficits in memory tasks are due to attentional deficits (Jackson & Van Dongen, 2011). Indeed, our results are more consistent with an explanation of performance impairment in terms of degraded attentional processes than in terms of item or associative memory impairment per se.

A recently proposed, qualitative theory posits that the effects of sleep deprivation are use-dependent, involving degraded information processing in neuronal networks that are most intensively used during performance of a given task (Van Dongen, Belenky, & Krueger, 2011). In the context of this theory, our quantitative diffusion modeling results suggest that attentional processes are the most intensively used processes in both recognition memory tasks. Sleep deprivation is well known to degrade task performance in tasks with a high attentional demand (Lim & Dinges, 2008).

It is noteworthy in this regard that our present results differ from those found earlier in aging, which reduces drift rates in associative recognition but not item recognition (Ratcliff, Thapar, & McKoon, 2011). In contrast with sleep deprivation, therefore, the breakdown of associative memory in aging may not be related to nonspecific impairment in attention, but rather to impairment of specific processes involved in associative memory. Using a battery of neuropsychological tests, Harrison and colleagues compared a group of young adults subjected to 36 hours of sleep deprivation to a group of healthy, alert, non-sleep-deprived people aged about 60 years (Harrison, Horne, & Rothwell, 2000). They observed that 36 hours of sleep deprivation in the young adult group produced effects on prefrontal cortex-mediated performance similar to those found in the nonsleep deprived older group. Our findings and those of others (Tucker, Stern, Basner, & Rakitin, 2011) are inconsistent with the idea that the effects of sleep deprivation on cognitive performance are comparable to those of aging.

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Call for Nominations

The Publications and Communications (P&C) Board of the American Psychological Association has opened nominations for the editorships of the *Journal of Experimental Psychology: Animal Learning and Cognition*, *Neuropsychology*, and *Psychological Methods* for the years 2020 to 2025. Ralph R. Miller, PhD, Gregory G. Brown, PhD, and Lisa L. Harlow, PhD, respectively, are the incumbent editors.

Candidates should be members of APA and should be available to start receiving manuscripts in early 2019 to prepare for issues published in 2020. Please note that the P&C Board encourages participation by members of underrepresented groups in the publication process and would particularly welcome such nominees. Self-nominations are also encouraged.

Search chairs have been appointed as follows:

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Prepared statements of one page or less in support of a nominee can also be submitted by e-mail to Sarah Wiederkehr, P&C Board Editor Search Liaison, at swiederkehr@apa.org.

Deadline for accepting nominations is Monday, January 8, 2018, after which phase one vetting will begin.



Note

Gatechol-O-methyltransferase (COMT) genotype affects cognitive control during total sleep deprivation

Briann C. Satterfield ^{a,1}, John M. Hinson ^{b,*}, Paul Whitney ^b,
Michelle A. Schmidt ^a, Jonathan P. Wisor ^a and Hans P.A. Van Dongen ^a

^a Sleep and Performance Research Center and Elson S. Floyd College of Medicine, Washington State University, Spokane, WA, USA

^b Department of Psychology, Washington State University, Pullman, WA, USA



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ABSTRACT

Adaptive decision making is profoundly impaired by total sleep deprivation (TSD). This suggests that TSD impacts fronto-striatal pathways involved in cognitive control, where dopamine is a key neuromodulator. In the prefrontal cortex (PFC), dopamine is catabolized by the enzyme catechol-O-methyltransferase (COMT). A functional polymorphism (Val158Met) influences COMT's enzymatic activity, resulting in markedly different levels of prefrontal dopamine. We investigated the effect of this polymorphism on adaptive decision making during TSD. Sixty-six healthy young adults participated in one of two in-laboratory studies. After a baseline day, subjects were randomized to either a TSD group ($n = 32$) with 38 h or 62 h of extended wakefulness or a well-rested control group ($n = 34$) with 10 h nighttime sleep opportunities. Subjects performed a go/no-go reversal learning (GNGr) task at well-rested baseline and again during TSD or equivalent control. During the task, subjects were required to learn stimulus–response relationships from accuracy feedback. The stimulus–response relationships were reversed halfway through the task, which required subjects to learn the new stimulus–response relationships from accuracy feedback. Performance on the GNGr task was quantified by discriminability (d') between go and no-go stimuli before and after the stimulus–response reversal. GNGr performance did not differ between COMT genotypes when subjects were well-rested. However, TSD exposed a significant vulnerability to adaptive decision making impairment in subjects with the Val allele. Our results indicate that sleep deprivation degrades cognitive control through a fronto-striatal, dopaminergic mechanism.

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* Corresponding author. Department of Psychology, Washington State University, P.O. Box 644820, Pullman, WA, 99164-4820, USA.

E-mail addresses: bsatterfield@psychiatry.arizona.edu (B.C. Satterfield), hinson@wsu.edu (J.M. Hinson), paul.whitney@wsu.edu (P. Whitney), maschmidt@wsu.edu (M.A. Schmidt), j_wisor@wsu.edu (J.P. Wisor), hvd@wsu.edu (H.P.A. Van Dongen).

¹ Present address: Department of Psychiatry, College of Medicine, University of Arizona, 1501 N. Campbell, Rm. 7304A, Tucson, AZ, 85724-0001, USA.

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1. Introduction

Sleep deprivation affects neurobehavioral performance across a variety of cognitive domains in differential ways (Killgore, 2010; Lim & Dinges, 2010). There are large, trait-like inter-individual differences in cognitive responses to sleep deprivation (Van Dongen, Baynard, Maislin, & Dinges, 2004), underlaid by systematic inter-individual differences in sleep/wake homeostasis (Rétey et al., 2006; Van Dongen, Bender & Dinges, 2012) and partially determined by a number of genetic variants (Bodenmann et al., 2012; Goel, Banks, Ling, Mignot, & Dinges, 2011; Satterfield, Wisor, Field, Schmidt, & Van Dongen, 2015; Viola et al., 2007). While the reasons why different cognitive functions are affected by sleep deprivation *differentially* have been discussed theoretically (Van Dongen, Belenky, & Krueger, 2011), they largely remain to be studied experimentally (Jackson et al., 2013).

Vigilant attention is among the cognitive functions most widely studied in this context. It is substantially degraded by total sleep deprivation (TSD), causing significant instability in performance (Doran, Van Dongen, & Dinges, 2001; Lim & Dinges, 2008). However, impairment in vigilant attention is dissociable from impairment in other aspects of cognition (Jackson et al., 2013; Tucker, Whitney, Belenky, Hinson, & Van Dongen, 2010). We recently demonstrated that adaptive decision making, in addition to – and distinct from – vigilant attention, is profoundly degraded by TSD (Whitney, Hinson, Jackson, & Van Dongen, 2015). This effect cannot be explained as a mere function of lapses in vigilant attention – we showed that masking as much as 40% of the feedback on the GNGr (simulating an overabundance of attentional lapses) did not produce the level of impairment on the GNGr that we saw during TSD (Whitney et al., 2015, supplement). The neurobiological mechanisms underlying the specific effect of sleep deprivation on adaptive decision making are as yet unknown.

Adaptive decision making requires cognitive control to balance cognitive stability – the ability to maintain task-relevant information in the focus of attention – with cognitive flexibility – the ability to update task-relevant information based on changes in contingencies, while at the same time suppressing irrelevant information in order to appropriately adapt behavior (Braver, 2012; Cools & Robbins, 2004). On a reversal learning task that requires adaptive decision making, we previously found that cognitive flexibility is considerably impacted by TSD, while stability is relatively maintained compared to well-rested baseline (Whitney et al., 2015). This finding points to the involvement of fronto-striatal pathways subserving cognitive control (Botvinick & Braver, 2015; Cole & Schneider, 2007; Cools, 2016; Klanker, Feenstra, Denys, Lo, & Tsing, 2013). Notably, damage to the orbital frontal cortex (OFC) results in impaired cognitive flexibility similar to our finding during TSD (Fellows, 2007; Frank & Claus, 2006).

Dopamine is a key neuromodulator in the fronto-striatal circuits involved in cognitive control (Floresco, Zhang, & Enomoto, 2009; Frank & Claus, 2006; Izquierdo et al., 2016; Klanker et al., 2013; Waltz, 2017). The prefrontal cortex (PFC) in particular is sensitive to fluctuations in dopamine, with marked downstream effects on cognitive performance. The

association between PFC-mediated cognition and dopaminergic tone shows an inverted-U relationship (Cools & D'Esposito, 2011; Cools & Robbins, 2004; Fallon, Williams-Gray, Barker, Owen, & Hampshire, 2013). That is, both sub- and supra-optimal dopamine levels in the PFC and/or the striatum result in cognitive performance deficits. While this is readily noticeable in psychiatric and neurological disorders such as schizophrenia and Parkinson's disease (Cools, Barker, Sahakian, & Robbins, 2001; Cools & Robbins, 2004; Tunbridge, Harrison, & Weinberger, 2006), it can also be observed in non-clinical populations as a consequence of genetic polymorphisms of the dopaminergic system (Klanker et al., 2013; Savitz, Solms, & Ramesar, 2006).

Within the PFC, dopamine levels are modulated by the enzyme catechol-O-methyltransferase (COMT). COMT is localized in the extrasynaptic spaces, where it metabolizes dopamine and renders it inactive (Chen et al., 2004; Savitz et al., 2006). The gene coding for COMT contains a single nucleotide polymorphism (SNP), which involves a valine (Val) to methionine (Met) substitution at codon 158 (Val158Met) (Lachman et al., 1996). The Met and Val alleles differentially affect COMT's enzymatic activity and thus influence PFC dopamine levels. The Met allele reduces the enzymatic activity of COMT three- to four-fold relative to the Val allele, leading to increased dopamine availability (Chen et al., 2004; Lachman et al., 1996; Weinshilboum, Otterness, & Szumlanski, 1999). Associations between COMT Val158Met genotypes and differences in PFC functioning and cognitive performance under well-rested conditions have been well established (Cools & D'Esposito, 2011; Dickinson & Elvevåg, 2009; Klanker et al., 2013; Mione et al., 2015).

Altered dopaminergic signaling in fronto-striatal circuits that mediate cognitive control may be part of the mechanisms underlying the substantial impairment in adaptive decision making previously documented during TSD (Whitney et al., 2015). Here we investigate whether the COMT Val158Met polymorphism mediates the impact of TSD on adaptive decision making.

2. Methods

We assessed adaptive decision making during TSD using a reversal learning paradigm (Whitney et al., 2015). $N = 66$ subjects each participated in one of two in-laboratory studies. In each study, subjects were assigned to either a TSD group ($n = 32$) or a well-rested control group ($n = 34$). Subjects performed a go/no-go reversal learning (GNGr) task, measuring adaptive decision making, once at baseline and once during TSD or well-rested control. Subjects were grouped by COMT genotype to investigate genotype–phenotype relationships associated with impairment in adaptive decision making during TSD.

2.1. Subjects

$N = 66$ healthy young adults (26.2 ± 4.5 years; 27 females) participated in one of two in-laboratory studies conducted in the Sleep and Performance Research Center at Washington State University Spokane. Subjects underwent rigorous

screening procedures, which included physical examination, history, blood and urine chemistry, breathalyzer test, baseline polysomnography, and a battery of questionnaires (see [supplemental material](#) for further screening details).

The studies were approved by the Institutional Review Board (IRB) of Washington State University. Subjects provided written informed consent and were financially compensated for their time.

2.2. Study design

Study 1: Forty-one healthy young adults (26.5 ± 4.7 years; 17 females) participated in a 4-day (3-night) laboratory study. All subjects had one baseline day with a 10 h sleep opportunity (22:00–08:00). They were then randomized to either a TSD condition ($n = 20$) with 38 h of extended wakefulness followed by a 10 h recovery sleep opportunity (22:00–08:00) on the third night, or a well-rested control condition ($n = 21$) with a 10 h sleep opportunity (22:00–08:00) on both the second and third nights. The laboratory conditions are described in the [supplemental material](#).

Subjects performed the GNGr task twice during the study, once at baseline (6 h awake) and again 24 h later during TSD (30 h awake) or well-rested control (6 h awake). Both task administrations occurred at 14:00. Two equivalent versions of the GNGr task, which differed only in the specific stimuli presented, were administered in randomized, counterbalanced order. The GNGr task was the first of three performance tasks in a larger test battery.

Additionally, subjects performed a 10 min psychomotor vigilance test (PVT; [Lim & Dinges, 2008](#)) as a measure of vigilant attention. The PVT was administered every 2–4 h during scheduled wakefulness. Here we used the PVT test bouts that were administered immediately prior to the GNGr, at 13:00 during baseline (5 h awake) and again 24 h later during SD (29 h awake) or well-rested control (5 h awake). See the [supplemental material](#) for a description of the PVT.

Study 1 has been described elsewhere ([Chavali, Riedy, & Van Dongen, 2017](#)), but the GNGr data and genotype–phenotype relationships presented here have not been published before.

Study 2: Twenty-five healthy young adults (25.8 ± 4.1 years; 10 females) participated in a 7-day (6-night) laboratory study. All subjects had two baseline days, each with a 10 h sleep opportunity (22:00–08:00). They were then randomized to either a TSD condition ($n = 12$) with 62 h of extended wakefulness or a well-rested control condition ($n = 13$) with two 10 h sleep opportunities (22:00–08:00). The study ended with two 10 h recovery sleep opportunities (22:00–08:00). The laboratory conditions are described in the [supplemental material](#).

Subjects performed an abbreviated version of the GNGr task during the first day in the laboratory for practice. Following, subjects performed the GNGr task three times during the study, once at baseline (7 h wake), again 48 h later during TSD (55 h wake) or well-rested control (7 h wake), and again another 48 h later after recovery sleep. Each task administration occurred at 15:20. Three equivalent versions of the GNGr task, which differed only in the specific stimuli presented, were administered in randomized,

counterbalanced order. Data from the third task administration (after recovery sleep) are not included here.

Subjects also performed a 10 min PVT every 2 h during scheduled wakefulness. Here we used the PVT test bouts that were administered immediately prior to the GNGr, at 15:00 during baseline (7 h awake) and again 48 h later during SD (55 h awake) or well-rested control (7 h awake). See [supplemental material](#) for a description of the PVT.

Study 2, including the GNGr data and subject sample, has been reported on previously ([Whitney et al., 2015](#)), but the genotype–phenotype relationships presented here have not been published before.

2.3. Reversal learning task

We employed a reversal learning task to measure adaptive decision making ([Whitney et al., 2015](#)). The specific task we used was a go/no-go reversal learning (GNGr) task, which was based on a standard go/no-go paradigm requiring subjects to respond to a specific set of stimuli (go stimuli) while withholding a response to a different set of stimuli (no-go stimuli). The probability of go and no-go stimuli was the same. Importantly, subjects were required to use accuracy feedback, provided in the form of hypothetical monetary gains and losses, to learn stimulus–response mappings. Additionally, approximately halfway through the task there was a reversal of contingencies, and subjects were to use accuracy feedback to learn the new stimulus–response mappings and adjust their response behavior.

Subjects performed the GNGr task on a desktop computer in their individual bedrooms. Prior to each task administration, subjects were presented with an instruction screen explaining how to perform the task. They were told that the goal of the task was to earn as much hypothetical money as possible. At the beginning of the task, four two-digit numbers were assigned to the go stimulus set and four two-digit numbers were assigned to the no-go stimulus set. Subjects were unaware of which numbers belonged to which stimulus set, and were required to learn the correct stimulus–response relationships from accuracy feedback. The reversal of the stimulus–response relationships approximately halfway through the task was not announced; subjects were required to discover the new stimulus–response relationships through accuracy feedback. See [Fig. 1](#).

In both studies, subjects were given 4 practice trials at the beginning of each test bout, which were excluded from analysis. In study 1, subjects performed two versions of the GNGr, with either 56 or 64 pre-reversal trials. In study 2, subjects performed an additional version of the task, which had 60 pre-reversal trials. After the reversal, there were 40 post-reversal trials, regardless of the task version. For analysis purposes, data were grouped into 4 pre-reversal trial blocks (with 14, 15 or 16 trials in each block) and 4 post-reversal trial blocks (with 10 trials per block).

A signal detection framework ([Stanislaw & Todorov, 1999](#)) was used to calculate the discriminability index (d') as a measure of subjects' ability to discriminate between go and no-go stimuli. Hits and false alarms were assessed and used to calculate the d' value for each pre-reversal and each post-reversal trial block. Each subject's d' values were used as the

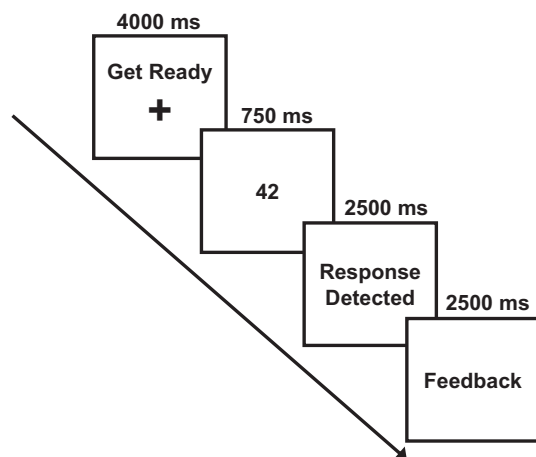


Fig. 1 – Schematic of the go/no-go reversal learning (GNGr) task. In each trial, subjects were given a get ready cue. The stimulus was then presented on the computer screen for 750 ms, during which the subjects were required to either respond or withhold a response. After each provided or withheld response, subjects were given accuracy feedback in the form of a monetary gain or loss. Subjects began the task with a hypothetical \$2.00. If the response (or lack of response) was correct for the presented stimulus, subjects earned \$0.20. If the response (or lack of response) was incorrect, subjects lost \$0.20. At some point during the task, unannounced, the response–stimulus contingencies were reversed. Both before and after the reversal, subjects had to learn the stimulus–response contingencies from the accuracy feedback.

primary outcome measure of GNGr performance. Hit and false alarm rates were considered as secondary outcome measures.

2.4. Genotyping

From each subject, a venous whole blood sample was collected in a Vacutainer tube coated with ethylenediaminetetraacetic dipotassium dihydrate (K_2EDTA) during a pre-study screening session. The blood samples were aliquoted and immediately stored at $-80^\circ C$ until time of analysis. Details of the assay for the Val158Met SNP are provided in the [supplemental material](#).

2.5. Statistical analysis

The genotype distribution in our subject sample was examined for deviation from Hardy–Weinberg equilibrium using a χ^2 goodness-of-fit test. Logistic regression was used to test COMT genotypes in the sample for differences in gender and race/ethnicity distributions; one-way analysis of variance (ANOVA) was used to test for age differences.

The discriminability index, d' , was used as the primary outcome measure of GNGr task performance. Hit rate (percent of correct responses to go stimuli) and false alarm rate (percent of incorrect responses to no-go stimuli) were analyzed as secondary outcome measures. Data were aggregated (not averaged) across the four pre-reversal trial blocks (pre-reversal phase) and across the four post-reversal trial blocks (post-reversal phase), separately for each subject in each of

the two studies. The first administration of the task, during baseline, was labeled session 1. As the experimental circumstances in the two study conditions (TSD and control) were identical at baseline, the session 1 data were pooled across the two conditions. The second administration of the task, during TSD or well-rested control, was labeled session 2. In our statistical analysis framework, the session 2 data were differentiated by condition. The same statistical framework was used for lapses (response times ≥ 500 ms) on the PVT (see [supplemental material](#)).

To analyze the primary and secondary outcome measures, therefore, mixed-effects ANOVA was used with fixed effects of session, session by condition interaction, phase, session by phase interaction, and session by condition by phase interaction. In addition, fixed effects were included for COMT genotype (Met/Met, Val/Met, Val/Val), alone and in interaction with the other fixed effects (see [Table S1](#)). Because the duration of wakefulness during TSD was different between the two studies, study number was included as a covariate. GNGr task version was also included as a covariate. A random effect over subjects was placed on the intercept. The primary statistical outcome of interest was the interaction between condition and COMT genotype.

The mixed-effects ANOVA was repeated controlling for age, gender, race/ethnicity, and menstrual cycle, respectively, to confirm robustness of the results.

3. Results

The demographics and COMT Val158Met genotypes of our subject sample are shown in [Table 1](#). The genotype distributions are presented in [Table 2](#). The variant allele (Met) was in the subject population at a frequency of .48. The ancestral allele (Val) was in our subject population at a frequency of .52. The allele frequencies were found to be in Hardy–Weinberg equilibrium ($\chi^2_1 < .01$, $p = .99$) and similar to those reported in the literature ([Jawinski et al., 2016](#); [Valomon et al., 2014](#)). The genotype distributions did not vary significantly by age ($F_{2,63} = 1.71$, $p = .19$), gender ($\chi^2_2 = .66$, $p = .72$), or race/ethnicity ($\chi^2_2 = 1.95$, $p = .38$).

[Fig. 2](#) shows the discriminability index (d') data for pre- and post-reversal performance on the GNGr task during session 1 (baseline) and session 2 (TSD or well-rested control), by COMT genotype. During session 1 ([Fig. 2](#), left), GNGr performance was similar for all subjects, regardless of genotype. During session 2, however, marked genotype differences emerged in the TSD condition, as compared to the control condition ([Fig. 2](#), right).

In the control group, all COMT genotypes showed improved performance during session 2 as compared to session 1, reflecting the practice effect previously observed for the GNGr task ([Whitney et al., 2015](#)). In the TSD group, subjects homozygous for the Met allele also showed improved performance, but subjects heterozygous or homozygous for the Val allele showed poor performance, both pre- and post-reversal, during session 2 as compared to session 1 ([Fig. 2](#)). We previously found that TSD causes considerable performance deficits on the GNGr task ([Whitney et al., 2015](#)). The present results reveal that the Met allele of COMT Val158Met provides resilience to this effect, while carriers of the Val allele are

Table 1 – Subject demographics and COMT Val158Met genotypes.

	Study 1			Study 2			Combined		
	TSD	Control	Total	TSD	Control	Total	TSD	Control	Total
<i>n</i>	20	21	41	12	13	25	32	34	66
Age (mean $\pm$ SD)	26.5 $\pm$ 4.8	26.5 $\pm$ 4.8	26.5 $\pm$ 4.7	26.6 $\pm$ 4.4	25.2 $\pm$ 3.8	25.8 $\pm$ 4.1	26.5 $\pm$ 4.1	26.0 $\pm$ 4.4	26.2 $\pm$ 4.5
Gender									
Female	9	8	17	7	3	10	16	11	27
Male	11	13	24	5	10	15	16	23	39
Race/ethnicity									
Caucasian	19	21	40	7	10	17	26	31	57
Mixed ^a	1	0	1	3	1	4	4	1	5
American Indian	0	0	0	0	1	1	0	1	1
Asian	0	0	0	1	0	1	1	0	1
Hispanic	0	0	0	1	0	1	1	0	1
Pacific Islander	0	0	0	0	1	1	0	1	1
Genotype									
Met/Met	4	8	12	1	2	3	5	10	15
Val/Met	11	8	19	6	8	14	17	16	33
Val/Val	5	5	10	5	3	8	10	8	18

^a Subjects reporting more than one race were classified as mixed.

Table 2 – COMT Val158Met genotype counts and frequencies in the overall sample.

	COMT Genotype		
	Met/Met	Val/Met	Val/Val
Genotype count			
Expected ^a	15	32.9	18
Observed	15	33	18
Genotype frequency			
Expected ^a	.23	.5	.27
Observed	.23	.5	.27
Published ^b	.33	.46	.22

^a Calculated based on Hardy–Weinberg equilibrium.

^b Valomon et al. (2014), 115 healthy subjects.

particularly vulnerable. Especially in subjects *homozygous* for the Val allele, post-reversal performance was profoundly impacted, to the point of performing no better than chance.

Our statistical results are shown in the [supplemental material](#) (Table S1). Focusing here on the primary statistical

outcome of interest, there was a significant interaction between session 2 condition and COMT genotype ($F_{2,973} = 4.41$, $p = .012$), indicating that the COMT genotype effect was specific to TSD. Also, when the session 2 data were expressed relative to the session 1 (baseline) data, the same pattern of results was seen (see Fig. S1). The finding also held true when controlling for age, gender, race/ethnicity, and menstrual cycle. There were no statistically significant effects in the absence of TSD during session 1 (see Fig. S2). Analysis of hit rates and false alarm rates further confirmed our finding (see Fig. S3).

The proportion of variance explained by COMT genotype in GNGr pre-reversal performance impairment during TSD was 3.89%. Furthermore, the proportion of variance explained by COMT genotype in post-reversal performance impairment during TSD was as much as 8.35%. This is substantial compared to variance explained by gene polymorphisms during TSD as previously reported for vigilant attention (Satterfield et al., 2015).

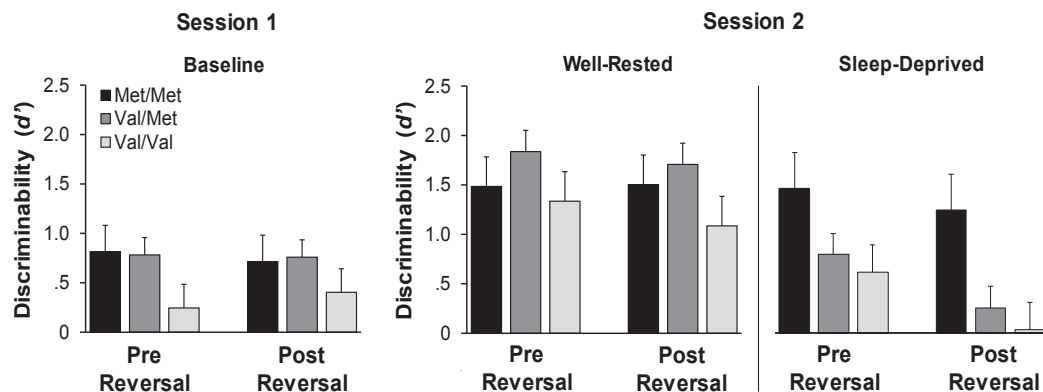


Fig. 2 – Means ($\pm$ standard errors) for the discriminability index (d') on the GNGr task, pre- and post-reversal, as a function of COMT genotype. Left: session 1 (baseline), pooled over conditions ($N = 66$) as the experimental circumstances were identical. Right: session 2, differentiated between the well-rested control condition ($n = 34$) and the TSD condition ($n = 32$).

For vigilant attention performance on the PVT, in contrast with the results for adaptive decision making performance on the GNGr, subjects *heterozygous* for the COMT Val158Met polymorphism showed the greatest level of impairment during TSD (see Fig. S4).

4. Discussion

In this laboratory research, sleep deprivation revealed a considerable vulnerability in adaptive decision making for subjects with the Val allele of COMT Val158Met, either as heterozygotes or homozygotes (Fig. 2, right). There were no significant differences between genotypes at baseline during session 1 (Fig. 2, left, and Fig. S2) or in the well-rested control group during session 2 (Fig. 2, right). The impairment in the carriers of the Val allele was thus specific to TSD. Moreover, the same genotype effect was not seen for vigilant attention as measured with the PVT (Fig. S4). Thus, the impairment observed in the carriers of the Val allele elucidates the *differential* effect of sleep deprivation on adaptive decision making.

The amount of variance explained by COMT genotype for GNGr post-reversal performance impairment during TSD (i.e., 8.35%) is among the highest reported for any gene associated with sleep-deprived performance documented to date (see Satterfield et al., 2015). As such, our finding sheds new light on earlier work that suggested that COMT genotype has little impact on cognitive performance (Ihne et al., 2016) – a conclusion that was drawn based on observations made under baseline conditions. Our results suggest that with moderate sample sizes, a powerful intervention such as TSD (or, for example, transcranial direct current stimulation; Nieratschker, Kiefer, Giel, Krüger, & Plewnia, 2015), a relatively high prevalence of each of the genotypes (see Table 1), and a performance task that captures specifically relevant aspects of cognition (such as the GNGr), are key elements for a strong phenotype–genotype relationship as needed to expose a genotypic performance vulnerability.

Neuroimaging research has shown that the Val158Met polymorphism of the COMT gene influences cognitive control processes (Jaspar et al., 2013). COMT activity affects dopamine levels within the PFC (Chen et al., 2004; Savitz et al., 2006), which is a key part of the fronto-striatal circuitry subserving cognitive control (Botvinick & Braver, 2015; Cole & Schneider, 2007; Cools, 2016; Klanker et al., 2013). Dopamine is important in cortical and striatal circuits for modulating glutamatergic and GABAergic signaling by balancing inhibitory and excitatory actions (Winterer & Weinberger, 2004). Dopamine transmission within the PFC occurs through a dual-state function (Durstewitz & Seamans, 2008), where the low-activity Met allele of COMT Val158Met, which is associated with high dopamine availability, favors a D1 receptor-dominated state that promotes stability of information; whereas the high-activity Val allele, which is associated with low dopamine availability, favors a D2 receptor-dominated state that promotes fast updating of information and improves cognitive flexibility (Bilder, Volavka, Lachman, & Grace, 2004; Cools, 2016; Durstewitz & Seamans, 2008; Winterer & Weinberger, 2004).

The trade-off between cognitive stability and cognitive flexibility involves a delicate balance between PFC and striatal dopamine signaling (Cools, 2016; Cools & D'Esposito, 2011; Fallon et al., 2013). Our results suggest that TSD disrupts this balance, especially in carriers of the Val allele. Expressed in terms of the inverted-U relationship between PFC-mediated cognition and dopaminergic tone (Cools & D'Esposito, 2011; Cools & Robbins, 2004; Fallon et al., 2013), it appears that under conditions of TSD, the dopaminergic tone associated with the Val allele is no longer beneficial to cognitive flexibility, and the Met allele now promotes optimal dopaminergic tone for adaptive decision making.

5. Conclusion

Building on the earlier observation that TSD profoundly impairs the ability of subjects to effectively acquire information and adapt to changes in that information based on feedback (Whitney et al., 2015), we found that subjects vary substantially in their vulnerability to this effect based on COMT Val158Met genotype. This finding is consistent with the idea that altered dopaminergic signaling in fronto-striatal circuits mediating cognitive control may be part of the mechanisms underlying substantial impairment in adaptive decision making during TSD.

The ability to adapt to changes in situational demands are critical in operational settings, especially in safety-sensitive industries where sleep loss is pervasive. Because the ancestral Val allele is common in the general population (46.9% worldwide; Cross, Ivacic, Stefanski, & McCarty, 2010), the real-world implications of the vulnerability it confers to adaptive decision making impairment due to sleep loss are potentially substantial.

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Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.cortex.2017.11.012>.

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SUPPLEMENTAL MATERIAL

Catechol-O-Methyltransferase (COMT) Genotype Affects Cognitive Control during Total Sleep Deprivation

Brieann C. Satterfield, PhD, John M. Hinson, PhD, Paul Whitney, PhD,

Michelle A. Schmidt, MS, Jonathan P. Wisor, PhD, Hans P.A. Van Dongen, PhD

S1. Subject Screening

Subjects eligible to participate in the study met the following criteria: age 22–40 y; physically and psychologically healthy; no sleep or circadian disorders; no current or past relevant history of psychiatric illness; no current drug or medical treatment (except hormonal contraceptives); no significant abnormalities in blood or urine; no history of moderate to severe brain injury; no history of learning disability; not a current smoker or tobacco user; no history of drug or alcohol abuse in the last year and no history of methamphetamine abuse; free of traces of drugs and alcohol; not pregnant; no previous adverse reactions to sleep deprivation; not vision impaired (unless corrected to normal); proficient English speaker; no travel across time zones one month prior to study participation; and no shift work three months prior to study participation. Study 2 included intravenous (IV) blood draws and performance testing on an auditory task and on a high-fidelity driving simulator, which required the following additional eligibility criteria: suitable veins for IV insertion; no history of blood draw complications; no blood donation within 2 months prior to study participation; no plans to donate blood within 2

months after study completion; not hearing impaired (unless corrected to normal); in possession of valid driver's license; and not susceptible to simulator adaptation syndrome.

Subjects reported to wake up between 06:00 and 09:00 regularly and to have habitual sleep durations between 6 and 10 h per night. Menstrual cycle phase in female subjects, which is potentially relevant for dopamine-dependent cognitive processes as they may be modulated by estrogen levels (Jacobs & D'Esposito, 2011), was not assessed. However, after study completion, female subjects reported whether or not menstruation had occurred during study participation.

In the week prior to the in-laboratory experiment, subjects were instructed to keep their habitual bed and wake times. This was verified with wrist actigraphy (Actiwatch-2, Phillips Respironics, Bend, OR), sleep diary, and subjects calling in their bed and wake times on a time-stamped voice-mail box. During this period subjects were to refrain from napping and abstain from caffeine, tobacco, alcohol, and drugs. Prior to admission to the laboratory, subjects were confirmed to be free of drugs and alcohol via urinalysis and breathalyzer test.

S2. Laboratory Conditions

Both studies were conducted in a strictly controlled laboratory environment, with up to four subjects participating at one time. Subjects were each assigned their own bedroom for sleeping and performance testing. Light levels were fixed below 100 lux during scheduled wakefulness; lights were off during scheduled sleep periods. The ambient temperature was maintained at 21 ± 1 °C at all times. Subjects were not allowed to perform any strenuous activity during the study. They were isolated from the outside environment – they did not have any contact with individuals outside the laboratory and did not have access to live radio or television. Additionally, subjects did not have access to phones, personal computers, the internet, or video

games. Between scheduled times for sleep, meals, and performance testing, subjects could watch DVDs, play board or card games, and interact with other subjects and the research staff. Subjects were continuously monitored by trained research assistants.

S3. Psychomotor Vigilance Test

The psychomotor vigilance test (PVT) is a standard measure of vigilant attention with high sensitivity to sleep deprivation (Lim & Dinges, 2008). A 10 min PVT was administered every 2–4 h over the course of the TSD period. During the task, subjects were asked to respond to a visual stimulus (a millisecond counter) as quickly as possible by pressing a button on a response box, while avoiding false starts. The stimulus appeared on the screen at intervals that varied randomly between 2 and 10 s. Vigilant attention impairment was quantified as the number of attentional lapses (response times ≥ 500 ms) in each 10 min test bout. Here, we focused on the PVT test bouts immediately preceding each administration of the GNGr task. For study 1, this was at 13:00 on days 2 and 3. For study 2, this was at 15:00 on days 3 and 5. Due to equipment failure, one subject in study 2 was missing the PVT test bout during SD.

Analogous to the analyses performed for the GNGr task, the number of lapses on the PVT was analyzed using mixed-effects ANOVA with fixed effects of session (test bout) and session by condition interaction. In addition, fixed effects were included for COMT genotype (Met/Met, Val/Met, Val/Val), alone and in interaction with the other fixed effects (cf. Table S1). Study number was included as a covariate, and a random effect over subjects was placed on the intercept. The statistical outcome of interest was the interaction between condition and COMT genotype.

Fig. S4 shows attentional lapses on the PVT, on the test bouts immediately prior to the GNGr administrations, as a function of genotype. During baseline (session 1), PVT performance

was similar for all subjects, regardless of genotype. During SD or well-rested control (session 2), subjects in the SD condition had significantly more PVT lapses ($F_{1,59}=53.80$, $P<0.001$). There was also a significant interaction between COMT genotype and condition ($F_{2,59}=7.77$, $P=0.001$). Unlike GNGr performance, subjects homozygous for the Val allele *were not* the group most vulnerable to TSD. Rather, heterozygous subjects (Val/Met) exhibited markedly more PVT lapses compared to the homozygous groups (Met/Met and Val/Val). This result implies that the impact of COMT genotype on the effect of GNGr performance during TSD was not mediated by COMT's effect on vigilant attention.

S4. Genotyping

Subjects' whole blood samples were red-cell depleted, during which time genomic DNA (gDNA) was extracted. The gDNA samples were assayed for the Val158Met SNP of the COMT gene (rs4680, chromosome 22). The Taqman Drug Metabolism Assay (Assay ID: C__25746809_50; ThermoFisher Scientific, Waltham, MA) was used to determine COMT genotype. Real-time PCR procedures were performed per manufacturer protocol using VIC/FAM context sequence CCAGCGGATGGTGGATTTCGCTGGC[A/G]GAAGGACAAGGTGTGCATGCCTGA. Wet DNA was used in a 96-well plate with a final reaction volume of 25 μ l. Samples were assayed in duplicate. All plates included a no-DNA negative control. Allelic discrimination analysis was performed using MJ Opticon Monitor Analysis Software v3.1 (Bio-Rad Laboratories, Hercules, CA).

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Table S1. Main effects and interactions in mixed-effects ANOVA on primary and secondary outcome variables. Bold indicates statistical significance ($P < 0.05$). HR: hit rate; FAR: false alarm rate.

Fixed Effect	<i>d'</i>		<i>HR</i>		<i>FAR</i>	
	<i>F</i>	<i>P</i>	<i>F</i>	<i>P</i>	<i>F</i>	<i>P</i>
Session (1 or 2)	73.12	<0.001	36.12	<0.001	38.74	<0.001
Condition ^a (TSD or control)	25.45	<0.001	23.00	<0.001	5.15	0.024
Phase (pre- or post-reversal)	4.89	0.027	10.22	0.001	0.57	0.450
Session by Phase Interaction	0.52	0.469	0.67	0.415	0.65	0.420
Condition ^a by Phase Interaction	2.18	0.140	0.77	0.380	4.69	0.031
COMT (Met/Met, Val/Met, Val/Val)	2.52	0.081	1.42	0.243	4.56	0.011
Session by COMT Interaction	0.69	0.502	1.18	0.309	2.59	0.075
Condition ^a by COMT Interaction	4.41	0.012	6.19	0.002	3.96	0.019
Phase by COMT Interaction	0.14	0.873	2.56	0.078	0.47	0.628
Session by Phase by COMT Interaction	0.59	0.555	1.52	0.220	0.08	0.926
Condition ^a by Phase by COMT Interaction	0.05	0.950	1.31	0.270	0.54	0.580
Task Version (1, 2 or 3)	17.90	<0.001	8.32	<0.001	9.57	<0.001
Study (1 or 2)	2.12	0.146	1.74	0.188	1.55	0.214
Condition ^a by COMT Interaction Controlling for:						
Age	5.51	0.004	7.24	0.001	4.44	0.012
Gender	4.69	0.009	6.56	0.002	4.05	0.018
Race/Ethnicity	4.46	0.012	6.35	0.002	3.83	0.022
Menstrual Cycle	4.46	0.012	6.27	0.002	3.99	0.019

^aCondition was implemented as an indicator variable equal to 1 only in session 2 in the TSD condition, and 0 otherwise. As such, it implemented the interaction of session by condition as a main effect, allowing for the session 1 data to be pooled and the session 2 data to be differentiated by condition.

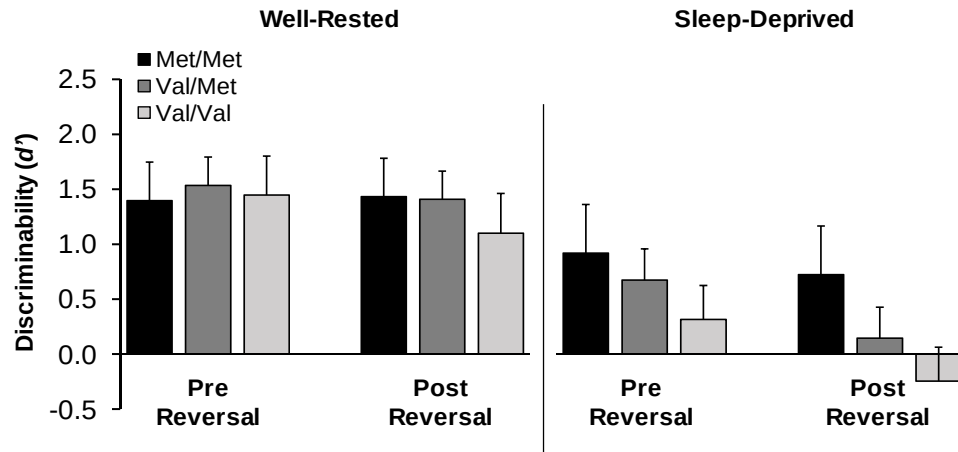


Figure S1. Relative means ($\pm$ standard errors) for the discriminability index (d') on the GNGr task, pre- and post-reversal, as a function of COMT genotype. Data shown are for session 2, differentiated between the well-rested control condition (left; $n=34$) and the TSD condition (right; $n=32$), controlling for session 1 (baseline) performance.

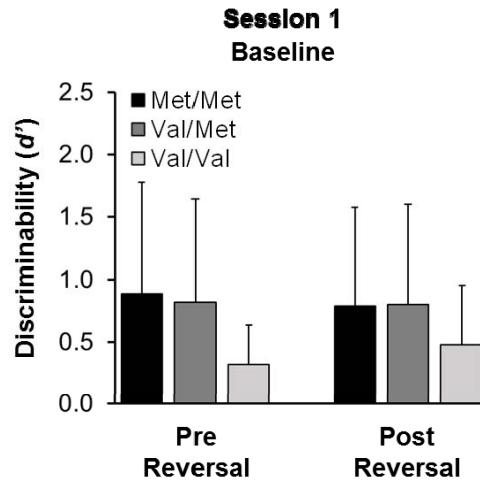


Figure S2. Means ($\pm$ standard errors) for the discriminability index (d') on the GNGr task, pre- and post-reversal, as a function of COMT genotype, at baseline. Data shown are for session 1 (baseline) only, pooled over session 2 condition assignments (N=66). Mixed-effects ANOVA showed no significant effects at baseline for phase (pre- or post-reversal; $F_{1,459}=0.01$, $P=0.91$), COMT genotype ($F_{2,459}=1.20$, $P=0.30$), or their interaction ($F_{2,459}=0.46$, $P=0.63$).

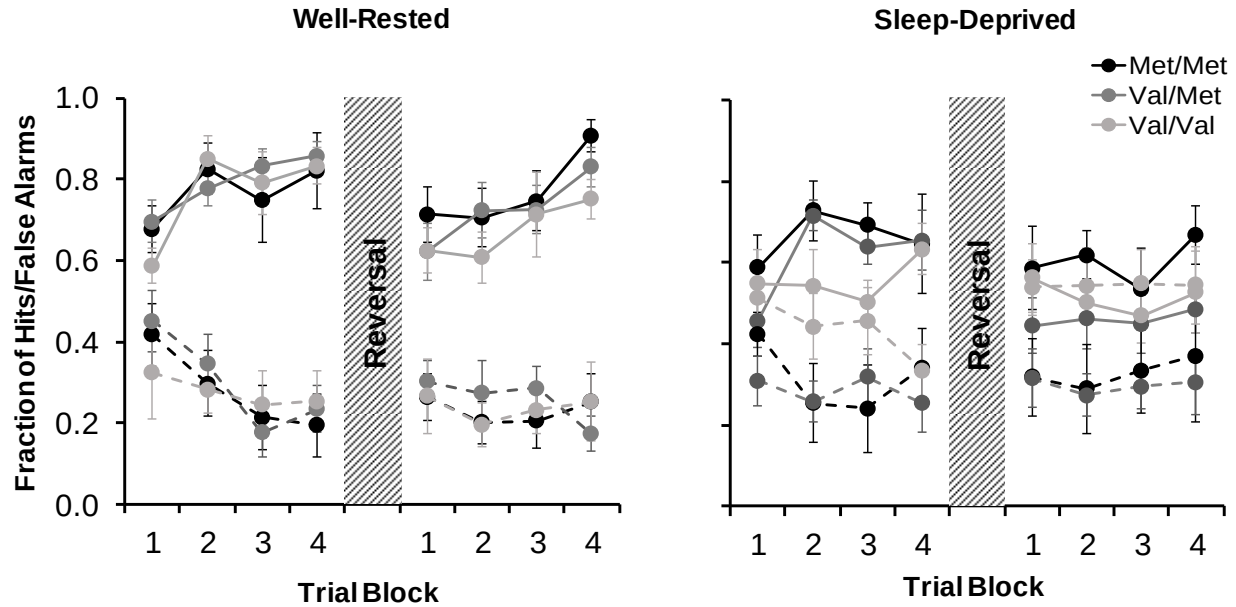


Figure S3. Means ($\pm$ standard errors) for hit rates (solid lines) and false alarm rates (dashed lines) for each trial block of the GNGr task, before (pre-) and after (post-) reversal of the stimulus-response relationships in session 2. For the well-rested controls (left), before the reversal, hits increased and false alarms decreased across trial blocks, regardless of genotype. After the reversal, there was a transient decrease in hits and increase in false alarms; however, subjects quickly recover. For the TSD group (right), before the reversal, hits increased and false alarms decreased across trials more slowly than for the controls. After the reversal, there was a decrease in hits and an increase in false alarms, from which subjects in the TSD group did not recover. The effects of TSD were particularly pronounced in subjects homozygous for the Val allele, who no longer managed to exceed chance performance after the reversal.

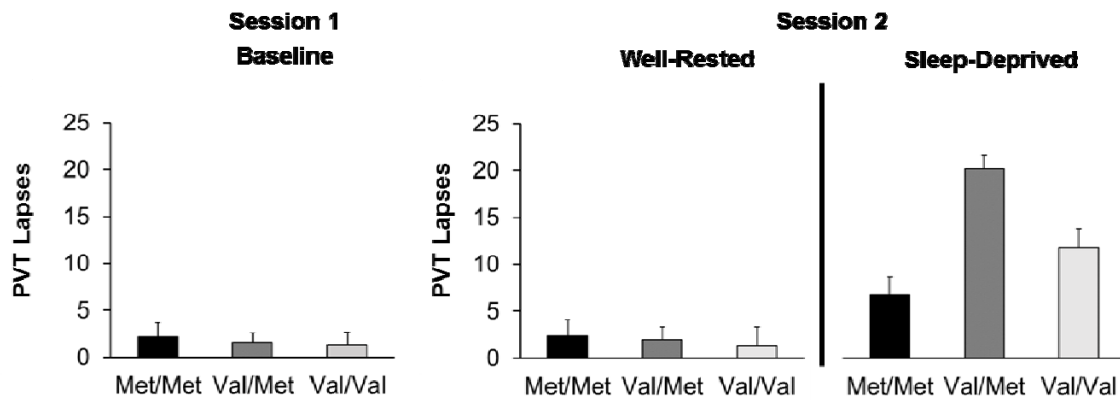


Figure S4. Means ($\pm$ standard errors) for the number of PVT lapses on test bouts immediately prior to GNGr administration, as a function of COMT genotype. Left: session 1 (baseline), pooled over conditions ($N=66$) as the experimental circumstances were identical. Right: session 2, differentiated between the well-rested control condition ($n=34$) and the TSD condition ($n=31$).

Unraveling the genetic underpinnings of sleep deprivation-induced impairments in human cognition

Brieann C. Satterfield^a, Benjamin Stucky^b, Hans-Peter Landolt^b
Hans P.A. Van Dongen^{c,*}

^a*Social, Cognitive, and Affective Neuroscience Laboratory, College of Medicine Department of Psychiatry, University of Arizona, Tucson, AZ, United States*

^b*Human Sleep Psychopharmacology Laboratory, Institute of Pharmacology and Toxicology, University Center of Competence Sleep & Health Zurich, University of Zurich, Zurich, Switzerland*

^c*Sleep and Performance Research Center, and Elson S. Floyd College of Medicine, Washington State University, Spokane, WA, United States*

**Corresponding author: Tel. +1-509-358-7755; Fax: +1-509-358-7810, e-mail address: hvd@wsu.edu*

Abstract

The biobehavioral phenomena of sleep and cognition involve complex phenotype-genotype associations, i.e., complex relationships between observable traits and the genetic variants that contribute to the expression of those traits. There is a general belief that investigating such relationships requires large sample sizes. However, sleep- and cognition-related phenotype-genotype associations may be strengthened through carefully controlled laboratory studies that amplify a given cognitive phenotype by perturbing the biobehavioral system through sleep deprivation and/or pharmacogenetic interventions. Utilization of performance tasks that dissociate cognitive processes allows for cognitive endophenotyping, that is, making precise measurements that capture the essence of a cognitive phenotype. This enables assessment of the genetic underpinnings of cognitive impairment due to sleep deprivation without necessarily requiring large samples. Theory-driven gene selection, selective population sampling techniques to avoid underrepresentation of rare genetic variants, and modern statistical techniques informed by prior knowledge further enhance statistical power. Here we illustrate these approaches on the basis of recent findings, supplemented with some new results, as well as a discussion of modern regression methods for statistical analysis. Ongoing research employing these methods is driving advancements in the understanding of the genetic underpinnings of cognitive impairment associated with sleep loss.

Keywords

Inter-individual differences, Gene polymorphisms, Gene expression, Cognitive impairment, Sleep loss, Endophenotyping, Pharmacogenetics, Phenotype-genotype relationships

1 Introduction

Even in normal, healthy human populations, inter-individual differences in complex biobehavioral phenomena such as sleep and cognition can be surprisingly trait-like (Deary, 2012; Kane and Engle, 2002; Landolt, 2011; Van Dongen et al., 2005). While this suggests profound phenotypic variability with strong genetic influence, complex traits typically involve multitudes of genes, most of which have variants that are too rare to contribute substantially to the population variance and/or represent very small effect sizes (Gibson, 2012). This is a problem for phenotype-genotype association studies, which aim to assess the relationship between the expression of a particular behavior or trait (phenotype) and the underlying genetic information that contributes to the manifestation of that behavior or trait (genotype). In such studies, it is generally difficult to explain much of the observed phenotypic variance, which has led to the conventional wisdom that phenotype-genotype association studies require very large sample sizes to reach statistical significance (e.g., Gottlieb et al., 2015).

Studying large samples addresses at least three critical issues:

- *Rare variants.* Many genetic mutations such as single nucleotide polymorphisms (SNPs) and other genetic variants occur infrequently, such that individuals homozygous (or even heterozygous) for these variants may be quite uncommon. Studying large samples increases the likelihood of capturing these individuals.
- *Missed associations.* Genetic variants that are rare in the sample at hand and/or that have weak influence on the biobehavioral phenomenon of interest produce small effect sizes. Studying large samples increases statistical power to detect them, which is especially important if adjustment of the statistical significance level is needed when multiple genes are being considered (multiple comparisons problem).
- *Spurious findings.* In the context of small effect sizes, there is considerable potential for spurious phenotype-genotype associations when the sample size is small, either because the sample is not sufficiently representative of the larger population from which it is drawn (generalizability problem) or because of random chance (replicability problem). Studying larger samples helps to statistically mitigate these problems.

For studies of sleep and cognition, where phenotyping may require elaborate measurement procedures in the laboratory and the research is usually labor-intensive, studying large samples is a slow and costly process. Also, if there is large heterogeneity across the population, then studying large samples does not adequately address

the generalizability problem, potentially turning it into a missed associations problem instead (as the differential effects in distinct subsamples may simply cancel each other out across the larger sample). The advent of genome-wide association studies (GWASs) has revealed that even in studies involving very large sample sizes, the genetic underpinnings of complex traits often remain elusive (Manolio et al., 2009). However, with such large-scale studies, the precision of phenotyping often suffers (e.g., Oexle, 2018).

In this paper we focus on alternative approaches to investigating phenotype-genotype associations in sleep and cognition that do not necessarily require large samples. Specifically, we focus on studies of the impairing effects of sleep deprivation on cognitive performance, which have been shown to be highly trait-like (Van Dongen et al., 2004a), to illustrate a number of complementary research methods. These research methods include:

Systems perturbation: The typically small effect sizes in phenotype-genotype associations may be increased by amplifying the expression of the phenotype and/or the effect of the genotype. Either or both could be achieved by perturbing the biobehavioral system through experimental intervention. Sleep deprivation is a good example of this, representing a powerful perturbation of sleep homeostasis with strong effects on cognitive performance and on post-deprivation recovery sleep (e.g., Bodenmann et al., 2012). Cognitive challenges can further amplify the effects of sleep deprivation to expose phenotype-genotype relationships (Satterfield et al., 2017; Whitney et al., 2017). Pharmacogenetic approaches involving pharmacological interventions on the neurotransmitter systems underlying sleep regulation provide additional means of perturbing the system, producing large effect sizes in phenotype observations and manifestly revealing genotype relationships with relatively small sample sizes (Urry and Landolt, 2015).

Theory-driven genotyping: The multiple comparisons problem of investigating phenotype-genotype associations may be mitigated by limiting the focus on a small number of genes of interest, selected on the basis of their a priori expected involvement in the biobehavioral phenomenon of interest (e.g., Holst et al., 2017). This approach is particularly powerful in the context of pharmacogenetics (i.e., the study of drug responses in relation to genetic factors). Pharmacogenetics provides a basis for the use of pharmacological agents to perturb systems for which the underlying mechanisms are already partially known or suspected, thereby providing a strong justification for a priori selection of specific target genes (e.g., Bodenmann et al., 2009b). Theoretical considerations pertaining to the involvement of specific genes can also be used to inform statistical regression models used to estimate phenotype-genotype relationships (Huang et al., 2011; Wang et al., 2013).

Selective sampling: The challenge of dealing with rare genetic variants may be circumvented by selective sampling. That is, the risk of undersampling of uncommon genotypes can be addressed directly by prospectively selecting

subjects from each of the different genotypes (i.e., homozygous mutant, heterozygous, and homozygous common) of the gene of interest (e.g., [Viola et al., 2007](#)). It could also be addressed indirectly by oversampling of portions of the distribution of inter-individual differences in a given biobehavioral phenomenon (e.g., [Allebrandt et al., 2010](#)). Care should be taken not to sample exclusively from the extremes of the genotype distribution (e.g., only homozygotes) or the phenotype distribution (e.g., only the phenotypic extremes), as the phenotype-genotype association may be nonlinear and could be obscured or misinterpreted this way. Although selective sampling precludes assessment of the amount of population variance explained by a particular gene, it can be particularly effective for studying underlying mechanisms (e.g., [Rétey et al., 2007](#)).

Cognitive endophenotyping: Paradoxically, inter-individual differences in the phenotypic effects of sleep deprivation on cognitive performance have been found to be outcome-specific (e.g., [Van Dongen et al., 2011a,b](#)). Research into this issue has revealed the importance of considering distinct components of cognition ([Jackson et al., 2013](#)), which are differentially vulnerable to impairment due to sleep deprivation ([Honn et al., 2018](#)). This points to the importance of cognitive endophenotyping, by which we mean the dissociation of phenotypic outcomes that are more neurocognitively specific than the overall biobehavioral phenomenon (i.e., performance impairment) and may therefore have more well-defined genetic connections. Cognitive performance tasks designed to assess such endophenotypic outcomes or “cognitive endophenotypes” may help to establish strong phenotype-genotype relationships ([Grant et al., 2018](#); [Satterfield et al., 2018](#); [Whitney et al., 2017](#)).

Here, we illustrate these approaches to studying phenotype-genotype associations using data from laboratory studies of the effects of sleep deprivation on cognitive performance. We show that robust findings can be achieved with relatively small samples by (1) using theory-driven selection of gene targets and pharmacogenetic perturbations to amplify phenotype-genotype associations, (2) outcome-specific endophenotyping of cognitive responses to sleep deprivation, and (3) application of cutting-edge statistical techniques informed in part by prior knowledge.

2 Pharmacogenetics to elucidate molecular-genetic contributions to sleep deprivation and cognition

Both sleep and cognition can be modulated with pharmacological interventions, and an experimental pharmacogenetic approach is a powerful tool to examine phenotype-genotype relationships between sleep deprivation and cognition. By examining the interactions of extended wakefulness and pharmacologically induced network modulations at different time scales, distinct molecular-genetic mechanisms underlying the consequences of sleep loss on cognitive functioning can be elucidated.

The daily alternation between wakefulness and sleep constitutes a fundamental temporal rhythm, which is tightly regulated by the fine-tuned interplay between homeostatic and circadian processes (Achermann and Borbély, 2016). Sleep need accumulates during wakefulness and dissipates during sleep (homeostatic process), whereas the circadian clock determines when sleep occurs as a function of time of day (circadian process). The interaction between the two processes determines daily fluctuations in subjective state, mood, alertness, and cognition (Boivin et al., 1997; Schmidt et al., 2007). Both homeostatic and circadian influences also affect brain electrical activity in a vigilance state-specific manner. Power (energy) in the electroencephalogram (EEG), especially in the theta range ($\sim 4\text{--}8\text{ Hz}$), provides a reliable biomarker of accumulated sleep need induced by sustained wakefulness (Bodenmann and Landolt, 2010; Finelli et al., 2001; Holst et al., 2017).

Conscious decisions and optimal interactions with the environment require alert wakefulness, and sleep is essential for maintaining optimal cognitive functioning. Extended wakefulness characteristically alters long-range temporal correlations (LRTCs) in the EEG alpha band ($\sim 8\text{--}12\text{ Hz}$), where overall signal power is virtually unchanged as a function of time awake (Holst et al., 2017; Meisel et al., 2017). The LRTCs slowly decay over seconds and reflect cortico-cortical connectivity and balanced cortical excitation and inhibition (E-I balance) (Meisel et al., 2017). The maintenance of an optimal E-I balance allows brain networks to function properly, and normal LRTCs are associated with optimal decision making and working memory task performance.

It has been proposed that sleep deprivation disrupts information processing by intrusions of sleep-like events into wakefulness (Doran et al., 2001; Nir et al., 2017; Van Dongen et al., 2011a,b; Vyazovskiy et al., 2011). LRTCs decline across prolonged wakefulness and normalize following recovery sleep, suggesting that sleep maintains LRTCs in the human brain and reorganizes cortical networks for optimal cognitive functioning (Meisel et al., 2017). Genetic factors contribute up to 60% to the strength of LRTC (Linkenkaer-Hansen et al., 2007) and can be pharmacologically modulated (Meisel et al., 2015; Yang et al., 2012). The monitoring of spontaneous brain activity and its modulation by pharmacological interventions in genetically characterized individuals may establish sleep-wake dependent timescales of information processing in cortical networks with link to cognition and reveal biomarkers of E-I balance and cortical dynamics during prolonged wakefulness.

2.1 System perturbations with pharmacological interventions and sleep deprivation

Pharmacogenetic approaches can be used to probe the causality of phenotype-genotype associations. The use of careful behavioral phenotyping and sleep deprivation opens the possibility for a closer examination of the effects of different pharmacological interventions on neurobehavioral performance. Stimulants have been of particular interest in the study of sleep deprivation and cognition. Stimulants are unique from a pure cognitive perspective because they offer direct

manipulation of specific signaling pathways that may underlie different aspects of cognition, and thus can offer insight into neurocognitive mechanisms that are impacted by sleep loss. For example, caffeine's main mode of action is adenosinergic, whereas modafinil and dextroamphetamine act upon different aspects of the dopaminergic system. Killgore et al. (2009) found that caffeine, modafinil, and dextroamphetamine had differential effects on three executive function tasks following 45–50h of sleep deprivation. Both modafinil and dextroamphetamine reduced the total number of moves required to complete the Tower of London, a task that involves planning and visuospatial working memory (Shallice, 1982), whereas caffeine was not found to be effective. Conversely, only caffeine significantly improved performance on the Tower of Hanoi, a task that involves planning, strategy, and response inhibition (Welsh et al., 1999). Individuals who received modafinil had significantly better performance on the Wisconsin Card Sorting Task (WCST), purportedly a measure of mental set-shifting (Killgore et al., 2009; Puente, 1985), although the WCST is complex and known to recruit several neurocognitive systems (Berman et al., 1995).

These results suggest that different stimulants may have different effects on various aspects of executive function, allowing a better understanding of the underlying cognitive processes based on the pharmacological effects of each (Killgore et al., 2009). In a follow-up study, none of the stimulants were found to significantly improve decision-making performance on the Iowa Gambling Task (Killgore et al., 2012). Similarly, Wesensten et al. (2005) found little effect of stimulants on a range of executive function tasks. Lack of significant findings may be contributable to the “task impurity” problem that any performance task involves a number of interrelated cognitive processes, which must be distinguished to understand the causal factors determining performance in any given circumstance (Whitney and Hinson, 2010). This highlights the importance of employing neurocognitive assessment batteries that offer distinct, and dissociable, measures of cognitive functioning, as will be discussed later.

2.2 Theory-driven selection of gene targets: Proof of concept

A pharmacogenetic approach has been successfully applied to deconstruct a role for a distinct adenosine receptor subtype and adenosinergic-dopaminergic mechanisms in regulating cerebral activity and neurobehavioral performance during sleep deprivation. Consistent with a long-proposed role for adenosine and its binding sites in sleep-wake regulation (Porkka-Heiskanen et al., 1997; Radulovacki, 2005), caffeine, which is an adenosine antagonist, attenuates EEG markers of sleep homeostasis in wakefulness and sleep (Landolt et al., 2004). Some individuals are very sensitive to caffeine's stimulant effects, whereas others are not. In part these individual differences are genetically determined (Yang et al., 2010).

Caffeine blocks adenosine A₁ and A_{2A} receptors in the central nervous system without preferred specificity (Lazarus et al., 2017). However, basic pharmacogenetic work in transgenic mice demonstrated that functional A_{2A} receptors are indispensable for the promotion of wakefulness by the stimulant (Huang et al., 2005).

Translating these insights to humans, complementary observational and laboratory studies confirmed that common variants of the A_{2A} receptor gene (*ADORA2A*) modulate the effectiveness of caffeine to counteract the consequences of sleep loss on EEG activity and neurobehavioral performance. [Table 1](#) summarizes a step-wise, pharmacogenetic approach to further elucidating a role for adenosine A_{2A} receptors in regulating neurophysiological and neurobehavioral markers of sleep homeostasis after sleep deprivation.

2.3 Selective sampling: Proof of concept

First, 20,343 university students were addressed with a brief internet questionnaire about self-rated caffeine sensitivity and sleep, and 4329 individuals responded. Habitual caffeine consumption was associated with subjectively reduced sleep quality in caffeine sensitive respondents, but not in caffeine insensitive respondents ([Rétey et al., 2007](#)). Intriguingly, in a laboratory study of 22 individuals from this sample, a night of sleep deprivation increased frontal EEG theta activity and impaired neurobehavioral function more in self-rated caffeine-sensitive than in caffeine-insensitive men ([Rétey et al., 2006](#)). Double-blind administration of the stimulant (2 times 200mg across a 12-h interval) during prolonged wakefulness confirmed the classification of caffeine sensitivity based on the questionnaire. Thus, caffeine counteracted the differences between the phenotypic groups, although the caffeine concentration in saliva did not differ ([Rétey et al., 2006, 2007](#)).

The genetic sequence of *ADORA2A* was not the same in caffeine sensitive versus insensitive individuals. More specifically, the C allele of the functional c.1976T>C SNP of *ADORA2A* (SNP-ID: rs5751876) appeared to be more frequent in sensitive individuals ($n=58$), whereas the T allele of this polymorphism occurred more frequently in insensitive individuals ($n=84$) ([Rétey et al., 2007](#)). By contrast, the prevalence of the C/T genotype was the same in sensitive and insensitive subjects. These findings were further corroborated in the laboratory ([Bodenmann et al., 2012](#)) and confirmed by an independent GWAS ([Byrne et al., 2012](#)). Together, these findings suggest an important role for A_{2A} receptors in sleep-wake regulation and sleep-dependent neurobehavioral performance.

Conceptually, the experimental roadmap outlined above ([Table 1](#)) highlights the usefulness of self-classification to estimate a subjective phenotype as an initial step in large-scale epidemiological studies, followed up by physiological studies aimed to provide insights into the molecular bases of sleep deprivation and cognition. Furthermore, the example of variation in caffeine sensitivity has implications for clinical studies of novel pharmacological interventions targeting A_{2A} receptors, such as in chronic sleep restriction ([Doty et al., 2017](#)) and insomnia ([Korkutata et al., 2018](#)). The proof of concept presented above suggests that such studies could yield clearer outcomes if participants were subdivided and analyzed by their genotypes for *ADORA2A* and other genes of interest ([Chen et al., 2013](#)). These genes may hint to pharmacogenetic markers of individual responses to novel compounds and offer a unique opportunity for personalized sleep-wake medicine ([Holst et al., 2016](#)).

Table 1 Step-wise elucidation of a role for adenosine A_{2A} receptors and dopamine transporters in regulating neurophysiological and neurobehavioral markers of sleep homeostasis after sleep deprivation using a translational pharmacogenetic approach.

Conventional method	Additional methods	Sample size	Outcome(s)	Genetic approach	References
Basic pharmacogenetics	Perturbation	Tens/ experiment (mice)	Sleep-wake neurophysiology	Genetic engineering	Wisor et al. (2001) , Hayaishi et al. (2004) and Huang et al. (2005)
Observational	Theory-driven genotyping	$n = 94-102$	Caffeine-induced anxiety	N/A	Alsene et al. (2003) and Childs et al. (2008)
	Selective sampling	$n = 20,343$	Sleep-wake habits, self-rated caffeine sensitivity	N/A	Rétey et al. (2007)
	Selective sampling	$n = 4329$	Caffeine consumption and sleep quality in extremes of caffeine sensitivity	N/A	Rétey et al. (2007)
Human pharmacology	Selective sampling, perturbation, deep phenotyping, within- and between-subjects variance	$n = 12-32$	Interaction of sleep deprivation and caffeine in caffeine sensitive and insensitive individuals	N/A	Landolt et al. (2004) , Gottselig et al. (2006) , Rétey et al. (2006) , and Landolt et al. (2012)
Human pharmacogenetics	Theory-driven genotyping, perturbation, deep phenotyping, within- and between-subjects variance	$n = 22-504$	Interaction of sleep deprivation and caffeine in genetically characterized individuals	ADORA2A c.1976T>C SNP ADORA2A haplotype DAT1 VNTR	Rétey et al. (2007) , Bodenmann et al. (2012) , and Holst et al. (2014)
Replication, observational		$n = 2402$	Coffee-attributed sleep disturbance	GWAS in twins	Byrne et al. (2012)
Back-translation, pharmacological innovation		Tens/ experiment (mice)	Sleep-wake neurophysiology, body temperature and heart rate measurement	N/A	Korkutata et al. (2018)

Perturbation approaches include sleep deprivation and pharmacological interventions. Deep phenotyping in humans includes subjective state questionnaires combined with neurophysiology (EEG quantification in waking and sleep) and neuropsychological assessment of sustained attention and executive functioning. ADORA2A=human gene encoding the adenosine A_{2A} receptor; DAT1=human gene encoding the dopamine transporter; GWAS=genome-wide association study; N/A=not applicable; SNP=single nucleotide polymorphism; VNTR=variable number tandem repeats.

2.4 System perturbation, theory-driven genotyping, and deep phenotyping

The A_{2A} receptor is primarily expressed in striatal nuclei (caudate nucleus, putamen, nucleus accumbens, globus pallidus) and the olfactory tubercle, and partly co-localizes in synapses with dopamine D₂ receptors. The D₂ receptors and dopamine transporters (DAT) are important regulators of dopaminergic neurotransmission in striato-pallidal pathways and main target proteins of psychostimulants and wake-promoting medications such as modafinil (Volkow et al., 2009; Wisor et al., 2001). Intriguingly, *Dat*^{-/-} knock-out mice and human homozygous 10-repeat (10R) carriers of the variable number tandem repeat (VNTR) polymorphisms of the *DAT1* gene encoding DAT (i.e., SNP-ID: rs28363170) are especially sensitive to the wake promoting action of caffeine (Holst et al., 2014; Wisor et al., 2001). Furthermore, compared to 9R-allele carriers, the homozygous 10R/10R variant has an accelerated build-up during extended wakefulness of the theta/alpha-ratio in the waking EEG, reflecting a faster increase of sleep drive during sleep deprivation (Holst et al., 2017). This notion is further corroborated by genotype-dependent differences in the time-on-task effect and performance instability during sleep deprivation and the effects of the DAT inhibitor, modafinil, on markers of sleep need (Holst et al., 2014; Lim et al., 2012; Satterfield et al., 2017). In conclusion, convergent findings in animals and humans suggest that adenosine-dopamine interactions in the striatum are important for regulating the neurobehavioral consequences of sleep deprivation.

The available knowledge accumulated by genetic studies in animals and humans suggests that each aspect of sleep-wake regulation is a complex phenotype with different molecular-genetic underpinnings (Andreatic et al., 2008; Landolt and Dijk, 2016). This notion is supported by the lack of clear associations between neurophysiological markers of vigilance and neurobehavioral performance during sleep deprivation (Bachmann et al., 2012; Galliaud et al., 2008; Leproult et al., 2003; Lim and Dinges, 2008; Van Dongen et al., 2004a). For example, recent findings indicate that theta activity or the theta/alpha-ratio in the waking EEG on one hand and attentional lapses on the psychomotor vigilance task on the other hand are governed by distinct mechanisms that may both, yet separately, be influenced by dopaminergic neurotransmission (Holst et al., 2017).

Functional variants in the *ADORA2A* and *DAT1* genes and in *DRD2* (encoding the dopamine D₂ receptor) may modulate sleep-wake mechanisms by affecting striato-pallidal dopaminergic neurotransmission. On the contrary, dopaminergic neurotransmission in the prefrontal cortex (PFC) is primarily regulated by catechol-O-methyltransferase (COMT), which has much less influence on striatal dopaminergic neurotransmission (Slifstein et al., 2008). The COMT enzyme degrades catecholamines, such as dopamine, and the Val158Met polymorphism of the *COMT* gene (SNP-ID: rs4680) has a consistent impact on metabolic, neurophysiological, behavioral, and cognitive markers of PFC functioning (Bodenmann et al., 2009a,b; Egan et al., 2001; Tunbridge et al., 2006). By contrast, functional *COMT* variants and pharmacological modulation of PFC dopaminergic neurotransmission do not significantly affect EEG markers of sleep pressure in wakefulness and sleep

(Bodenmann and Landolt, 2010; Bodenmann et al., 2009b; Jawinski et al., 2016). This was confirmed by a pharmacogenetic study of tolcapone, a specific inhibitor of COMT (Farrell et al., 2012) that allows for probing the causal relationships between mesocortical dopaminergic signaling and neurobehavioral performance after sleep deprivation.

Some cognitive differences among genotypes only become apparent when individuals are challenged by sleep deprivation (Whitney et al., 2017). For the *COMT* Val158Met polymorphism, on both a vigilant attention task called the psychomotor vigilance test (PVT; Lim and Dinges, 2008) and a go/no-go reversal learning task (GNGr; Whitney et al., 2015), Val/Val, Val/Met and Met/Met allele carriers performed similarly in a well-rested baseline condition. However, systems perturbation with sleep deprivation consistently revealed that the homozygous Met/Met genotype provides a certain degree of resilience to performance impairment, whereas both heterozygous and homozygous carriers of the Val allele are more vulnerable (Satterfield et al., 2018; Valomon et al., 2018). This result suggests that mesocortical dopaminergic neurotransmission contributes to the regulation of distinct sleep-wake dependent cognitive functions, while neurophysiologic markers of elevated sleep pressure after sleep deprivation are controlled by different underlying mechanisms.

3 Sleep deprivation, individual differences, and cognitive endophenotyping

Further insight into phenotype-genotype relationships can be gained by focusing on the large inter-individual differences observed in studies of sleep deprivation (Tkachenko and Dinges, 2018). These inter-individual differences constitute robust phenotypes (Rupp et al., 2012; Van Dongen et al., 2004a). Given a representative sample of the population, investigation of the amount of variance explained by a genotype provides insight into how much of any given cognitive effect of sleep deprivation may be attributable to the gene in question.

3.1 Genetically explained phenotypic variance

Through theory-driven selection of target genes (e.g., see the previous section) and the use of well-designed tasks performed during sleep deprivation, recent studies have shown that individual SNPs can explain a substantial portion of the variance—much more than has been seen in traditional genotype studies and GWASs of cognition (Barnett et al., 2008; Davies et al., 2015, 2016; Ihne et al., 2015). For example, in what was arguably the first sleep deprivation study to quantify the amount of variance explainable by a genetic polymorphism, a SNP of the tumor necrosis factor alpha gene (*TNFA308*, SNP-ID: rs1800629) explained 6.4% of the variance in PVT performance during sleep deprivation (Satterfield et al., 2015). In another study, the Val158Met SNP of the *COMT* gene explained as much as 8.4% of the variance in GNGr performance during sleep deprivation (Satterfield et al., 2018). Similarly, the combination of two genetic variants of the dopaminergic

system, the above-referenced VNTR of *DAT1* and a SNP of *DRD2* (C957T, SNP-ID: rs6277) explained 15% of the variance in PVT performance during sleep deprivation (Holst et al., 2017). All three studies were conducted under carefully controlled laboratory conditions in samples drawn from a general population of healthy young adults.

In yet another such study (Whitney et al., 2017), a task designed to measure cognitive flexibility (the AX Continuous Performance Task with switching, AX-CPT-s) was administered during sleep deprivation. Cognitive flexibility was probed by changing the requirements of the task approximately halfway the duration of the task. The ability to flexibly adapt to the change was severely degraded by sleep deprivation ($F_{1,47} = 19.0$, $P < 0.001$; see supplementary information in Whitney et al. (2017). The amount of variance in the cognitive flexibility data that was explained by sleep deprivation in this experiment was 34.6%. Of this amount, a portion of 22.9% (i.e., 7.9% of the total variance) was associated with a SNP in *DRD2* (C957T, SNP-ID: rs6277). Importantly, while sleep deprivation also significantly degraded performance on the PVT, the *DRD2* SNP did not significantly predict the inter-individual differences in responses to sleep deprivation on this task (Whitney et al., 2017), with *DRD2* genotype explaining only 2.8% of the total variance; see Fig. 1.

3.2 Statistical focus on between-subject variance

Another way to look at explained variance is to focus specifically on the between-subjects variance, that is, the variance associated with systematic differences between individuals that could reasonably be expected to have genetic underpinnings. Between-subjects variance can be separated from within-subjects variance

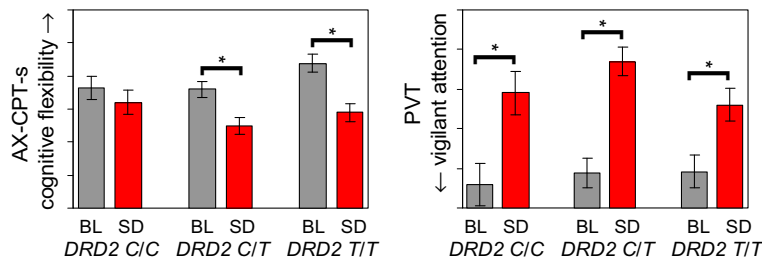


FIG. 1

Performance (mean $\pm$ SE) on the AX-CPT-s (left) and the PVT (right) during rested baseline (BL) and after sleep deprivation (SD) for each genotype of the *DRD2* C957T polymorphism. Whereas individuals homozygous for the C allele were relatively resilient to sleep deprivation-induced impairment in cognitive flexibility on the AX-CPT-s, there was no significant difference among the genotypes in vigilant attention on the PVT. Note that performance impairment is downward in the AX-CPT-s graph, but upward in the PVT graph. Brackets with asterisk indicate significant difference between BL and SD ($P < 0.05$).

Graphs adapted from Whitney, P., Hinson, J.M., Satterfield, B.C., Grant, D.A., Honn, K.A., Van Dongen, H.P.A., 2017. Sleep deprivation diminishes attentional control effectiveness and impairs flexible adaptation to changing conditions. *Sci. Rep.* 7, 16020. doi:10.1038/s41598-017-16165-z, with permission.

(general changes over time and measurement noise) by means of mixed-effects regression techniques, which are explained elsewhere (e.g., [Van Dongen et al., 2004b](#)). Analyzed this way, it was found that 23.8% of the between-subjects variance in the cognitive flexibility data ([Fig. 1](#)) was associated with *DRD2* C957T. By contrast, only 2.9% of the between-subjects variance in the PVT data was associated with the *DRD2* SNP. Thus, regardless of how explained variance is calculated, the phenotype-genotype relationship was profoundly dependent on the cognitive performance task being investigated.

3.3 Cognitive endophenotyping

Underlying this paradoxical finding is the reality that cognitive performance is not a unitary concept ([Whitney and Hinson, 2010](#)). Standard tasks often used to measure performance during sleep deprivation depend on multiple cognitive components simultaneously, which each may be affected differently by an intervention such as sleep deprivation ([Jackson et al., 2013](#))—i.e., the task impurity problem already referenced in the previous section. The task impurity problem reduces the strength of phenotype-genotype relationships. Conversely, performance tasks designed to address the task impurity problem can strengthen and help to expose phenotype-genotype relationships. The PVT, GNGr, and AX-CPT-s used in the studies described above meet this criterion, effectively measuring *cognitive endophenotypes*. The assessment of cognitive endophenotypes contributed to the substantial amounts of variance explained by the genes investigated in these studies.

3.4 Challenges of inferring genetic mechanisms

It should be noted that the amount of variance explained by genotype differences depends on a number of factors only indirectly related to the strength of the genotype to (endo)phenotype relationship per se. These factors include the nature of the population being studied, the specific sample drawn from that population and the inclusion and exclusion criteria being used, and the genotype distributions (i.e., the allele frequencies in the general population and the study sample). They also include the overall study design, the degree of sleep deprivation, the timing and frequency of performance measurements, the level of measurement noise, and the specific outcome measures employed. Any enduring physiological states, such as those that may be induced by a history of chronic sleep restriction or by illness, may further shape genotype findings.

Rapid population growth and mixing of ancestries over the last several hundred years has shifted population genetic equilibriums, resulting in genotypic frequency and diversity variations across racial and ethnic groups ([Ortega and Meyers, 2014](#)). This introduces a systematic source of genetic variation that must be considered when interpreting between-subject variances and their generalizability across populations. Thus, while between-subjects variance serves as a useful tool to quantify phenotype-genotype relationships, these factors make it difficult to compare explained variance statistics between studies.

Even when phenotype-genotype associations are well established and quantified, inferring the genetic mechanisms underlying cognitive functioning may nonetheless be difficult, because knowledge of the functional consequences of genetic variants of interest (e.g., changes in protein expression levels, or differences in receptor affinity) is often incomplete. For example, the literature is mixed regarding the effects of the VNTR polymorphism of *DAT1*, with some studies suggesting that the 9R allele results in the downregulation of *DAT1* activity, and others finding the same for the 10R allele (Faraone et al., 2014). Further, individual genes do not act in isolation, and gene-gene interactions may alter or obscure the effects of the individual genes. And there are complex interactions between different neurotransmitter systems, further complicating the interpretation of genotype effects.

Genotype effects may also be brain region-specific. This is well illustrated by differential mechanisms for the clearing of dopamine from the extracellular space. Within the prefrontal cortex, extracellular dopamine is metabolized, with the *COMT* gene modulating the clearance rate (Savitz et al., 2006). Within the striatum, cellular reuptake is the dominant mechanism for dopamine clearance, with *DAT* genes modulating the reuptake rate (Ettinger et al., 2016). Striatal-dependent probabilistic learning and PFC-dependent cognitive flexibility are both aspects of reward-based learning, but mediated by different dopaminergic gene polymorphisms which offer different perspectives on how sleep deprivation may impact various aspects of cognition that utilize fronto-striatal neural pathways.

4 Biomarker panels and statistical tools

Whereas genotypes modulate the effects of sleep deprivation, the actual profiles of gene expression—i.e., the conversion of genetic information into functional products such as proteins—are an essential part of the biomolecular pathways underlying the impact of sleep deprivation on cognition. Indeed, gene expression profiles change dynamically with increasing levels of sleep deprivation (Möller-Levet et al., 2013; Pellegrino et al., 2014; Uyhelji et al., 2018), and may one day serve as biomarkers of individuals' cognitive responses to sleep loss (Mullington et al., 2016; Uyhelji et al., 2018). Given the involvement of multiple genes, the search for biomarkers involves the identification of biomarker panels that can act like a fingerprint, a so-called biosignature (Laing et al., 2018; McDermott et al., 2013). Recent advances in high-throughput technologies have enabled the rapid production of large gene expression data sets. These data sets tend to have many more gene-related predictors than phenotypic outcome data, which presents a serious challenge for data analysis but is well-suited for the utilization of modern, multivariate statistical approaches.

4.1 Data-driven and theory-driven statistical approaches

The search for meaningful biomarkers can either be knowledge-driven (also termed theory-driven) or data-driven. Knowledge-driven approaches focus on a carefully chosen set of (potentially) biologically relevant variables, whereas data-driven

strategies explore patterns in the data that are not readily apparent from theory or human reasoning. Both these approaches have advantages and disadvantages. The theory-driven approach is often concerned with testing of an a-priori stated hypothesis, where mitigating type I error (the probability of reporting false positive findings) becomes important. This can be achieved by limiting the number of hypotheses (e.g., by investigating only one or a small number of carefully selected genes), and/or by applying a type I error adjustment for multiple comparisons during statistical testing. The latter may involve adjusting the significance level of each test, such that the Family-Wise Error Rate (FWER) is controlled. The FWER seeks to limit the probability of any false positives among a set of tests. While statistically powerful, the theory-driven approach has a fundamental limitation, captured by the words of Einstein (quoted in [Salam et al., 1990](#)): “It is the theory which decides what can be observed.” In other words, this approach may miss important features of the data set that are not in the focus of investigation.

By contrast, data-driven investigations attempt to identify the potentially interesting features of the data set ([Jaeger and Halliday, 1998](#)). This approach emphasizes controlling the type II error (the probability of failure to report true positive findings). Strict control of type I error (like in theory-driven research) would be too restrictive in this context, and is therefore not commonly applied in data-driven research. However, the type I error cannot be entirely neglected, as that could lead to too many false positives in the results, rendering the data analysis uninformative. To address this issue, alternative type I error control methods have been developed ([Benjamini and Hochberg, 1995](#)). These include false discovery rate (FDR) methods, which seek to curb the expected proportion of false positive findings among all reported findings from a study; and Per-Family Error Rate (PFER) methods, which aim to limit the expected total number of false positive findings being reported. While poised to yield rich findings, the data-driven approach has a fundamental limitation as well, in that the results may not reflect any concrete biological mechanisms or lead to significant new insights.

4.2 Exploratory statistical techniques: Proof of concept

Modern statistical methods allow the theory- and data-driven approaches to be combined by including prior knowledge into exploratory statistical techniques ([McDermott et al., 2013](#)). Here we discuss a set of modern, multivariate statistical tools called penalized regression, and review its contributions and pitfalls in the identification of biomarker panels. For illustration purposes, we show different ways to apply these methods in the statistical environment “R” (version 3.5.1), using a gene expression data set that is publicly available (NCBI GEO online repository; accession number GSE98582). The data were collected in the laboratory in a relatively small sample of 17 healthy young adults, 11 of which were subjected to 62h of total sleep deprivation and 6 of which served as well-rested controls. To measure cognitive impairment due to sleep deprivation, subjects performed a PVT at intervals of 2–4h during scheduled wakefulness. Blood samples were taken and gene

expression was quantified, using microarrays, for specific times of day—08:00, 12:00, 16:00 and 20:00—at baseline, after one night of sleep deprivation (or well-rested control), and after recovery sleep. In the publication where these data were introduced (Uyhelji et al., 2018), the gene expression data were filtered for low expression levels, and data from 8397 genes were retained (where some genes that would a priori be potentially relevant, such as *DAT1* or *BDNF*, were not included). Further details can be found in the original publication (Uyhelji et al., 2018).

The gene expression data set considered here is characterized by “high-dimensionality,” which means that there are many more variables (i.e., 8397 genes) than samples (i.e., 17 subjects times 12 samples per subject = 204 samples). This situation entails several challenges that have been coined “the curse of dimensionality” (Bellman, 1961). An attempt to include all 8397 genes in a single analysis would normally result in an underdetermined regression model, and application of standard estimation methods such as least-squares fitting would lead to overfitting—such that not only the gene expression signal but also the noise in the data is fitted and predictions derived from the model would be unreliable. Therefore, some form of data processing or dimensionality reduction must occur, which may be achieved by optimization algorithms applied in advance of, or embedded in, the regression analysis. For example, the data could first be subjected to principal component analysis (PCA), which organizes the data in a number of clusters that show similar behavior (i.e., gene expression levels increasing and decreasing in tandem over time and/or across subjects). Together these clusters capture the bulk of the variance in the data set. A drawback of PCA and related methods is that they transform the data set, which may make it difficult to interpret the results they yield.

Alternatively, the data could be submitted to penalized regression, which as part of the regression algorithm selects only the most predictive subset of the genes in the data set. The published literature provides detailed introductions into penalized regression and related statistical methods (Bühlmann and van de Geer, 2011; James et al., 2013) and their application (McDermott et al., 2013; Price et al., 2006, 2010; Wang and Huang, 2014)—here we provide just a brief introduction. A common approach to fitting a regression equation to data is the ordinary least squares method. This method estimates the parameters of the regression model (here reflecting the estimated impact of each of the genes) by minimizing the squared differences between the model predictions and the actual data points. This optimization scheme ensures a good fit, especially if the noise in the data is approximately normally distributed. Penalized regression adds to this approach the concept of “sparsity,” or the idea that not all potentially explanatory variables (genes) are relevant for the phenotype of interest (Candès, 2006).

4.3 LASSO and cvLASSO

The best-known implementation of penalized regression is the “least absolute shrinkage and selection operator” (LASSO; Tibshirani, 1996). This method balances finding a good fit of the phenotype data (PVT performance) with only including a

parsimonious set of influential variables (a small panel of genes). It does this by adding a penalty for each gene used in the regression equation. Thus LASSO sets the model parameters for genes that are not likely to be predictive of the observations to zero, thereby effectively removing them from consideration in the regression model. Achieving a compromise between goodness-of-fit (i.e., how well the model fits the data) and parsimony (i.e., how many parameters are retained in the model) becomes of central importance. Overemphasizing goodness-of-fit would lead to overfitting, whereas overemphasizing parsimony (by applying a penalty that is too harsh) would lead to not including enough genes and thereby compromising the fit. In the LASSO algorithm, the balance between goodness-of-fit and parsimony is mediated by a tuning parameter, which determines the magnitude of the penalty for including additional genes—the higher the tuning parameter, the greater the penalty, and the fewer variables (genes) are included in the model.

In LASSO regression, the tuning parameter (denoted by λ) is usually chosen by a cross-validation (CV) scheme (Bühlmann and van de Geer, 2011). First, a grid of λ values is selected to try out. Then for each λ , the data set is randomly divided into a training subset and a test subset. The model with tuning parameter λ is fit to the training subset, and goodness-of-fit (quantified as the mean squared error; MSE) is calculated for the test subset. The λ value that produces the greatest goodness-of-fit is picked as the tuning parameter to be used in the LASSO regression on the whole data set. A variation on this theme is n -fold CV LASSO (cvLASSO), in which the tuning parameter is determined by dividing the data set into n subsets with similar number of data points, each of which is once used as a test subset. This thus yields an average of n estimates of goodness-of-fit for each λ in the grid, and the λ with the best average goodness-of-fit (MSE) is picked as the tuning parameter for use on the whole data set.

Other implementations of penalized regression are based on variations on the same theme; they include Ridge Regression (Hoerl and Kennard, 1970), group LASSO (Yuan and Lin, 2005), and elastic net regression (Zou and Hastie, 2005). While these methods are inherently linear, generalized versions exist, which allow for non-linear predictor effects while retaining high interpretability of results (Meier et al., 2009; Petersen and Witten, 2019).

We applied a few different variations on the LASSO method to the gene expression data set described above. LASSO regressions assume that the distribution of the error (noise) in the dataset is normal, but the method can be extended to a generalized linear model (GLM) in which the error distribution is assumed to be non-normal. This is relevant here, as PVT performance outcomes in the data set were measured in terms of “lapses,” defined as the number of response times longer than 500 ms (Doran et al., 2001). Noise in this discrete outcome variable would be expected to have a distribution that is approximately Poisson-like, and therefore we implemented a Poisson error distribution. The first analysis we performed in this framework was a 10-fold cvLASSO (R package glmnet version 2.0-16). Fixed regression terms (covariates) were included for study condition (2 levels), day (3 levels), time of day (4 levels), and their interactions, as well as sex and age. The selected value of the tuning parameter was 0.075. The results of the analysis are discussed later.

4.4 Stability selection LASSO

One problem with the cvLASSO method is that the presence of noisy (i.e., biologically unrelated) genes in the data set may lead to less meaningful results (Wang and Huang, 2014). This is an issue of stability, which entails that findings in one part of the data set should also be found in the remaining part of the data set (Bühlmann and van de Geer, 2018). Stability Selection LASSO is a recently developed approach to identifying stable results in LASSO regression analysis (Meinshausen and Bühlmann, 2010). This method considers the selection probabilities of the different variables, essentially asking how often the different genes are selected in subsets of the data set. Genes are retained in the model based on a pre-specified selection probability cutoff. This strategy naturally allows for control of type I error in terms of PFER (Meinshausen and Bühlmann, 2010). Alternatively, confidence intervals can be used for gene selection (Stucky and van de Geer, 2018; van de Geer et al., 2014). The second analysis of the gene expression data set we performed was a Stability Selection LASSO regression (R package stabs version 0.6-3). In addition to a Poisson error distribution, fixed regression terms were included for study condition, day, time of day, and their interactions, as well as sex and age. The PFER threshold was set to 1 (i.e., allowing no more than 1 false positive), and a pre-specified selection probability cutoff of 0.6 was used. The selection probabilities of the top 30 genes are shown in Fig. 2; only genes to the right of the gray vertical line were retained. The results of this analysis are further discussed below.

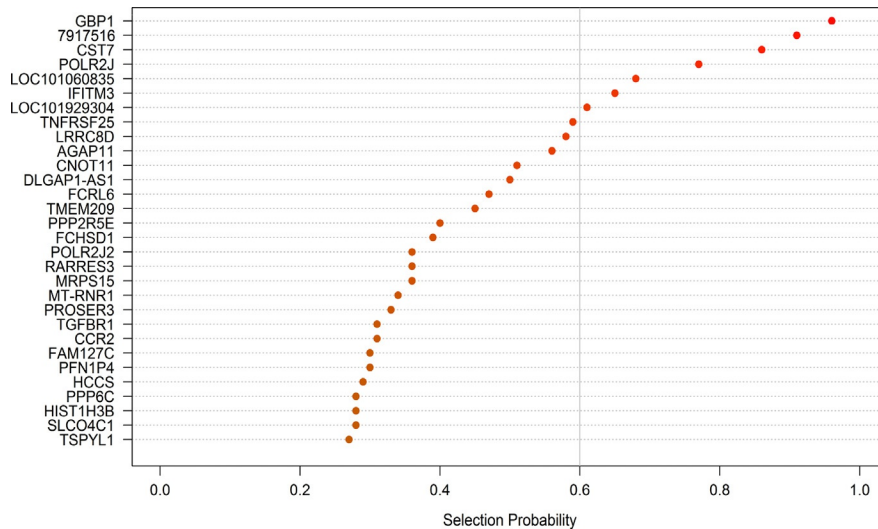


FIG. 2

Illustration of Stability Selection LASSO regression results. The selection probabilities for the top 30 genes are shown; the selection probability cutoff of 0.6 used in the analysis is indicated by the gray vertical line. The genes starting with LOC are unnamed and are identified here by their gene id number.

4.5 Hierarchical inference

Another problem in high-dimensional settings is the fact that single genes cannot be unambiguously identified, because the effects of different genes are often highly correlated and/or because there are not enough data in the sample to uniquely tell the genes apart (Renaux et al., 2018). Various generalizations of the LASSO method have tried to circumvent this problem by either only testing for group variables (clusters) or including some prior biological knowledge. The recently introduced Hierarchical Inference method (Buzdugan et al., 2016; Renaux et al., 2018) clusters correlated genes in an adaptive way, such that the size of the clusters is as small as possible while still contributing significantly to the overall model. We applied the Hierarchical Inference method as the third analysis of the gene expression data set (R package hierinf version 1.1.0 using the standard function “cluster_position()” together with Bioconductor version 3.7.4). Fixed regression terms were included for study condition, day, time of day, and their interactions, as well as sex and age. No Poisson GLM implementation is currently available in the R package hierinf—therefore, PVT lapses were log-transformed before analysis. The results of the Hierarchical Inference analysis can be found in Table 2 (left side).

4.6 Group LASSO

Several of the clusters in the Hierarchical Inference analysis retain many genes. To help with interpretation of such abundant results, functional gene networks can be plotted using the R package FGNet (version 3.14.0), which performs functional enrichment analysis and clustering through the GeneTerm Linker online tool (<https://omictools.com/geneterm-linker-tool>) based on reciprocal linkage (Fontanillo et al., 2011). See Fig. 3 for an illustration, focused on the 16th cluster (see Table 2). This gene expression cluster contains many adenosine- and dopamine-related genes (e.g., *ADA*, *ADORA2A*, *COMT*), which is consistent with the phenotype-genotype associations discussed earlier in this paper.

Instead of using a purely data-driven approach, it is also possible to incorporate prior knowledge to guide the regression algorithms. General frameworks and examples for such “structured sparsity” methods can be found elsewhere (Morales et al., 2010; Stucky and van de Geer, 2017; van de Geer, 2014). Signaling pathways, functional groupings and gene ontological groupings are available from online tools such as the meta-database consensuspathDB (<http://cpdb.molgen.mpg.de/CPDB>). A simple extension of the LASSO method that can make use of this information is the group LASSO (Yuan and Lin, 2005). This structured sparsity method can select groups of genes instead of individual genes, which is useful to identify genetic pathways. One drawback of this method is that it does not consider that genes may be members of more than one group. Therefore, the group LASSO with overlaps was introduced (Jacob et al., 2009).

Another useful approach, termed bi-level selection, seeks sparsity at the level of genes and at the level of groups of genes simultaneously (Park et al., 2015), so that

Table 2 Hierarchical inference results for the relationship between gene expression profiles and PVT performance, and comparison with cvLASSO, stability selection LASSO, and oGEL results.

Hierarchical inference results					Shared members		
Number	<i>P</i> value	<i>R</i> ²	Cluster	Potentially interesting members	cvLASSO	Stability selection	oGEL
1	0.001	0.13	FCRL3 [1]	FCRL3	FCRL3	No element	No element
2	0.001	0.15	MT-TA [1]		No element	No element	No element
3	0.005	0.24	USP24,...,[62]	SLC17A7	LINC01356, GBP1	GBP1	RPS26P15, GBP1, LINC01356
4	0.007	0.23	PRKAB1,...,[252]	TNFRSF1A, UBE2N	NUP37, ACRBP	No element	Unknown.393
5	0.008	0.14	KIAA1715 [1]		No element	No element	No element
6	0.011	0.30	ABI1,...,[505]	COMTD1, GLUD2, AMPD3, TNFAIP3, PIK3AP1, UBE4A, PIK3C2A, UBE2L6	EIF3F, KMT2A, RARRES3, TMEM138, WDR74, OSBP, IFITM3, HBB, DKFZp779M0652, KRTAP5-7, VPS37C	IFITM3	NLRP6, RARRES3, KMT2A, TPT1-AS1, unknown.186, KBTBD4, VPS37C
7	0.012	0.13	PI3 [1]		No element	No element	No element
8	0.013	0.21	TMUB1,...,[126]	GRINA, ERICH1, TNFRSF10C	PROSC	No element	PTP4A3
9	0.014	0.14	Unknown.9 [1]	Unknown.9	No element	No element	Unknown.9
10	0.015	0.15	SNORD56B [1]		No element	No element	No element
11	0.016	0.17	CDK11A,...,[31]	TNFRSF14, TNFRSF25	TNFRSF25	TNFRSF25	MAD2L2
12	0.019	0.20	UBR5,...,[62]		KRT18	No element	KRT18
13	0.024	0.23	ADSL,...,[505]	PIK3IP1, CYP2D6, UBE2E2, UBE2E1, PIK3CA, PIK3R4, PIK3CB	ZNF654, PPP4R2, GLT8D1, NEK4, RASSF1, SLC9A9, EIF4ENIF1, RABL2B, HSPBAP1, GHRL	Unknown	Unknown.550, GPR27, TFG, RNU6-736P, unknown, unknown.492, DVL3, NICN1, GLT8D1
14	0.025	0.17	SNORD116-2, SNORD116-6 [2]		No element	No element	No element

Continued

Table 2 Hierarchical inference results for the relationship between gene expression profiles and PVT performance, and comparison with cvLASSO, stability selection LASSO, and oGEL results.—cont'd

Hierarchical inference results					Shared members		
Number	P value	R ²	Cluster	Potentially interesting members	cvLASSO	Stability selection	oGEL
15	0.029	0.24	EDC4,...,[252]	ADAT1	TERF2IP, TXNL4B, VPS4A, PSMB10, LOC642533, EDC4	No element	TERF2IP, FAM192A, C16orf80, FAM96B
16	0.029	0.19	FKBP1A,...,[252]	ADA, ADARB1, COMT, SPECC1L-ADORA2A, ADORA2A, UBE2D3P1, UBE2V1, UBE2G2, UBE2L3	CCT8, SNORA80A, APOL6, RNA5SP474, CABIN1, C21orf33, TMEM191C, SEPT5-GP1BB	No element	RNA5SP474, RN7SKP111, MAP3K7CL, CCT8, KRTAP12-4, SEPT5-GP1BB.1, TMEM191C, CABIN1, APOL6
17	0.029	0.13	CD7,...,[63]	PIK3C3	DLGAP1-AS1	No element	No element
18	0.031	0.18	ACO1,...,[63]	UBE2R2	No element	No element	Unknown.488, TGFB1
19	0.033	0.19	GDAP2,...,[31]		No element	No element	No element
20	0.033	0.33	NRF1,...,[252]	POLR2J, UBE3C, UBE2H	ZNF394, NSUN5, TMEM209, FAM185A, POLR2J2, POLR2J3	POLR2J	RASA4CP, STYXL1, ZNF394, TMEM209, CNOT4
21	0.034	0.26	GSTM4,...,[3]	GSTM4	No element	No element	GSTM4
22	0.034	0.22	GPR171,...,[252]	TNFSF10, UBE2K, CYP4V2, TNIP2	RUFY3, CCR2, MIR4800, TMEM41A	No element	CCR2, RUFY3, unknown.212, unknown.37
23	0.049	0.20	MAK,...,[125]	GABBR1, GCLC	DNPH1, OARD1, HIST1H3B, HIST1H1C, NEU1	No element	HIST1H4I, unknown.136, TAF11, SYNCRIP

Rows correspond to significant clusters from Hierarchical Inference. On the left side of the table, cluster numbers, P values, aggregated explained variances (R²), cluster descriptors and the number of cluster members (in square brackets), and some potentially interesting members are shown for illustration purposes. On the right side of the table, the clusters are compared to results from the other methods used for analysis of the data set.

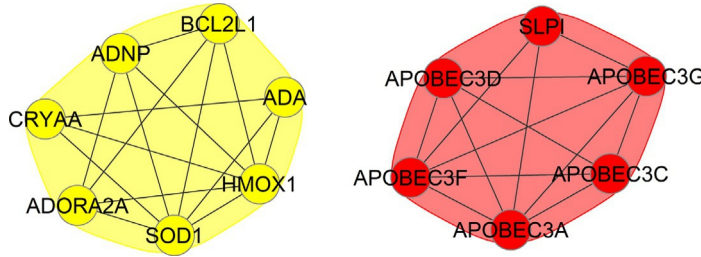
**FIG. 3**

Illustration of a functional gene network plot for the Hierarchical Inference method. Results are shown for the 16th significant cluster (see Table 2). Different colors (yellow and red) indicate different biological processes found in the cluster based on the R package FGNet (version 3.14.0) using the GeneTerm Linker tool.

sparse pathways with relatively few members can be identified. One implementation thereof is Group Exponential LASSO (GEL; [Breheny, 2015](#)). Again a version with overlaps exists, called the overlapping Group Exponential LASSO (oGEL). The fourth (and last) analysis of the gene expression data set we performed here was an oGEL analysis based on 10-fold cvLASSO regression, as implemented in the R package `grpregOverlap` (version 2.2). It is not yet possible to include fixed regression terms within this implementation; therefore, study condition, time of day, sex, and age were not controlled for in this analysis. Table 3 shows the gene groups (pathways) selected by the analysis.

The results of the four analyses of the gene expression data set are compared in Table 2. There are large differences in the findings, which is not unusual in case of high-dimensionality. However, some of the genes in the data set were identified consistently across the different methods. For example, all four analyses identified the guanylate binding protein 1 (*GBP1*) gene. A SNP of *GBP1* (SNP-ID: rs10801703) was found to be associated with caffeine-induced insomnia in a GWAS study ([Byrne et al., 2012](#)), suggesting it is a candidate for further study. Tumor necrosis factor receptor superfamily member 25 (*TNFRSF25*), which is part of the tumor necrosis factor-mediated signaling pathway, was also identified repeatedly. Related genes were shown to be affected by sleep deprivation ([Maret et al., 2007](#)) and have been proposed as biomarkers for acute total sleep deprivation ([Laing et al., 2018](#); [Satterfield et al., 2015](#)). Histone-lysine *N*-methyltransferase 2A (*KMT2A*) is another notable finding, as it might play a crucial role in prefrontal synaptic plasticity and working memory ([Jakovcevski et al., 2015](#)), which could have negative downstream consequences on cognitive performance during sleep deprivation.

In the original analysis of the gene expression data set ([Uyhelji et al., 2018](#)), 28 genes were identified for which the expression was specifically associated with PVT performance impairment due to sleep deprivation (and not just sleep deprivation per se). Of these, 13 were identified by cvLASSO (*POTEKP*, *SPDYE2*, and *WWC3*) or as members in Hierarchical Inference clusters (*ODF2L*, *IPMK*, *LPCAT2*, *LITAF*, *APIG1*, *KCNJ15*, *ETS2*, *RAB7A*, *FLOT1*, *ELOVL5*, *STEAP4*, *SPDYE8P*, and *SDCBP*).

Table 3 Results of the oGEL model analysis. Gene groupings were extracted from the consensuspathDB tool with the setting “pathways.”

Apoptosis	Influenza A	Rho GTPase effectors
Beta-catenin independent	JAK STAT pathway and regulation	Rho GTPases activate formins
Wnt signaling	Kaposi's sarcoma-associated herpesvirus infection	Ribosome
Bisphosphonate pathway, pharmacodynamics	Late phase of HIV life cycle	RNA degradation
Cargo recognition for clathrin-mediated endocytosis		
Cell cycle	M phase	RNA polymerase II pre-transcription events
		RNA polymerase II transcribes snRNA genes
Cellular responses to external stimuli	Membrane trafficking	RNA polymerase II transcription
Cellular senescence	Metabolism	Role of calcineurin-dependent NFAT signaling in lymphocytes
		Role of MEF2D in T-cell apoptosis
Chromatin modifying enzymes	Metabolism of proteins	
		Shigellosis
Chromosomal and microsatellite instability in colorectal cancer	Metabolism of RNA	
Control of skeletal myogenesis by HDAC and calcium	miR-targeted genes in leukocytes—TarBase	Signaling by Rho GTPases
C-type lectin receptor signaling pathway	miR-targeted genes in lymphocytes—TarBase	Spliceosome
Deadenylation of mRNA	Mitochondrial translation	TCF dependent signaling in response to Wnt
Disease	Mitotic prometaphase	TCR
		TGFbeta receptor
DNA damage response (only ATM dependent)	mRNA processing	Thermogenesis
EGF-core	mTOR signaling pathway	
EGFR1	NOD-like receptor signaling pathway	Transcriptional regulation by TP53
		Tuberculosis
Endocytosis	Pathogenic <i>Escherichia coli</i> infection	Ub-specific processing proteases
		Validated targets of C-MYC transcriptional repression
Gene expression (transcription)	Pathways in cancer	Vesicle-mediated transport
Generic transcription pathway	Phagosome	
Hepatocellular carcinoma	Post-translational protein modification	Viral carcinogenesis
		Wnt signaling pathway
HTLV-I infection	Processing of capped intron-containing pre-mRNA	
Immune system	Protein processing in endoplasmic reticulum	
Infectious disease	Regulation of TP53 activity	

The oGEL model selected a sparse set of these consensuspathDB grouping (pathways) to model PVT performance. The resulting groupings are (arbitrarily) shown here in alphabetical order.

This convergence across different analysis methods makes these genes strong candidates for further study. This could include investigation of new data from different samples, and it may involve inclusion of genes previously determined to be potentially relevant as fixed (unpenalized) regression terms for specific hypothesis testing and further discovery.

5 Conclusion

In this paper we outlined a roadmap for the investigation of phenotype-genotype relationships in sleep deprivation and its effects on cognitive performance showed the power of cognitive endophenotyping by focusing on specific cognitive functions and illustrated modern statistical tools to address the high-dimensionality of gene expression data sets that is typical in this domain. Application of the methods described here does not obviate the need for replication studies (or rather, extension studies; see [Zatz, 2000](#)) and investigations of generalizability to other populations (e.g., children or older adults or patients with sleep disorders or other medical conditions) to further unravel the genetic underpinnings of human sleep deprivation and its effects on cognition. We also did not cover twin study paradigms, which provide another powerful strategy for studying phenotype-genotype associations (e.g., [Pellegrino et al., 2014](#)).

Systems biology approaches beyond the scope of this paper will be needed to further clarify the mechanisms implicated in the results of phenotype-genotype analyses, as genetic, neural, cognitive, and behavioral systems do not work in isolation, but rather in complex interacting frameworks. Also, translational research will be needed to understand how results apply to real-world settings and real-world performance tasks, where sleep deprivation and cognitive functioning interact with circumstantial and environmental factors that may profoundly shape performance outcomes ([Riggs et al., 2018](#)). This, in turn, may yield new insights into the underlying mechanisms.

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ORIGINAL ARTICLE

Time-on-Task Effect During Sleep Deprivation in Healthy Young Adults Is Modulated by Dopamine Transporter Genotype

Briann C. Satterfield, PhD¹; Jonathan P. Wisor, PhD¹; Michelle A. Schmidt, MS¹; Hans P.A. Van Dongen, PhD¹

¹*Sleep and Performance Research Center and Elson S. Floyd College of Medicine, Washington State University, Spokane, WA*

Briann C. Satterfield is now at Department of Psychiatry, College of Medicine, University of Arizona, Tucson, AZ

Study Objectives: The time-on-task (TOT) effect and total sleep deprivation (TSD) have similar effects on neurobehavioral functioning, including increased performance instability during tasks requiring sustained attention. The TOT effect is exacerbated by TSD, suggesting potentially overlapping mechanisms. We probed these mechanisms by investigating genotype–phenotype relationships on psychomotor vigilance test (PVT) performance for 3 *a-priori* selected genes previously linked to the TOT effect and/or TSD: dopamine active transporter 1 (DAT1), catechol-O-methyltransferase (COMT), and tumor necrosis factor alpha (TNFα).

Methods: *N* = 82 healthy adults participated in 1 of 3 laboratory studies. A 10-min PVT was administered repeatedly during 38 h of TSD. We assessed changes in response time (RT) across each minute of the PVT as a function of time awake and genotype. Additionally, cumulative relative RT frequency distributions were constructed to examine changes in performance from the first to the second 5 min of the PVT as a function of genotype.

Results: DAT1, COMT, and TNFα were associated with differences in the build-up of the TOT effect across the 10-min PVT. DAT1 additionally modulated the interaction between TSD and the TOT effect. Subjects homozygous for the DAT1 10-repeat allele were relatively protected against TOT deficits on the PVT during TSD compared to carriers of the 9-repeat allele.

Conclusions: DAT1 is known to regulate dopamine reuptake and is highly expressed in the striatum. Our results implicate striatal dopamine in mechanisms involved in performance instability that appear to be common to TSD and the TOT effect. Furthermore, DAT1 may be a candidate biomarker of resilience to the build-up of performance impairment across TOT due to TSD.

Keywords: cognitive performance, fatigue, vigilance decrement, mental workload, dopamine active transporter 1 (DAT1), catechol-O-methyltransferase (COMT), tumor necrosis factor alpha (TNFα), striatum, psychomotor vigilance test (PVT), total sleep deprivation.

Statement of Significance

The time-on-task effect—the performance decrement across the duration of a performance task—is substantially amplified by sleep deprivation. Both the time-on-task effect and sleep deprivation are characterized by performance instability, separately and in interaction, suggesting overlapping mechanisms. Previous work implicated dopamine active transporter 1 (DAT1) genotype in the magnitude of the time-on-task effect. We showed that DAT1 is also associated with the amplification of performance instability due to interaction between the time-on-task effect and sleep deprivation, implicating DAT1 in shared underlying mechanisms. DAT1 is highly expressed in the striatum, where dopaminergic cognition-related mechanisms intertwine with adenosinergic mechanisms of sleep/wake homeostasis, thus suggesting that the striatum is involved in performance instability from time-on-task and sleep deprivation.

INTRODUCTION

The “time-on-task effect” or “vigilance decrement” refers to a progressive decrement of performance across the duration of a cognitive task. The phenomenon tends to be particularly pronounced during sustained engagement in a vigilance task,¹ and a rest break provides recuperation.² The time-on-task (TOT) effect is a critical determinant of productivity and safety in systems monitoring, transportation, and security operations.^{3–9} Yet, the neurobiological mechanisms underlying the TOT effect remain unclear.¹⁰

Importantly, the TOT effect entails an increase in performance “variability” over the duration of a task.¹¹ On the psychomotor vigilance test (PVT)—a vigilance task with a well-documented TOT effect¹²—this is observed as a steady increase in the standard deviation of response times (RTs) across the 10-min duration of the task.¹³ Interestingly, increased RT variability is also a hallmark of how sleep deprivation affects performance on the PVT.¹⁴ Moreover, the TOT effect interacts with sleep deprivation, such that prior sleep loss amplifies the increase in RT variability from the TOT effect.¹³ This interaction has been observed for sleep loss from total sleep deprivation (TSD) as well as sustained sleep restriction^{15,16} and suggests that the effects of TOT and sleep loss on vigilance task performance may have shared underlying mechanisms.^{13,15,17,18}

It has been posited that the effects on vigilance performance due to TOT, sleep loss, and their interaction may collectively be the result of sleep-regulatory processes induced by sustained use of neuronal networks subserving task performance.¹⁵ Specifically, it has been speculated that these effects are caused by failure in cognitive pathways to adequately process information due to local, use-dependent expression of a neuronal, sleep-like state.¹⁹ This “local sleep”²⁰ would lead to cognitive instability during otherwise functional wakefulness, thus presumably giving rise to the observed performance variability.²¹ Neuroimaging studies have provided findings that appear to be consistent with this view,^{19,22,23} but more conclusive evidence is needed.

We set out to further examine the idea that the effects of TOT and sleep loss on vigilance task performance have shared underlying mechanisms, by investigating genetic polymorphisms implicated in the TOT effect or the performance variability associated with sleep deprivation. *A priori* we selected 3 genes of interest:

- **DAT1:** The dopamine transporter 1 gene (DAT1, also known as the dopamine active transporter or SLC6A3) has a polymorphism involving a variable number tandem repeat (VNTR) of 40 base pairs in the 3′ untranslated region, of which the 9- and 10-repeat alleles are the most common in the popu-

lation.²⁴ Under well-rested (baseline) laboratory conditions, this polymorphism has been found to moderate the magnitude of the TOT effect on PVT performance.²⁵ DAT1 has also been implicated in homeostatic sleep–wake regulation^{26,27} and the mechanisms of action of the wake-promoting compound modafinil.^{26,28} Modafinil has been found to mitigate the effect of TSD on the TOT effect.²⁹ Taken together, these findings suggest that the VNTR polymorphism of DAT1 may be involved in a shared mechanism underlying the effects of TOT and sleep loss on performance.

- COMT: The catechol-*O*-methyltransferase gene (COMT) has a functional single-nucleotide polymorphism (SNP) involving a valine (Val) to methionine (Met) substitution at codon 158 (COMT Val158Met).³⁰ Under well-rested laboratory conditions, this polymorphism has been shown to moderate the magnitude of the TOT effect on PVT performance.²⁵ COMT has also been implicated in homeostatic sleep–wake regulation³¹ and the effect of the wake-promoting compound modafinil.^{31,32} Therefore, like the VNTR polymorphism of DAT1, the Val-158Met polymorphism of COMT may be involved in a shared mechanism underlying the effects of TOT and sleep loss on performance.
- TNF α : The tumor necrosis factor alpha gene (TNF α) has a functional SNP in the promoter region involving a guanine (G) to adenine (A) substitution at position 308 (TNF α G308A).³³ This polymorphism has been shown to moderate the magnitude of the effect of TSD on PVT performance.³⁴ TNF α has been implicated in local sleep,³⁵ which is also a hypothesized mechanism for the effect of the G308A polymorphism of TNF α on PVT performance during sleep deprivation.³⁴ If local sleep is involved in the TOT effect as well, then the G308A polymorphism of TNF α may be linked to a shared mechanism underlying the effects of TOT and sleep loss on performance.

For each of the 3 genes of interest, we investigated whether and how their respective polymorphisms affect PVT performance, with a particular focus on the interaction between the TOT effect and the effect of sleep deprivation.

We investigated this interaction in 2 complementary ways. First, we analyzed changes in RT across 1-min bins of the 10-min task duration of the PVT, as a function of time awake. See Figure 1 (left) for results from an earlier study³⁶ to illustrate this approach. Second, we analyzed differences in cumulative relative frequency distributions of the RTs¹⁴ in the first versus second 5 min on the PVT, comparing sleep deprivation against baseline. See Figure 1 (right) for an illustration of this procedure.

METHODS

Overview

We analyzed data from $N = 82$ subjects who each participated in 1 of 3 in-laboratory TSD studies. The 10-min PVT¹⁴ was administered every 2–5 h across 38 h of continuous wakefulness common to all 3 studies; see Figure 2. For each test bout, performance across TOT was quantified based on the raw RT data for every 1-min interval of the PVT (see Figure 1, left). Subjects were grouped by genotype for DAT1, COMT, and TNF α to investigate polymorphism-specific performance degradation due to the TOT effect, sleep deprivation, and their interaction.

Subjects

$N = 82$ healthy young adults (ages 27.0 ± 4.8 y; 43 females) participated in 1 of 3 laboratory studies conducted in the Sleep and Performance Research Center at Washington State University Spokane. The studies were approved by the Institutional Review Board (IRB) of Washington State University. Subjects gave written informed consent and were compensated for their time.

Subjects eligible for study participation met the following criteria: age 22–40 y; physically and psychologically healthy; no current medical or drug treatment (except contraceptives); no current or relevant history of psychiatric illness; no clinically significant irregularities in blood or urine; no sleep or circadian disorders; no history of moderate to severe brain injury; no history of learning disabilities; proficient in English; not a current smoker; free from traces of drugs and alcohol; no history of drug or alcohol abuse in the last year; no history of methamphetamine abuse; not pregnant; no past adverse reactions to sleep deprivation; no vision impairment, unless corrected to normal; no hearing impairment, unless corrected to normal (for studies 1 and 2 only); no travel across time zones 1 month prior to the study; no shift work 3 months prior to the study; habitual sleep duration between 6 h and 10 h per night; and usual wake times between 06:00 and 09:00. Study 3 included performance testing on a high-fidelity driving simulator and intravenous (IV) blood draws (from hours 12 to 36 during sleep deprivation). This required the following additional eligibility criteria: valid driver's license; not susceptible to simulator adaptation syndrome; suitable veins for IV insertion; no history of complications with blood draws or blood donations; and not having donated blood within 2 months of entering the study. Subjects' eligibility was confirmed with physical examination, history, blood and urine chemistry, breathalyzer, baseline polysomnography, and a battery of questionnaires.

For the 7 days prior to entering the laboratory, subjects were instructed to refrain from caffeine, alcohol, tobacco, and drug use. Subjects were also instructed to avoid napping, and to maintain their habitual sleep/wake times, which was verified by means of wrist actigraphy (studies 1 and 2: Actiwatch-2, Philips Respironics, Bend, OR; study 3: MicroMini Motionlogger, Ambulatory Monitoring, Ardsley, NY) and sleep diary, along with twice-daily phone calls to a time-stamped voice recorder to report bedtimes and wake-up times. Actigraph records were scored for sleep using computer software (studies 1 and 2: Actiware, Philips Respironics; study 3: Act Millennium, Ambulatory Monitoring), and average sleep duration across the 7 days was calculated as an index of habitual sleep duration. Due to equipment failure, actigraphy data were missing for 1 subject; for this individual, the sleep diary data were used to calculate sleep duration.

Prior to admission into the laboratory, subjects were confirmed to be free of traces of alcohol and drugs by means of breathalyzer test and urinalysis.

Subject demographics and genotypes (see below) are shown in the Supplementary Material (Table S1).

Experimental Design

Studies 1 and 2

These 2 studies were similar in design. In study 1, $n = 34$ healthy young adults (ages 27.7 ± 5.0 y; 14 females) lived in

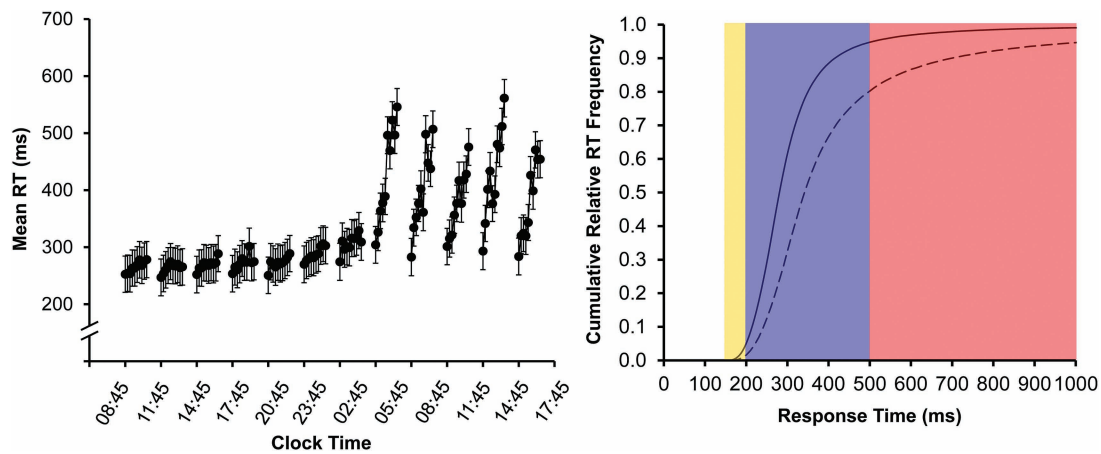


Figure 1—Illustration of analysis approaches. *Left*: mean RT ($\pm$ standard error) in 1-min bins for each of twelve 10-min PVTs administered at 3-h intervals across 38 h of total sleep deprivation in an earlier study (16 healthy subjects).³⁶ The graph shows the increase in mean RT across the 1-min bins in each test bout, with the rate of change increasing substantially with progressing time awake. Data are plotted against the start times of the PVT bouts; placement of the 1-min bins in each test bout is not to scale on the clock time axis. Graph modified from Grant et al.³⁶ with permission from Springer Science+Business Media. *Right*: cumulative relative RT frequency distributions, showing on the ordinate the number of responses (expressed relative to the grand total number of responses) that is equal to or faster than a given RT on the abscissa. The curves shown here represent cumulative relative RT frequency distributions in the first 5 min (solid curve) versus second 5 min (dashed curve) of the 10-min PVT under conditions of sleep deprivation (simulated based on the diffusion model for one-choice reaction-time tasks⁴³ using exaggerated parameter values for illustration purposes). The yellow-shaded area contains the fastest RTs, where the 2 curves begin to separate (notice they start at the same point on the RT axis in this illustration). The purple-shaded portion shows the heart of the cumulative relative frequency distributions, where the curves are separating progressively. Notice that the vertical separation is maximal at ~ 500 ms, which coincides with the cut-off traditionally used to define lapses of attention (ie, RTs ≥ 500 ms) on the PVT.¹⁴ The red-shaded area shows the slower RTs or lapse domain, where the curves begin to approach each other again (ultimately asymptoting on 1 if the abscissa were extended). PVT = psychomotor vigilance test; RT = response time.

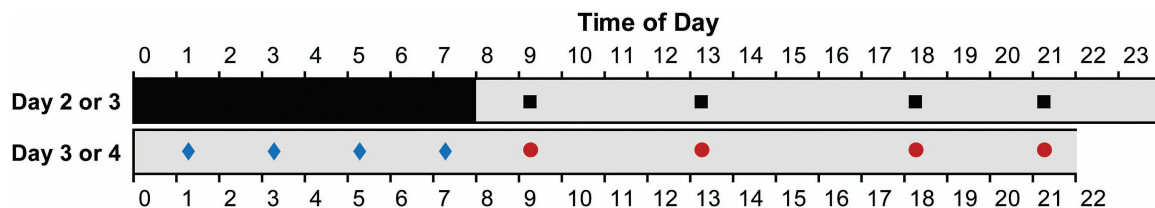


Figure 2—Simplified schematic of the laboratory study design. After 1 (studies 1 and 2) or 2 (study 3) baseline days with 10 h sleep opportunities (22:00–08:00), subjects were kept awake for at least 38 h under constant behavioral monitoring. The PVT was administered at 2–5 h intervals throughout scheduled wakefulness. Test bouts serving as baseline (hours 1–14 of wakefulness) are indicated with a black square; test bouts capturing nighttime sleep deprivation (hours 15–24 of wakefulness) are indicated with a blue diamond; and test bouts capturing daytime sleep deprivation (hours 25–38 of wakefulness) are indicated with a red circle. Gray denotes scheduled wakefulness, and black indicates a baseline sleep opportunity (starting at 22:00 on the preceding day). Subjects went to bed for recovery sleep at 22:00 on day 3 (studies 1 and 2) or were kept awake for an additional 24 h (study 3) (not shown). PVT = psychomotor vigilance test.

the laboratory for 4 days (3 nights). In study 2, $n = 36$ healthy young adults (ages 26.6 ± 4.8 y; 22 females) likewise lived in the laboratory for 4 days (3 nights). During both studies, subjects had a baseline day with a 10-h sleep opportunity (22:00–08:00), subsequently underwent 38 h of TSD, and then had a 10-h recovery sleep opportunity (22:00–08:00). During the 38 h of TSD, the PVT was administered 12 times at 2–5 h intervals (see Figure 2). Studies 1 and 2 have previously been described elsewhere.^{34,37}

Study 3

In study 3, $n = 12$ healthy young adults (ages 26.6 ± 4.4 y; 7 females) lived in the laboratory for 7 days (6 nights). Subjects had 2 baseline days, each with a 10-h sleep opportunity (22:00–08:00), subsequently underwent 62 h of TSD—of which only the first 38 h were used for analysis here—and then had 2 recovery days with 10-h sleep opportunities (22:00–08:00). During the first 38 h of TSD, the PVT was administered 12 times at 2–5 h intervals (see Figure 2). Study 3 has previously been described elsewhere.³⁸

For each of the 3 studies, the laboratory conditions were strictly controlled. Light levels were fixed below 100 lux during scheduled wakefulness and lights were off during scheduled sleep periods. The ambient temperature was maintained at 21°C ($\pm 1^\circ\text{C}$). Subjects were not allowed to engage in strenuous physical activity while in the laboratory. They did not have contact with individuals outside the laboratory, and did not have access to live television or radio, phones, personal computers, internet, or video games. Subjects participated in groups of up to 4 and were each assigned their own room for performance testing and for baseline and recovery sleep. Trained research assistants monitored subjects' behavior around the clock.

Genotyping

A venous whole blood sample was collected from each subject during a prestudy screening session. Blood was collected in Vacutainer tubes coated with ethylenediaminetetraacetic dipotassium dihydrate (K_2EDTA). Samples were immediately aliquoted and stored at -80°C until analysis.

The whole blood samples were red-cell depleted and genomic DNA (gDNA) was extracted. The DNA samples were assayed for the VNTR of the DAT1 gene (rs28363170, chromosome 5) and the SNPs COMT Val158Met (rs4680, chromosome 22) and TNF α G308A (rs1800629, chromosome 6).

DAT1 genotyping was performed using standard polymerase chain reaction (PCR) procedures described in the literature.³⁹ Samples were amplified with 20 μM of forward primer 5'-TGTGGTGTAGGGAACGGCCTGAG-3' and 20 μM of reverse primer 5'-CTTCCTGGAGGTCACGGCTCAAGG-3'. PCR procedures were carried out in a final reaction volume of 20 μl containing the following: 10 μl of Go-Taq Hot Start Green Master Mix (Promega, Madison, WI), 1 μl of each primer (forward and reverse), 6 μl of nuclease-free water, and 2 μl of gDNA. PCR conditions involved initial denaturation at 94°C for 3 min, followed by 39 cycles of: denaturation at 94°C for 45 s, annealing at 69°C for 30 s, and extension at 72°C for 30 s. Final extension was at 72°C for 5 min. Amplified products were electrophoresed on a 3% agarose gel stained with ethidium bromide and visualized under UV light. DAT1 fragment sizes for 8-, 9-, 10-, and 11-repeats were 360 bp, 400 bp, 440 bp, and 480 bp, respectively.³⁹

Three subjects were not included in the overall analysis of DAT1 due to the rarity of their genotypes in the general population (8/8 for 1 subject and 10/11 for 2 subjects), leaving 79 subjects for DAT1 statistical analyses. Seven homozygous and 27 heterozygous subjects carrying the 9-repeat allele were grouped together and labeled as 9R.

COMT genotyping was performed using the Taqman Drug Metabolism Assay (Assay ID: C__25746809_50; ThermoFisher Scientific, Waltham, MA). Real-time PCR was carried out per the manufacturer protocol using VIC/FAM context sequence CCAGCGGATGGTGGATTTCGCTGGC[A/G] GAAGGACAAGGTGTGCATGCCTGA. Wet DNA was used, and reactions were carried out on a 96-well plate with a final reaction volume of 25 μl . All samples were assayed in duplicate, and a no-DNA negative control was included. Allelic discrimination analysis was performed using MJ Opticon

Monitor Analysis Software v3.1 (Bio-Rad Laboratories, Hercules, CA).

TNF α 308 genotyping was performed using standard PCR and restriction enzyme digestion procedures described in the literature,⁴⁰ and as described in detail previously.³⁴

A χ^2 goodness-of-fit test was used to test for deviations from Hardy-Weinberg equilibrium in the subject sample for each of the 3 genes examined. Furthermore, Fisher's exact testing was used to determine if any of the genotypes were associated with one another. One-way analysis of variance (ANOVA) was used to test for differences in age between genotypes, and logistic regression was used to test for differences in gender and race/ethnicity between genotypes.

Performance Testing

The 10-min PVT was administered on a desktop computer. Subjects were presented with a visual stimulus in the form of a millisecond counter. The stimulus was presented at random intervals between 2 and 10 s. Subjects were instructed to respond to the stimulus as quickly as possible, without making false starts, by pressing a button on a response box.

The raw RT data recorded during the 12 test bouts across the 38-h TSD period (see Figure 2) were used to assess the TOT effect. For each 10-min test bout of each individual subject, the RT data were grouped into ten 1-min bins. On average, the number of RTs per bin was 9.3 (see Table S2 in the Supplemental Material for descriptive statistics by bin). False starts, including RTs <100 ms, were not included.

Additionally, cumulative relative RT frequency distributions (see Figure 1, right) were constructed from the combined data in the first five 1-min bins (first half of task duration) and from the combined data in the second five 1-min bins (second half of task duration). This was done separately for baseline test bouts (bouts 1–4) and daytime sleep deprivation bouts (bouts 9–12), so as to be able to compare the TOT effect (first versus second half of task duration) between well-rested and sleep-deprived states while controlling for time of day (see Figure 2). To construct the cumulative relative RT frequency distributions, the RT data sets were aggregated across test bouts and pooled over subjects by genotype, and then divided into 28 logarithmically sized RT bins. (To obtain RT counts of the same order of magnitude across RT bins, the bins were bounded by [in ms]: 175, 188, 203, 222, 246, 277, 315, 363, 424, 500, 597, 718, 871, 1063, 1304, 1609, 1992, 2475, 3082, 3847, 4809, 6021, 7547, 9468, 11886, 14931, 18763, 23588, 30000. Here, RTs <175 ms [which were rare, constituting less than 0.5% of the data set] were counted as false starts and were not included.)

For 7 of the 82 subjects, 1 or 2 PVT bouts were potentially confounded by a microsleep event, a distraction, or failure to put effort into the task, as documented by our trained research assistants during the experiments. These test bouts were removed from the data set, leaving a total of 974 test bouts comprising 90494 RTs (98.9% of the original total) for analysis.

Statistical Analyses

For each of the 12 PVT test bouts of each individual subject, the RTs were grouped into 1-min bins across the 10-min

task duration. The raw RTs thus binned were analyzed using a mixed-effects ANOVA with fixed effects of time awake (test bouts 1–12), TOT (1-min bins 1–10), genotype, and their interactions, controlling for study and with a random effect over subject on the intercept. The analysis was carried out separately for DAT1 (9R, 10/10), COMT (Met/Met, Val/Met, Val/Val), and TNF α (A/G, G/G). The primary effect of interest was the interaction between time awake, TOT, and genotype. For graphical representation, test bouts were also divided into 3 phases of the 38-h TSD period (see Figure 2): baseline (bouts 1–4), nighttime sleep deprivation (bouts 5–8), and daytime sleep deprivation (bouts 9–12). Secondary analyses repeated the mixed-effects ANOVA controlling for age, gender, race/ethnicity, and habitual sleep duration, in addition to study.

The cumulative relative frequency distributions of the PVT RTs were analyzed using a mixed-effects ANOVA with fixed effects of RT bin (1–28) alone and in interaction with TOT (first, second half of task duration) and genotype and their interaction. This analysis was controlled for study, included a random effect over subjects on the intercept (with a Toeplitz covariance structure to account for autocorrelation in the cumulative frequency data), and was weighted by total number of RTs contributed by each subject. The analysis was carried out separately for baseline (aggregated over PVT bouts 1–4; hours 1–14 of wakefulness) and daytime sleep deprivation 24 h later (aggregated over bouts 9–12; hours 25–38 of wakefulness).

RESULTS

Table 1 shows the genotype counts and frequencies for our sample. The relative allele frequencies were as follows: DAT1, 9-repeat allele 0.26, 10-repeat allele 0.74; COMT, Met allele

0.49, Val allele 0.51; TNF α , A allele 0.15, G allele 0.85. The allele frequencies were found to be in Hardy–Weinberg equilibrium for each gene (DAT1: $\chi^2_1 = 0.97$, $p = .33$; COMT: $\chi^2_1 = 2.19$, $p = .14$; TNF α : $\chi^2_1 = 2.41$, $p = .12$). Our observed genotype frequencies were comparable to those in the published literature.^{41,42} Fisher's exact tests showed that in our sample, the DAT1, COMT, and TNF α genotypes did not co-segregate. DAT1 was not significantly associated with COMT ($p = .18$) or TNF α ($p = .81$). COMT and TNF α were also not significantly associated ($p = .54$).

Subjects' habitual sleep duration, as estimated by the average sleep duration assessed using wrist actigraphy in the week before the experiment, was 7.3 ± 0.8 h. Habitual sleep duration did not differ by genotype for any of the 3 genes considered here (see Table S3 in the Supplemental Material).

Figure 3 shows TOT performance data from each of the 12 PVT test bouts across 38 h of continuous wakefulness for the different genotypes of DAT1, COMT, and TNF α . The full set of statistical results from each mixed-effects ANOVA is reported in the Supplemental Material (Table S3). Each of the graphs in Figure 3 shows the well-established effects of time awake ($F > 223$, $p < .001$), TOT ($F > 54$, $p < .001$), and their interaction ($F \geq 4.9$, $p < .001$) on RT for each of the genotypes. Furthermore, the data replicated previously observed interactions of time awake with genotype^{27,32,34} ($F \geq 9.2$, $p < .001$); see the Supplementary Material (Figure S1) for graphs depicting this interaction independent of TOT.

In what follows, we focus on our novel findings pertaining to the interaction between TSD, TOT, and genotype. For comparison, results from a well-rested control group are shown in the Supplementary Material (Figure S2).

For DAT1 (Figure 3, top), performance diverged across TOT between the 9R and 10/10 genotypes as TSD progressed,

Table 1—Genotype counts and frequencies for each gene.

	Genotype Count		Genotype Frequency		
	Observed	Expected ^a	Observed	Expected ^a	Published ^b
DAT1					
9/9 ^c	7	5.32	0.09	0.07	0.06
9/10 ^c	27	30.36	0.34	0.38	0.37
10/10	45	43.32	0.57	0.55	0.56
COMT					
Met/Met	17	19.51	0.21	0.24	0.33
Val/Met	46	40.98	0.56	0.50	0.46
Val/Val	19	21.51	0.23	0.26	0.22
TNF α					
A/A	0	1.76	0.00	0.02	0.04
A/G	24	20.49	0.29	0.25	0.26
G/G	58	59.76	0.71	0.73	0.69

^aCalculated based on Hardy–Weinberg equilibrium.

^bDAT1 and COMT: Valomon et al.,³⁹ 115 healthy subjects; TNF α : Almpandou et al.,⁴⁰ 318 healthy subjects.

^cThe 9-repeat homozygous and heterozygous individuals were combined for analysis purposes as 9R.

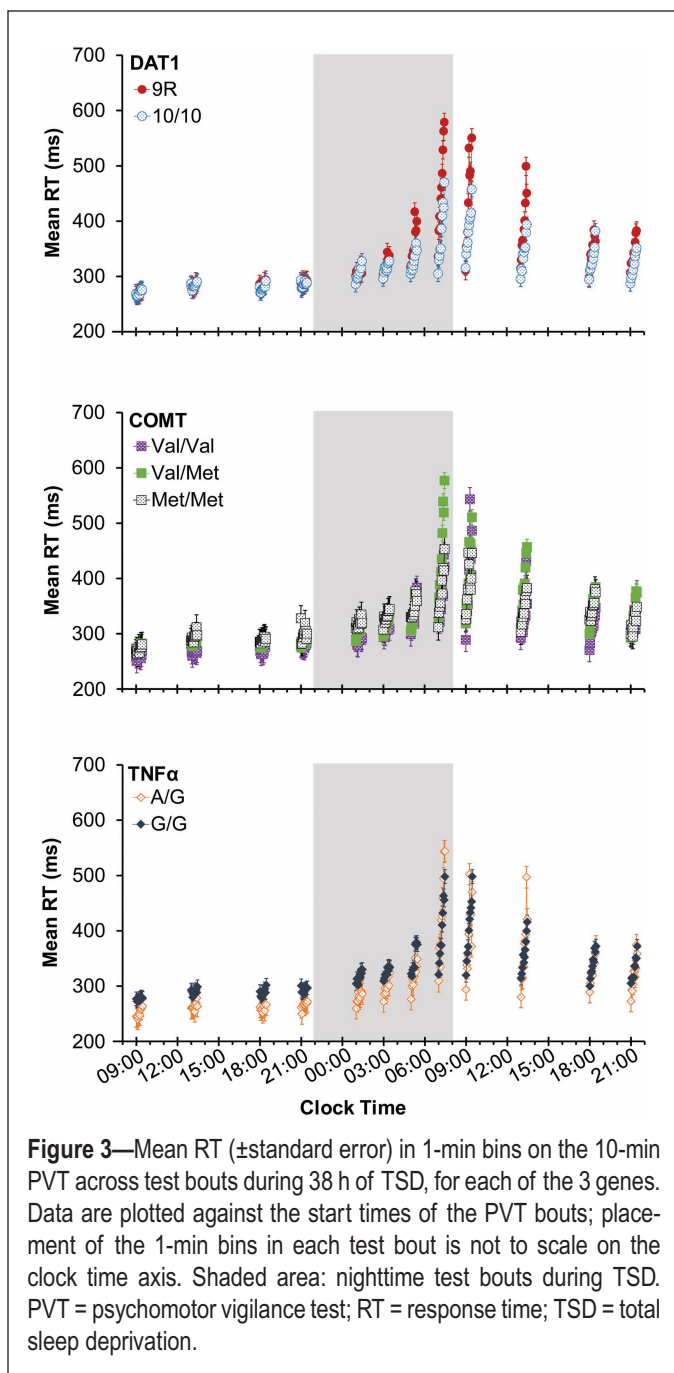


Figure 3—Mean RT ($\pm$ standard error) in 1-min bins on the 10-min PVT across test bouts during 38 h of TSD, for each of the 3 genes. Data are plotted against the start times of the PVT bouts; placement of the 1-min bins in each test bout is not to scale on the clock time axis. Shaded area: nighttime test bouts during TSD. PVT = psychomotor vigilance test; RT = response time; TSD = total sleep deprivation.

especially during the early and late morning hours. There was a significant interaction between time awake, TOT, and DAT1 genotype ($F_{99,87000} = 1.35, p = .011$), which captured 23.2% of the overall variance explained by DAT1 genotype. Subjects homozygous for the 10-repeat allele showed a substantially reduced TOT effect during TSD compared to subjects homozygous or heterozygous for the 9-repeat allele. Subjects in the well-rested control group did not show any performance impairment or any differences by DAT1 genotype (see Supplementary Material, Figure S2). This confirms that the divergence across TOT between genotypes in Figure 3 (top) was due to the interaction with TSD.

For COMT and TNF α (Figure 3, middle and bottom, respectively), there was no divergence across TOT by genotype as TSD

progressed. There was no significant interaction between time awake, TOT, and COMT genotype ($F_{198,90000} = 1.13, p = .10$). There was a trend for the interaction between time awake, TOT, and TNF α genotype ($F_{99,90000} = 1.21, p = .080$). However, both TNF α genotypes (A/G and G/G) showed similar TOT effects across the entire 38-h TSD period, but the G/G subjects tended to have slower RTs (Figure 3, bottom). Subjects in the well-rested control group did not show any performance impairment or any differences by COMT or TNF α genotype (see Supplemental Material, Figure S2).

To further clarify the results regarding TOT, Figure 4 shows the build-up of PVT performance impairment across TOT for DAT1, COMT, and TNF α , collapsed across test bouts for well-rested baseline (left), nighttime TSD (middle), and daytime TSD (right). For DAT1 (Figure 4, top), performance across TOT was nearly identical for the 9R and 10/10 genotypes at baseline. However, in line with the significant interaction between time awake, TOT, and DAT1 genotype discussed above, clear differences in the rate of change across TOT appeared during TSD. Subjects homozygous for the 10-repeat allele showed less performance impairment build-up over the 10-min PVT than the 9-repeat allele carriers.

Consistent with the absence of a 3-way interaction for COMT and TNF α (see above), no such clear picture emerged for these 2 genes. For COMT (Figure 4, middle), subjects homozygous for the Val allele exhibited overall faster RTs, especially at baseline. Likewise, for TNF α (Figure 4, bottom), carriers of the A allele had overall faster RTs, especially at baseline. For both genes, TSD increased the rate of change across TOT; however, there were no pronounced differences in the rate of impairment build-up between genotypes. This shows that divergence across TOT between genotypes in interaction with time awake was a property specific to DAT1.

There were no significant differences between DAT1, COMT, and TNF α genotypes based on age, gender, race/ethnicity, and habitual sleep duration (see Supplemental Material, Table S3). All significant effects described above held true in secondary analyses controlling for age, gender, race/ethnicity, and habitual sleep duration.

Figure 5 shows the cumulative relative RT frequency distributions for PVT test bouts performed during well-rested baseline and during daytime TSD (at the same times of day). Each panel depicts the relative RT frequency distributions during the first 5 min versus the second 5 min of the PVT. During TSD (Figure 5, right), as compared to baseline (Figure 5, left), the distributions displayed the expected skewing to the right that is characteristic of sleep loss.¹⁴ Furthermore, during baseline—and especially during TSD—the distributions showed the expected skewing to the right from the first 5 min (solid curves) to the second 5 min (dashed curves) of the PVT, congruent with the previously reported increase in performance variability across TOT¹¹ (cf. illustration in Figure 1, right). However, the patterns of change were not the same for the 3 genes considered. The full set of statistical results pertaining to the cumulative relative RT frequency distributions is reported in the Supplemental Material (Table S3); here, we only describe the effects involving interactions with genotype.

For DAT1, the 2 genotypes had similar RT distributions during well-rested baseline (Figure 5, top left), with no significant

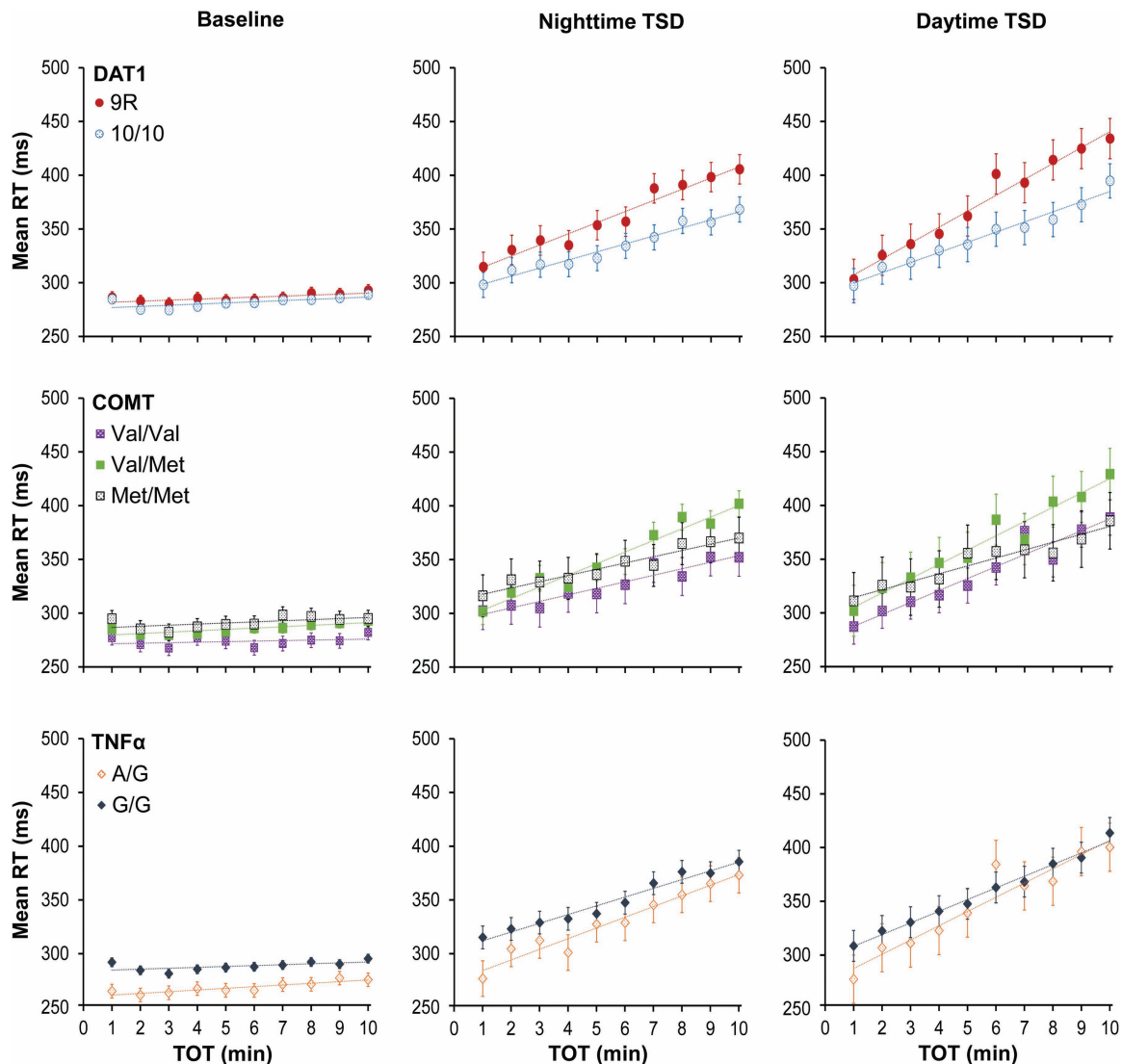


Figure 4—Mean RT ($\pm$ standard error) in 1-min bins on the 10-min PVT, collapsed over intervals of time awake, for each of the 3 genes. Left panels correspond to the baseline period (09:00–21:59; from 1 up to 14 h wakefulness); middle panels correspond to the nighttime TSD period (23:00–07:59; from 15 up to 23 h wakefulness); right panels correspond to the daytime TSD period (09:00–21:59; from 25 up to 38 h wakefulness). Trend lines are included to depict the general rate of change in RTs across the 10-min PVT. PVT = psychomotor vigilance test; RT = response time; TOT = time-on-task; TSD = total sleep deprivation.

genotype interactions. During TSD, however, the distribution curves for the DAT1 genotypes diverged (Figure 5, top right). There was a significant interaction of RT bin by genotype ($F_{28,4235} = 1.61, p = .022$). The RT distributions diverged in the lapse domain (Figure 5, top right, red-shaded area). In the 9R group, longer RTs occurred more frequently during the second 5 min (dashed red line) than during the first 5 min (solid red line), whereas this was not seen in the 10/10 group (dashed versus solid blue line). This is consistent with the results of Figure 3 (top) and Figure 4 (top) indicating that subjects homozygous for the 10-repeat allele exhibited a significantly reduced TOT effect during TSD compared to subjects homozygous or heterozygous for the 9-repeat allele. Figure 5 (top right) elucidates that this group difference was due to relatively greater skewing of the RT distribution due to interaction of TSD with the TOT effect in the subjects homozygous or heterozygous for the 9-repeat allele of DAT1.

For COMT and TNF α , in contrast to DAT1, a significant genotype difference in the cumulative relative RT frequency distribution was already apparent during well-rested baseline. For COMT (Figure 5, middle left), there was a significant interaction of RT bin by genotype ($F_{56,4345} = 2.24, p < .001$). For TNF α (Figure 5, bottom left), there was also a significant interaction of RT bin by genotype ($F_{28,4400} = 15.76, p < .001$). Subjects homozygous for the Val allele of the Val158Met polymorphism of COMT, and especially subjects carrying the A allele of the G308A polymorphism of TNF α , produced fast RTs more frequently at baseline.

TSD further amplified these genotype differences for COMT and TNF α . For COMT (Figure 5, middle right), there was again a significant interaction of RT bin by genotype ($F_{56,4345} = 1.73, p = .001$). For TNF α (Figure 5, bottom right), there was also again a significant interaction of RT bin by genotype ($F_{28,4400} = 3.37, p$

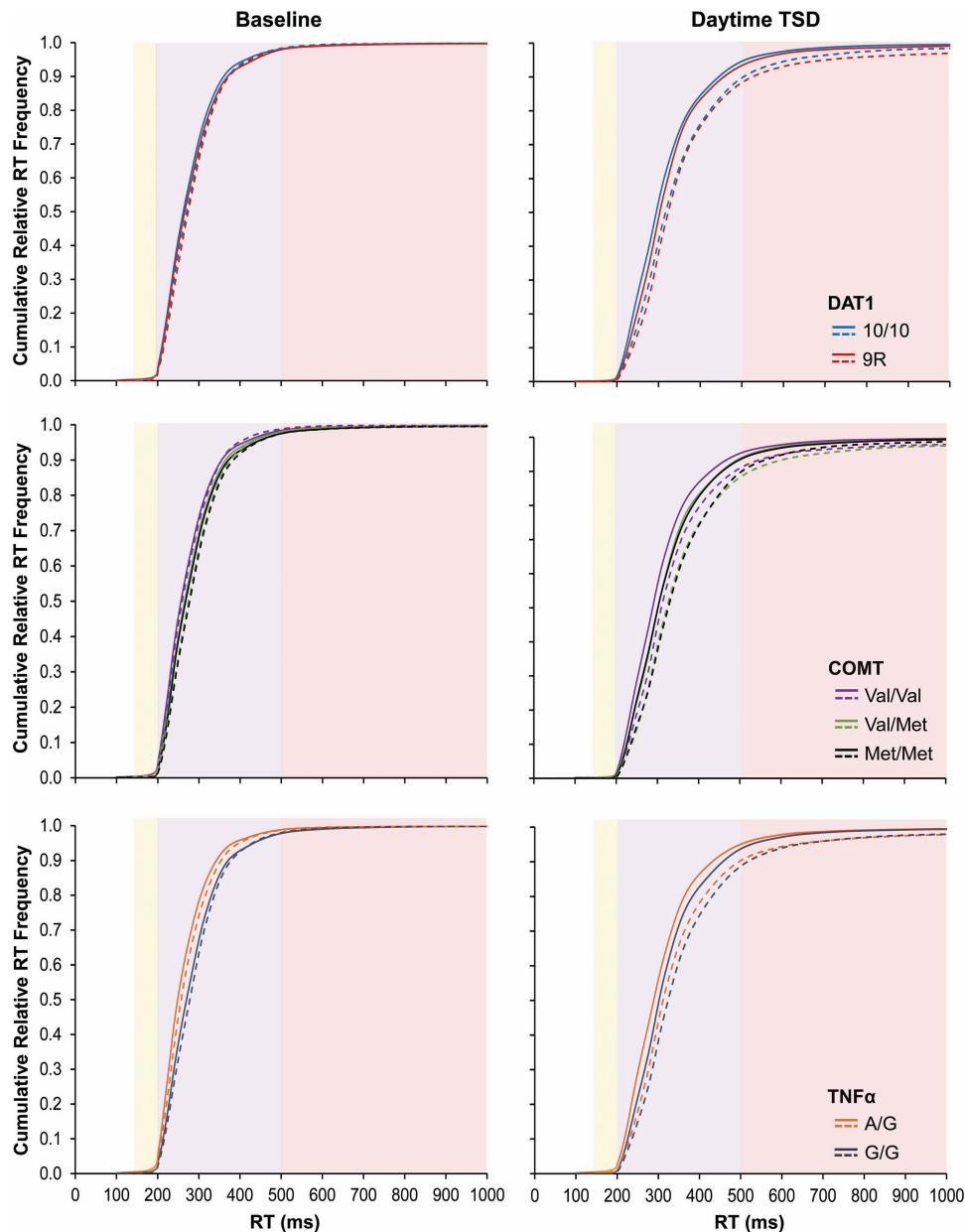


Figure 5—Cumulative relative RT frequency distributions for each gene during the baseline period (left panels) and the daytime TSD period (right panels). Solid curves correspond to performance during the first 5 min (1–5) of the 10-min PVT; dashed curves correspond to performance during the second 5 min (6–10) of the 10-min PVT. The yellow-shaded area contains the fastest RTs; the purple-shaded area shows the heart of the cumulative relative frequency distributions; and the red-shaded area shows the slower RTs or lapse domain (cf. Figure 1, right). PVT = psychomotor vigilance test; RT = response time; TSD = total sleep deprivation.

< .001). After TSD, as during baseline, subjects homozygous for the COMT Val allele and carriers of the TNFα A allele produced fast RTs more often relative to the other COMT and TNFα genotypes, during both the first 5 min and the second 5 min of the PVT. In contrast to DAT1, the differences between the COMT and TNFα genotypes were most prominent in the heart of the RT distribution (Figure 5, middle and bottom right, purple-shaded area) and vanished in the lapse domain. This is consistent with the lack of significant interactions between TSD, TOT, and COMT or TNFα genotype in Figure 3 (middle and bottom, respectively) and Figure 4 (middle and bottom, respectively).

DISCUSSION

In this study, we observed systematic interaction of the TOT effect with TSD. Matching earlier findings,^{12,13,15–17} both TOT and TSD increased RT mean and RT variability on the PVT; moreover, TSD amplified the changes across TOT. The similarities of the TOT and TSD effects on PVT performance, as well as their interplay, suggest that there may be shared underlying mechanisms.^{15,17} To examine this possibility, we investigated 3 genetic polymorphisms, selected *a priori* because of previously documented associations with TOT or TSD^{25,34}: DAT1 (VNTR), COMT (Val158Met), and TNFα (G308A). For all 3 genes, we

observed effects of polymorphisms on the RT distribution, especially during TSD (Figure 5). However, only DAT1 genotype affected the interaction between TOT and TSD (Figures 3 and 4). Specifically, compared to carriers of the DAT1 9-repeat allele, subjects homozygous for the 10-repeat allele were relatively protected against TOT-induced performance deficits during TSD.

In line with our findings, Holst and colleagues²⁷ recently reported that the DAT1 10-repeat allele confers resilience to PVT performance impairment across 40 h of TSD. They did not report DAT1 genotype modulation of the interaction between TSD and TOT. To investigate the TOT effect, however, they divided the task duration into quintiles and characterized each quintile by the number of responses in the lapse domain or by the variability in RTs. This approach yields considerably less statistical power than using the individual RTs in 1-min bins, and may have obscured a TSD by TOT by DAT1 genotype interaction in their study. In contrast, Lim and colleagues²⁵ found that subjects homozygous for the 10-repeat allele of DAT1 and subjects homozygous for the Val allele of COMT Val158Met are relatively resilient to the decline of performance across TOT on a 20-min PVT under well-rested baseline conditions. These results are consistent with our findings, in that increasing the task duration from 10 to 20 min would be expected to enhance the TOT effect similar to what TSD did in our study. Thus, the present study extends and integrates the work of Holst and colleagues²⁷ and that of Lim and colleagues.²⁵

Whereas COMT and TNF α were associated with genotype differences in the heart of the RT distribution (Figure 5, middle and bottom right, purple-shaded area), DAT1 was associated with genotype differences in the lapse domain of the RT distribution (Figure 5, top right, red-shaded area). This distinction may be interpreted by means of a cognitive model called the diffusion model of one-choice reaction-time tests,⁴³ which abstractly describes performance on the PVT as a one-boundary diffusion process symbolizing the accumulation of stimulus information (evidence) until a decision criterion is reached and a response is initiated. The rate of evidence accumulation is represented by a drift ratio parameter, while the decision criterion is represented by a boundary separation parameter. Differences in the boundary separation parameter impact the heart of the RT distribution, and differences in the drift ratio parameter impact the lapse domain of the RT distribution (see Supplemental Material, Figure S3).

In the context of our study, this cognitive modeling perspective implies that the COMT and TNF α polymorphisms may be associated with differences in the propensity to respond earliest after the detection of a stimulus.⁴⁴ This suggests that even though subjects were instructed to respond to PVT stimuli as quickly as possible, without making false starts, there may have been systematic differences among them in the level of effective cognitive control. In line with this interpretation is the observation that the COMT and TNF α genotypes influenced the RT distribution both at baseline and after TSD (Figure 5, middle and bottom). Also in line with this interpretation is that TNF α G308A has been linked with cognitive control⁴⁵; and, more indirectly, that COMT activity is localized predominantly in the prefrontal cortex,⁴⁶ which has been linked with cognitive control as well.⁴⁷

The DAT1 polymorphism, on the other hand, appears to be associated with a differential rate of evidence accumulation (Figure 5, top; cf. Supplemental Material, Figure S3, left). The rate of evidence accumulation during PVT performance is a strong correlate of the fidelity of information processing.³⁷ Both the rate of evidence accumulation and the fidelity of information processing on the PVT have been shown to be affected substantially by TSD.^{37,43} Our finding that DAT1 genotype affected the interaction between TOT and TSD (Figures 3 and 4)—and may thus be involved in shared mechanisms underlying both TSD and TOT—leads to 2 central hypotheses: (1) the TOT effect, like TSD, involves degradation of the fidelity of information processing; and (2) the degree to which TSD, TOT, and their interaction degrade the fidelity of information processing is modulated by dopaminergic mechanisms.

These hypotheses are compatible with results from studies of sleep deprivation and striatal dopamine.^{48,49} DAT1, the dopamine transporter 1, is highly localized to the striatum, where it regulates dopamine levels via reuptake from the synaptic cleft to the presynaptic terminal.⁵⁰ Neuroimaging studies have shown that sleep deprivation does not change synaptic dopamine or dopamine transporter expression within the striatum over time.⁴⁸ However, the DAT1 VNTR polymorphism modulates the expression of the transporter between subjects, and although the literature is mixed on whether the 9- and 10-repeat alleles increase or decrease the transporter's expression, a meta-analysis concluded that the 9-repeat allele increases it.⁵¹ The implication is that subjects homozygous for the DAT1 10-repeat allele are expected to have increased synaptic dopamine levels in the striatum compared to carriers of the 9-repeat allele. DAT1 knock-out studies in rodents²⁸ and pharmacologic blocking studies in humans⁵² have shown that increased synaptic dopamine levels promote wakefulness. A recent neuroimaging study found that DAT1 genotype modulates neural responses during sleep loss and alters cognitive functioning.⁵³ Taken together, the literature suggests that increased dopamine availability in the striatum may be causally related to the relatively improved PVT performance in subjects homozygous for the DAT1 10-repeat allele, as compared to carriers of the 9-repeat allele, during TSD and across TOT.

In the striatum, dopamine D₂ receptors are co-localized and functionally interact with adenosine A_{2A} receptors (ADORA2A).⁵⁴ Adenosine has been implicated in mediating the effects of sleep deprivation,⁵⁵ and has been hypothesized to be involved in the effects of TOT as well.¹⁹ Activation of the A_{2A} receptor modulates dopaminergic neurotransmission in an antagonistic manner.⁵⁴ As such, increased dopamine levels in subjects homozygous for the DAT1 10-repeat allele could potentially provide relative resilience to the interacting effects of TSD and TOT on performance simply by counteracting the antagonistic effect of adenosine. This would suggest that a striatal adenosinergic/dopaminergic mechanism underlies the cognitive impact of TSD interacting with TOT. A previously reported effect of polymorphisms of the ADORA2A gene on psychomotor vigilance performance during sleep loss⁵⁶ is congruent with this idea.

It should be noted that the subject sample of our study consisted only of young adult women and men (ages 22–40) with limited racial and ethnic diversity. We do not know to what extent

our results may generalize to other populations. Additionally, we note that our sample size was modest, which is of concern when effect sizes are small (as if often the case in studies of cognition⁵⁷). However, the effects of time awake and time-on-task, alone and in interaction, on PVT performance produce robust phenotypes (see [Figures 3 and 4](#)). DAT1 is therefore a promising candidate biomarker of resilience to psychomotor vigilance performance impairment due to TSD, TOT, and their interaction.

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SUPPLEMENTARY MATERIAL

Supplementary data are available at *SLEEP* online.

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Address correspondence to: Hans P.A. Van Dongen, PhD, Director, Sleep and Performance Research Center, Washington State University Spokane, PO Box 1495, Spokane, WA 99210-1495. Telephone: +1-509-358-7755; Fax: +1-509-358-7810;

Email: hvd@wsu.edu

ALL WORK CONDUCTED AT

Sleep and Performance Research Center, Washington State University Spokane, PO Box 1495, Spokane, WA, 99210-1495

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Supplemental Material

**Time-on-Task Effect during Sleep Deprivation in Healthy Young Adults Is Modulated by
Dopamine Transporter Genotype**

Brieann C. Satterfield, PhD^{a,b}, Jonathan P. Wisor, PhD^a, Michelle A. Schmidt, MS^a,
Hans P.A. Van Dongen, PhD^a

^a Sleep and Performance Research Center and Elson S. Floyd College of Medicine, Washington
State University, Spokane, WA, USA

^b Currently at the Department of Psychiatry, College of Medicine, University of Arizona,
Tucson, AZ, USA

Table S1. Subject demographics and genotypes for the three studies used for analysis. Subjects in a well-rested control group (used only in the supplemental material, Fig. S1) are indicated in parentheses. The TNF α 308 assay failed for 1 control subject, leaving 57 subjects for analysis. Note that DAT1 8/8 and 10/11 genotypes are included here for representation of our sample; these genotypes were excluded from analysis. SD: standard deviation.

	Study 1 <i>n</i> =34 (<i>n</i> =15)	Study 2 <i>n</i> =36 (<i>n</i> =30)	Study 3 <i>n</i> =12 (<i>n</i> =13)	Total <i>N</i> =82 (<i>N</i> =58)
Sex				
Female	14 (9)	22 (12)	7 (3)	43 (24)
Male	20 (6)	14 (18)	5 (10)	39 (34)
Age (mean $\pm$ SD)	27.7 $\pm$ 5.0 (26.3 $\pm$ 4.3)	26.6 $\pm$ 4.8 (26.4 $\pm$ 4.9)	26.6 $\pm$ 4.4 (25.2 $\pm$ 3.8)	27.0 $\pm$ 4.8 (26.1 $\pm$ 4.5)
Race/Ethnicity				
Caucasian	30 (14)	33 (30)	7 (10)	70 (53)
Hispanic	0 (0)	1 (0)	1 (0)	2 (0)
African-American	1 (0)	0 (0)	0 (0)	1 (0)
Asian	0 (0)	0 (0)	1 (0)	1 (0)
American Indian	0 (0)	0 (0)	0 (1)	0 (1)
Pacific Islander	0 (0)	0 (0)	0 (1)	0 (1)
Mixed	1 (1)	2 (0)	3 (1)	6 (2)
Undisclosed	2 (0)	0 (0)	0 (0)	2 (0)
DAT1				
8/8	1 (1)	0 (0)	0 (0)	1 (1)
9/9	4 (0)	2 (3)	1 (1)	7 (4)
9/10	10 (4)	14 (12)	3 (2)	27 (18)
10/10	19 (10)	18 (15)	8 (10)	45 (35)
10/11	0 (0)	2 (0)	0 (0)	2 (0)
COMT				
Met/Met	9 (3)	7 (11)	1 (2)	17 (16)
Val/Met	19 (9)	21 (12)	6 (8)	46 (29)
Val/Val	6 (3)	8 (7)	5 (3)	19 (13)
TNFα				
A/A	0 (0)	0 (0)	0 (0)	0 (0)
A/G	8 (5)	14 (7)	2 (3)	24 (15)
G/G	26 (10)	22 (22)	10 (10)	58 (42)

Table S2. Descriptive statistics for number of responses in each 1 min bin of the 10 min PVT.

SD: standard deviation.

Bin	Minimum	Median	Maximum	Mean	SD
1	6	9	13	9.08	1.19
2	7	9	14	9.43	1.19
3	6	9	13	9.32	1.14
4	6	9	14	9.42	1.26
5	6	9	13	9.31	1.20
6	5	9	14	9.33	1.19
7	6	9	13	9.29	1.22
8	6	9	14	9.31	1.21
9	4	9	14	9.24	1.17
10	6	9	13	9.28	1.14

Table S3. Summary of statistical results for the TSD group discussed in the main text. Bold indicates statistical significance ($P < 0.05$). df: degrees of freedom; RT: response time; TOT: time on task; TSD: total sleep deprivation.

	DAT1			COMT			TNF α		
Genotype Analyses	χ^2 / F	df	P	χ^2 / F	df	P	χ^2 / F	df	P
Gender	<0.01	1	0.97	1.15	2	0.56	0.59	1	0.44
Race/Ethnicity	2.01	1	0.16	1.59	2	0.45	2.22	1	0.14
Age (<i>F</i> test)	<0.01	1, 77	0.95	1.43	2, 79	0.25	0.81	1, 80	0.37
Sleep Duration (<i>F</i> test)	0.10	1, 77	0.75	0.29	2, 79	0.75	0.14	1, 80	0.71
Time-on-Task Analyses	<i>F</i>	df	P	<i>F</i>	df	P	<i>F</i>	df	P
Time Awake (bout)	321.66	11, 86772	<0.001	223.02	11, 90055	<0.001	296.57	11, 90174	<0.001
TOT (bin)	81.01	9, 86772	<0.001	54.59	9, 90055	<0.001	75.33	9, 90174	<0.001
Genotype	3.18	1, 86772	0.075	1.04	2, 90055	0.352	1.52	1, 90174	0.217
Time Awake x TOT	7.56	99, 86772	<0.001	4.9	99, 90055	<0.001	7.01	99, 90174	<0.001
Time Awake x Genotype	21.9	11, 86772	<0.001	9.2	22, 90055	<0.001	9.20	11, 90174	<0.001
TOT x Genotype	3.07	9, 86772	0.001	2.93	18, 90055	<0.001	2.16	9, 90174	0.022
Time Awake x TOT x Genotype	1.35	99, 86772	0.011	1.13	198, 90055	0.103	1.21	99, 90174	0.08
Study	2.86	2, 86772	0.057	2.09	2, 90055	0.124	2.55	2, 90174	0.078
RT Distribution Analyses	<i>F</i>	df	P	<i>F</i>	df	P	<i>F</i>	df	P
<i>Baseline</i>									
RT bin	4353.28	27, 4235	<0.001	3664.3 ₃	27, 4345	<0.001	3869.53	27, 4400	<0.001
RT bin x 5 min block	2.95	28, 4235	<0.001	2.02	28, 4235	0.001	3.02	28, 4400	<0.001
RT bin x Genotype	0.54	28, 4235	0.976	2.24	56, 4235	<0.001	15.76	28, 4400	<0.001
RT bin x 5 min block x Genotype	0.05	28, 4235	>0.999	0.17	56, 4345	>0.999	0.09	28, 4400	>0.999
Study	0.68	2, 4235	0.508	1.36	2, 4345	0.258	0.42	2, 4400	0.655
<i>Daytime TSD</i>									
RT bin	4804.49	27, 4235	<0.001	4134	27, 4345	<0.001	4213.75	27, 4400	<0.001
RT bin x 5 min block	17.99	28, 4235	<0.001	16.17	28, 4345	<0.001	17.72	28, 4400	<0.001
RT bin x Genotype	1.6	28, 4235	0.022	1.73	56, 4345	0.001	3.37	28, 4400	<0.001
RT bin x 5 min block x Genotype	0.15	28, 4235	>0.999	0.11	56, 4345	>0.999	0.34	28, 4400	>0.999
Study	1.58	2, 4235	0.206	1.07	2, 4345	0.344	1.51	2, 4400	0.222

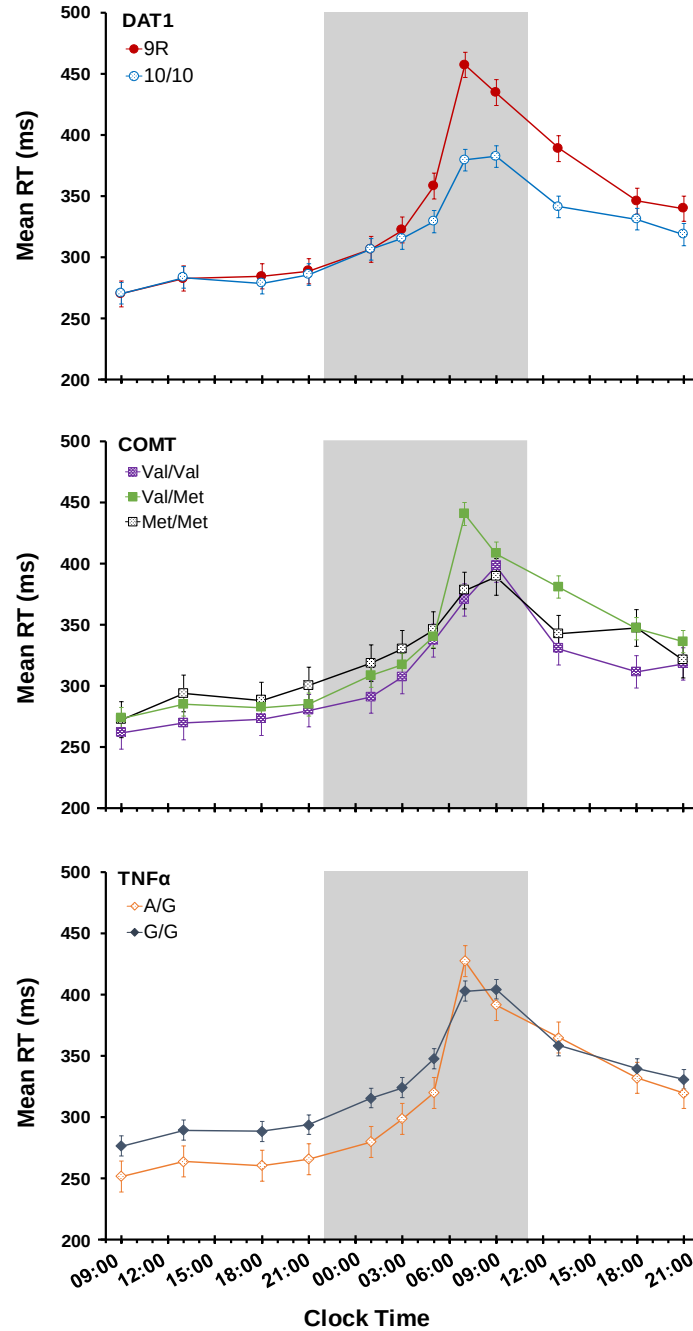


Figure S1. Mean RT ($\pm$ standard error) on the 10 min PVT across test bouts during 38 h of TSD, for each of the three genes, collapsed across TOT. Shaded area: nighttime test bouts during TSD. PVT: psychomotor vigilance test; RT: response time; TOT: time-one-task; TSD: total sleep deprivation.

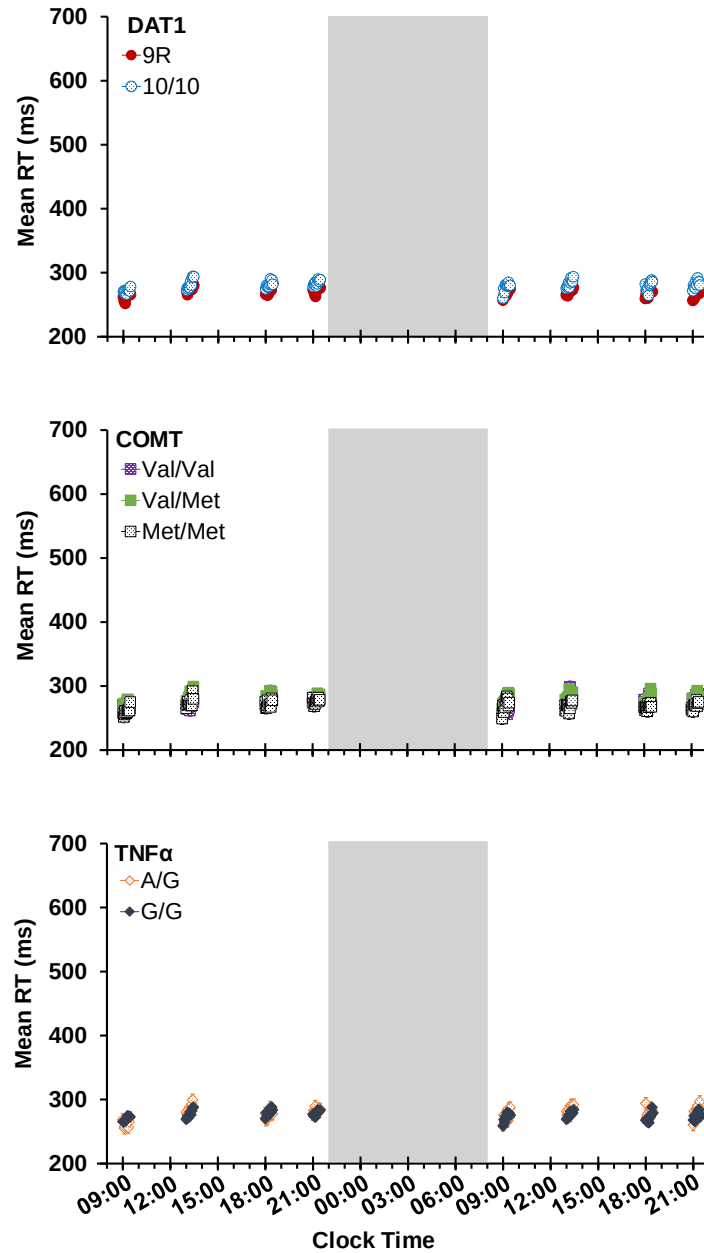


Figure S2. Mean RT ($\pm$ standard error) in 1 min bins on the 10 min PVT across test bouts in the well-rested control group, for each of the three genes. Data are plotted against the start times of the PVT bouts; placement of the 1 min bins in each test bout is not to scale on the clock time axis. The shaded area represents a nighttime sleep opportunity (22:00–08:00).

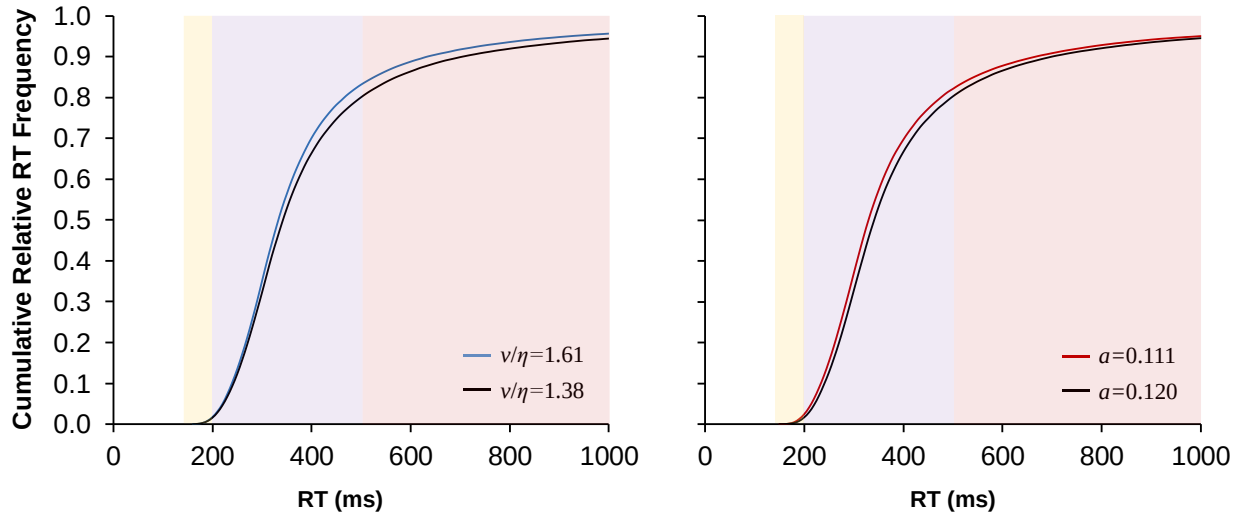


Figure S3. Computer simulations of cumulative relative RT frequency distributions using the diffusion model for the PVT.³⁷ These simulations are based on model parameters fixed at values previously observed for TSD (Table S1 in the PVT diffusion model publication³⁷) but with varying drift ratio v/η (left panel) or boundary separation a (right panel). In the left panel, resilience to performance impairment is simulated by changing drift ratio from $v/\eta=1.38$ (previously observed TSD value) to $v/\eta=1.61$ (20% toward previously observed baseline value). This manipulation affects RTs in the lapse domain of the distribution (red-shaded area). In the right panel, resilience to performance impairment is simulated by changing boundary separation from $a=0.120$ (previously observed TSD value) to $a=0.111$ (previously observed baseline value). This manipulation primarily affects RTs in the heart of the distribution (purple-shaded area). The yellow-shaded area contains the fastest RTs; the purple-shaded area shows the heart of the cumulative relative frequency distributions; and the red-shaded area shows the slower RTs or lapse domain (cf. Fig. 1, right).

Separation of circadian- and behavior-driven metabolite rhythms in humans provides a window on peripheral oscillators and metabolism

Debra J. Skene^a, Elena Skorniyakov^{b,c}, Namrata R. Chowdhury^a, Rajendra P. Gajula^d, Benita Middleton^a, Briann C. Satterfield^{b,e}, Kenneth I. Porter^d, Hans P. A. Van Dongen^{b,f,1,2}, and Shobhan Gaddameedhi^{b,d,1}

^aFaculty of Health and Medical Sciences, University of Surrey, Guildford GU2 7XH, United Kingdom; ^bSleep and Performance Research Center, Washington State University, Spokane, WA 99210; ^cDepartment of Physical Therapy, Eastern Washington University, Spokane, WA 99202; ^dDepartment of Pharmaceutical Sciences, College of Pharmacy and Pharmaceutical Sciences, Washington State University, Spokane, WA 99210; ^eDepartment of Psychiatry, College of Medicine, University of Arizona, Tucson, AZ 85724; and ^fElsion S. Floyd College of Medicine, Washington State University, Spokane, WA 99210

Edited by Joseph S. Takahashi, Howard Hughes Medical Institute and University of Texas Southwestern Medical Center, Dallas, TX, and approved June 19, 2018 (received for review January 21, 2018)

Misalignment between internal circadian rhythmicity and externally imposed behavioral schedules, such as occurs in shift workers, has been implicated in elevated risk of metabolic disorders. To determine underlying mechanisms, it is essential to assess whether and how peripheral clocks are disturbed during shift work and to what extent this is linked to the central suprachiasmatic nuclei (SCN) pacemaker and/or misaligned behavioral time cues. Investigating rhythms in circulating metabolites as biomarkers of peripheral clock disturbances may offer new insights. We evaluated the impact of misaligned sleep/wake and feeding/fasting cycles on circulating metabolites using a targeted metabolomics approach. Sequential plasma samples obtained during a 24-h constant routine that followed a 3-d simulated night-shift schedule, compared with a simulated day-shift schedule, were analyzed for 132 circulating metabolites. Nearly half of these metabolites showed a 24-h rhythmicity under constant routine following either or both simulated shift schedules. However, while traditional markers of the circadian clock in the SCN—melatonin, cortisol, and *PER3* expression—maintained a stable phase alignment after both schedules, only a few metabolites did the same. Many showed reversed rhythms, lost their rhythms, or showed rhythmicity only under constant routine following the night-shift schedule. Here, 95% of the metabolites with a 24-h rhythmicity showed rhythms that were driven by behavioral time cues externally imposed during the preceding simulated shift schedule rather than being driven by the central SCN circadian clock. Characterization of these metabolite rhythms will provide insight into the underlying mechanisms linking shift work and metabolic disorders.

circadian misalignment | gastrointestinal tract | liver | metabolomics | shift work

Endogenous circadian rhythms exist in nearly all physiological and behavioral processes, including metabolism. In normal physiology, the central circadian clock, located in the hypothalamic suprachiasmatic nuclei (SCN), synchronizes the timing of peripheral clocks in the liver, gut, pancreas, and adipose tissue via multiple neural and hormonal pathways (1). Desynchronization of this circadian timing system from externally imposed behavioral rhythms (light/dark exposure; sleep/wakefulness; rest/activity; feeding/fasting)—such as occurs in shift workers—over time results in a number of metabolic disorders including obesity, metabolic syndrome, and type 2 diabetes (2). To determine the underlying mechanisms linking shift work to metabolic disorders, it is essential to understand whether and how peripheral clocks are disturbed during shift work and to what extent these peripheral clocks are driven by the central SCN pacemaker versus misaligned behavioral time cues. Investigating rhythms in circulating metabolites as biomarkers of peripheral clock disturbances may enable this, thereby offering an important step forward.

Previous circadian and sleep metabolomics studies have shown time-of-day variation in plasma metabolites. As expected under fully entrained conditions with alignment of the central SCN pacemaker and behavioral cycles, a large number of metabolites are rhythmic (3, 4). However, under constant routine conditions in which exogenous factors are removed or fixed, only 10–20% of metabolites appear rhythmic (5–7). It remains unknown whether the oscillations seen in metabolites that remain rhythmic under constant routine conditions are driven by the central SCN pacemaker or whether they are reflections of peripheral oscillators that continue to cycle in the absence of externally imposed behavioral time cues that were initially driving them. Distinguishing these possibilities is critical for understanding how shift work may lead to peripheral rhythm disturbances that may be involved in the etiology of metabolic disorders.

The rhythmic production of the hormones melatonin and cortisol is driven directly by SCN timing; these hormones are therefore considered reliable markers of the phase of the central SCN clock (8). Rhythms that reflect the SCN pacemaker have

Significance

Shift workers, whose schedules are misaligned relative to their suprachiasmatic nuclei (SCN) circadian pacemaker, are at elevated risk of metabolic disorders. In a study of simulated day-versus night-shift work followed by a constant routine, we separated plasma-circulating metabolites according to whether their 24-h rhythms aligned with the central SCN pacemaker or instead reflected externally imposed behavioral schedules. We found that rhythms in many metabolites implicated in food metabolism dissociated from the SCN pacemaker rhythm, with the vast majority aligning with the preceding sleep/wake and feeding/fasting cycles. Our metabolomics study yields insight into the link between prolonged exposure to shift work and the spectrum of associated metabolic disorders by providing a window into peripheral oscillators and the biobehavioral factors that orchestrate them.

Author contributions: H.P.A.V.D. and S.G. designed research; E.S. and B.C.S. performed research; D.J.S., E.S., N.R.C., R.P.G., B.M., K.I.P., and H.P.A.V.D. analyzed data; and D.J.S., H.P.A.V.D., and S.G. wrote the paper.

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¹H.P.A.V.D. and S.G. contributed equally to this work.

²To whom correspondence should be addressed. Email: hvd@wsu.edu.

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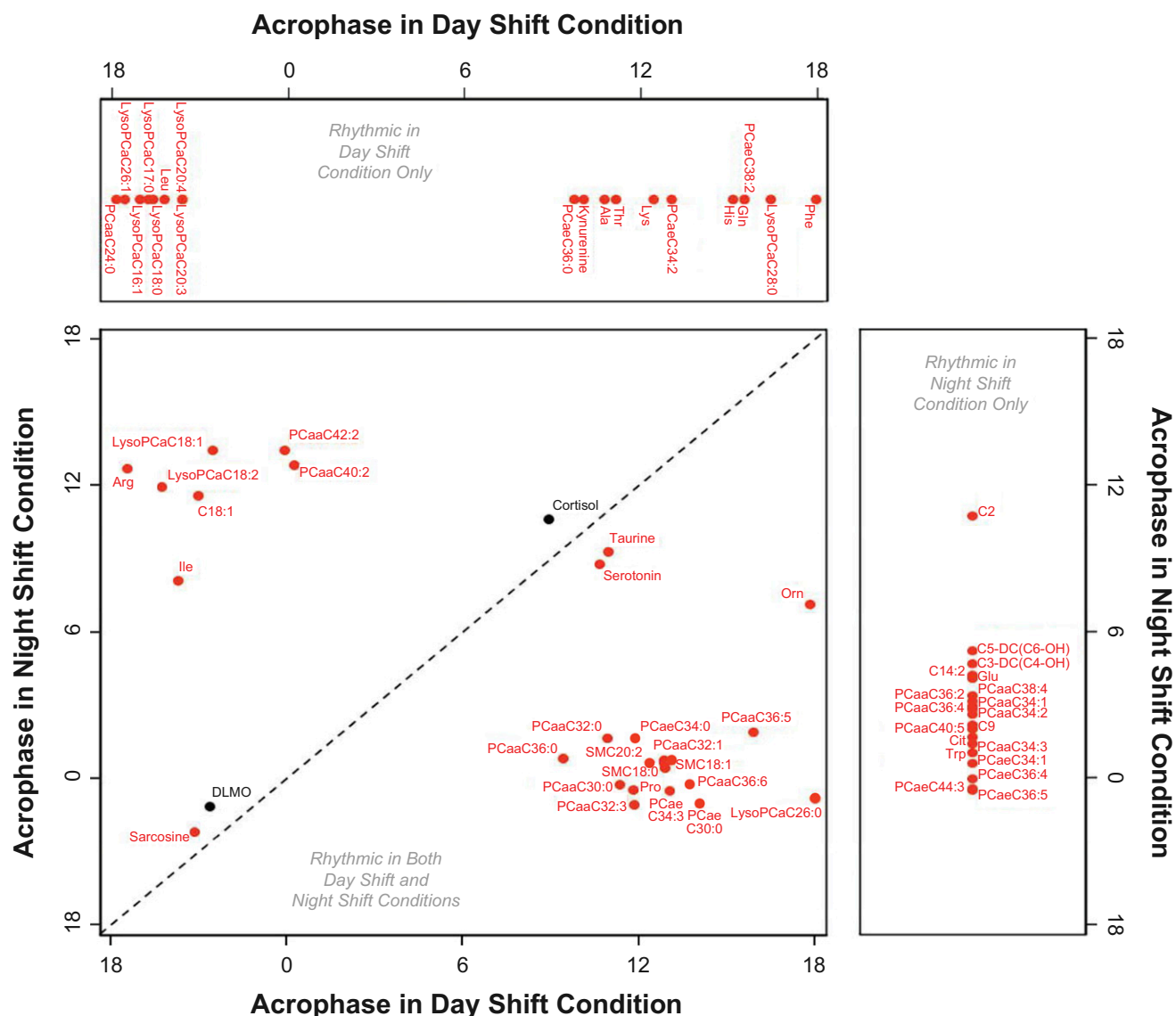


Fig. 1. Timing of the peak of the 24-h rhythm (acrophase) during constant routine following the day-shift condition and following the night-shift condition in 27 metabolites with significant 24-h rhythmicity for both conditions (*Bottom Left*), in 19 metabolites with significant 24-h rhythmicity for the day-shift condition only (*Top*), and in 19 metabolites with significant 24-h rhythmicity for the night-shift condition only (*Right*). Time is indicated as clock time in hours (0 = midnight). Red: metabolites. Black: timing of melatonin onset (DLMO) and timing of cortisol peak (for reference). The dashed diagonal line indicates where metabolites would fall if the timing of their rhythmicity during constant routine was unperturbed by the night-shift condition relative to the day-shift condition.

also been observed in the expression of core clock genes, such as *Period3* (*PER3*), that can be measured in blood-borne cells (9). Previous studies in both simulated (10, 11) and real-world (12, 13) shift work have shown that the rhythms of these circadian markers are resistant to phase shifting, indicating that the endogenous SCN rhythm is slow to adapt to shift work schedules. As such, exposure to a night-shift schedule produces misalignment between behavioral rhythms and the rhythm of the central SCN pacemaker.

In a between-groups, in-laboratory study, we assigned healthy volunteers (ages 22–34 y) to 3 d of either a simulated night-shift schedule (seven subjects) or a simulated day-shift (i.e., control) schedule (seven subjects). In each group, this was followed by a 24-h constant routine protocol, during which blood was drawn at 3-h intervals to measure plasma metabolite profiles using a targeted liquid chromatography/mass spectrometry (LC/MS) metabolomics approach (*SI Appendix, Fig. S1*). We thus characterized 24-h

rhythms in metabolites, free of exogenous factors, after the central SCN clock and behaviorally induced rhythms were experimentally misaligned (night-shift condition) or aligned (day-shift condition). This allowed us to assess whether oscillations observed in metabolites are driven by the central SCN pacemaker—or whether they are the signature of shifted behavioral rhythms during the preceding days of shift work.

Results

During the constant routine after 3 d of simulated shift work, the dim light melatonin onset (DLMO) and the 24-h rhythm of plasma cortisol (traditional markers of the central SCN pacemaker) as well as the 24-h rhythm in clock gene *PER3* expression all showed relatively little phase difference between the day-shift and night-shift conditions (*SI Appendix, Figs. S2–S4*). A delay of ~2 h was observed after the night-shift condition, regardless of which rhythm marker was used, which is congruent with a

free-running rhythm (circadian period $\tau > 24$ h) (14). This indicates that the SCN pacemaker was resistant to phase shifting by the behaviorally imposed schedule, as expected, and that adaptation of the endogenous SCN timing system to the night-shift schedule was limited. Thus, the night-shift condition successfully produced misalignment between behavioral rhythms (light/dark exposure; sleep/wakefulness; rest/activity; feeding/fasting), which were shifted by 12 h under the simulated night-shift condition, and the relatively unyielding rhythm of the central SCN pacemaker.

The blood samples taken during the 24-h constant routine were analyzed for 132 circulating metabolites from 5 metabolite classes using targeted LC/MS metabolomics. For each of these metabolites, the samples were analyzed with cosinor analysis to assess the presence and timing of 24-h rhythmicity (*SI Appendix, Table S1*). Nearly half of the metabolites analyzed (i.e., 65 of 132) showed significant 24-h rhythmicity during the constant routine under either or both conditions. Of these, a group of 27 metabolites showed rhythmicity following both the simulated day-shift and night-shift schedules. A group of 19 metabolites lost their rhythmicity under constant routine following the night-shift schedule. For another group of 19 metabolites, no significant rhythmicity was observed following the day-shift schedule, but rhythmicity emerged under constant routine following the night-shift schedule. For each of the metabolites that showed a significant 24-h rhythm, Fig. 1 shows the clock time at which the rhythm peaked (acrophase).

Fig. 1, *Bottom Left*, shows the 27 metabolites with significant 24-h rhythmicity under both conditions. Only three of these metabolites maintained approximately the same peak time following both the simulated day-shift and night-shift schedules (as did the traditional circadian markers, DLMO and cortisol peak): serotonin, taurine, and sarcosine (Fig. 2, *Left*). By contrast, under constant routine following the simulated night-shift schedule, 24 metabolites significantly shifted—and in most cases essentially reversed (i.e., shifted by 12 h)—their rhythms. These metabolites comprised four amino acids (ornithine, arginine, isoleucine, and proline), octadecanoylcarnitine (AC-C18:1), and a collection of glycerophospholipids, lysophosphatidylcholines (lysoPCs), and sphingolipids (for an example, see Fig. 2, *Right*).

Fig. 1, *Top*, shows the metabolites that exhibited significant 24-h rhythmicity following the day-shift condition, but lost rhythmicity following the night-shift schedule. These metabolites included half of the measured lysoPCs, and 7 of the 20 amino acids, all of which peaked during the daytime hours. Fig. 1, *Right*, on the other hand, shows the metabolites that did not exhibit significant 24-h rhythmicity following the day-shift condition, but exhibited rhythmicity following the night-shift condition. These metabolites comprised half of the measured acylcarnitines, glutamate, tryptophan, citrulline, and 11 phosphatidylcholines, all but 1 peaking during the nighttime hours.

Fig. 2, *Top*, illustrates the contrast between one of the three metabolites that maintained a stable peak time following both the simulated day-shift and night-shift schedules, namely the amino acid sarcosine (*N*-methylglycine, *Left*), and one of the 24 metabolites that reversed their rhythms under constant routine following the simulated night-shift schedule, namely the sphingolipid SM C20:2 (*Right*). As shown in Fig. 2 (*Middle*), when plotted against circadian time—i.e., relative to DLMO (which itself remained relatively stable between the two schedules)—the 24-h rhythm in sarcosine aligned nearly perfectly between the day- and night-shift schedules, indicating a strong influence of the central SCN pacemaker; but this was not the case for SM C20:2. By contrast, as shown in Fig. 2 (*Bottom*), when plotted against zeitgeber time—i.e., relative to the scheduled timing of the light/dark, sleep/wake, rest/activity, and feeding/fasting cycles in the preceding shift days—the 24-h rhythm in SM C20:2 lined up nearly perfectly between the day- and night-shift conditions. This was observed despite the fact

that these behavioral cycles were no longer present under the constant routine conditions in which these metabolites were measured, providing substantial evidence that the observed rhythms in this metabolite (and others like it) were driven by behavioral rhythms in the preceding shift days and were subsequently retained.

The subdivision according to the observed rhythms following the day- and night-shift schedules as captured in Fig. 1 was corroborated by principal component analysis, which yielded three distinct clusters of metabolites (*SI Appendix, Table S2*). Cluster 1 represented the group of metabolites that showed 24-h rhythmicity under constant routine following both the day- and night-shift schedules, but reversed their rhythms following the night-shift schedule (*SI Appendix, Fig. S5, Top*). Heat maps revealed that this pattern was the primary response to the experiment in the overall data set (*SI Appendix, Fig. S6*). Cluster 1 was dominated by glycerophospholipids and sphingolipids. Cluster 2 represented the group of metabolites that showed significant 24-h rhythmicity under constant routine only after the day-shift schedule (*SI Appendix, Fig. S5, Middle*). This cluster was dominated by lysophosphatidylcholines and a variety of amino acids. Cluster 3 represented the group of metabolites that did not show significant 24-h rhythmicity under constant routine after the day-shift schedule, but was rhythmic after the night-shift schedule (*SI Appendix, Fig. S5, Bottom*). Similar to the other two clusters, cluster 3 was dominated by acylcarnitines, some amino acids, glycerophospholipids, and sphingolipids.

The 65 metabolites that showed significant rhythmicity during constant routine following the day-shift and/or night-shift schedules were entered into pathway analyses. Under the day-shift condition, nine pathways were significantly enriched (*SI Appendix, Table S3*), including aminoacyl-tRNA biosynthesis, nitrogen metabolism, arginine-proline metabolism, and D-glutamine-glutamate metabolism—as well as alanine-aspartate-glutamate metabolism, cyanoamino acid metabolism, D-arginine and D-ornithine metabolism, glutathione metabolism, and glycine-serine-threonine metabolism, which were not significantly enriched under the night-shift condition. Under the night-shift condition, five pathways were significantly enriched (*SI Appendix, Table S4*), including aminoacyl-tRNA biosynthesis, nitrogen metabolism, arginine-proline metabolism, and D-arginine-ornithine metabolism—as well as valine-leucine-isoleucine biosynthesis, which was not significantly enriched under the day-shift condition. As such, the observed rhythms in circulating metabolites and the metabolic pathways affected appear to reflect metabolic processes in the liver, pancreas, and digestive tract.

Discussion

Night-shift workers are at elevated risk of a wide range of chronic medical conditions, including gastrointestinal disorders and debilitating metabolic disorders such as metabolic syndrome and type 2 diabetes mellitus (2, 15). It has been hypothesized that misalignment between internal circadian rhythmicity and externally imposed behavioral schedules associated with night-time wakefulness underlies this elevated risk (15, 16). However, a reliable tool to separate circadian- and behavior-driven rhythms in metabolism to test this hypothesis has been lacking.

In the current laboratory-controlled, simulated shift work study, we investigated the metabolic consequences of misaligned sleep/wake and feeding/fasting cycles using a targeted metabolomics approach. We found that, whereas traditional markers of the circadian clock in the SCN (melatonin, cortisol, *PER3* expression) remained relatively stable after 3 d of simulated shift work, many of the plasma metabolites (62 of 132) showed profound changes in the timing of their rhythms following simulated night work (Fig. 1; *SI Appendix, Table S1*). In the majority of cases, these changes involved nearly complete reversal of the 24-h rhythmicity in the metabolites (*SI Appendix, Figs. S5 and S6*)—typically peaking during the daytime after the day-shift condition

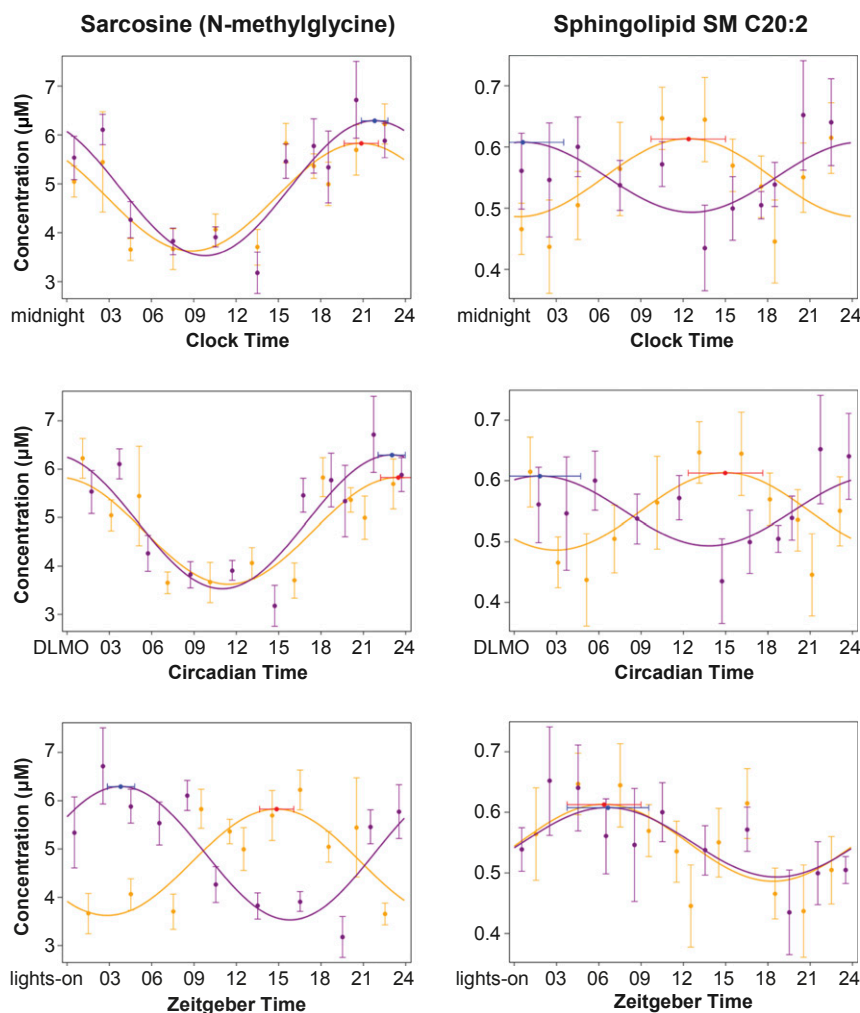


Fig. 2. Three representations of the cosinor fits for two example metabolites: a biogenic amine, sarcosine (*N*-methylglycine, *Left*); and a sphingolipid, SM C20:2 (*Right*). (*Top*) By clock time (i.e., time of day, relative to midnight). (*Middle*) By circadian time (relative to the timing of melatonin onset, DLMO). (*Bottom*) By zeitgeber time (i.e., time awake, relative to lights on). Orange/red: constant routine after simulated day-shift condition. Purple/blue: constant routine after simulated night-shift condition. Circles: group means ($\pm$ SE). Curves: cosinor fits. Red and blue markers: timing of acrophase (and 95% confidence interval).

and during the nighttime after the night-shift condition (e.g., Fig. 2, *Right*). In other instances, 24-h rhythms were seen only after the day-shift condition, peaking during the daytime, or only after the night-shift condition, peaking during the nighttime (*SI Appendix, Fig. S5*). Although with 14 subjects our sample was relatively small, these effects were robust and highly statistically significant. Importantly, the altered rhythms persisted under constant routine conditions in the absence of any externally imposed rhythms. This provides strong evidence that most of the metabolite rhythms observed were driven by behavioral time cues—from the light/dark exposure, sleep/wakefulness, rest/activity, and/or feeding/fasting cycles—during the preceding simulated shift schedules. Exogenous, behavioral time cues associated with externally imposed schedules thus have the capacity to drive endogenous rhythmicity in metabolism, likely by impacting on peripheral oscillators (17, 18) and dissociating them from the rhythm of the central SCN pacemaker.

The mechanisms linking shift work with an increased risk of type 2 diabetes are not well understood. Although metabolic profiling (metabolomics) has been used to investigate pre-diabetic/obese and type 2 diabetic phenotypes (19–21), this has been limited to single-time-point samples. To assess the interaction between circadian timing and metabolic physiology, we

recently compared 24-h metabolite rhythms in overweight/obese individuals and in individuals with type 2 diabetes to age- and weight-matched controls (4). Several metabolites, including proline, sarcosine, and lysoPC a C18:1 and C18:2, exhibited robust daily rhythms in the majority of participants in all study groups and showed a progressive change in concentration from lean to overweight/obese to type 2 diabetes groups. Isoleucine and valine rhythms were lost in patients with type 2 diabetes compared with controls. These metabolites may play a role or act as biomarkers in the progression from a healthy weight to obesity with type 2 diabetes. In the current study, rhythms in proline, lysoPC a C18:1 and C18:2, leucine, and isoleucine were altered by externally imposed behavioral time cues (Fig. 1), and pathway analysis implicated proline metabolism and biosynthesis of branched-chain amino acids (leucine, isoleucine, valine) as impacted by simulated night-shift work (*SI Appendix, Table S4*). Whether these metabolite rhythms and pathways reflecting disrupted circadian rhythms in peripheral metabolism due to simulated night-shift work link to the metabolic phenotype of type 2 diabetes remains to be studied.

In addition to type 2 diabetes, shift work has been linked to a host of other chronic medical conditions, including renal dysfunction (22, 23) and various types of cancer (24–27). There is

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Supplementary Information for

Separation of circadian- and behavior-driven metabolite rhythms in humans provides a window on peripheral oscillators and metabolism

Debra J. Skene, Elena Skorniyakov, Namrata R. Chowdhury, Rajendra P. Gajula, Benita Middleton, Briann C. Satterfield, Kenneth Porter, Hans P.A. Van Dongen, Shobhan Gaddameedhi

Hans P.A. Van Dongen, Ph.D.

Email: hvd@wsu.edu

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Figs. S1 to S6

Tables S1 to S4

References for SI reference citations

Materials and Methods

Clinical study. $N=14$ volunteers (10 men, 4 women) aged between 22 y and 34 y (mean $\pm$ SD: 25.8 ± 3.2 y) with a body mass index (BMI) of 25.7 ± 3.2 kg/m² completed the study. The participants were randomized to either the simulated day shift condition (7 participants) or the simulated night shift condition (7 participants); see Fig. S1. There was a small age difference between the two groups (day shift condition: 24.0 ± 2.2 y; night shift condition: 27.6 ± 3.2 y; $t_{12}=2.4$, $p=0.031$). The groups were not significantly different with regard to BMI (day shift condition: 25.9 ± 3.4 kg/m²; night shift condition: 25.6 ± 3.3 kg/m²; $t_{12}=0.14$, $p=0.89$) or sex distribution (day shift condition: 4 men; night shift condition: 6 men; $\chi^2_1=1.4$, $p=0.24$).

Participants were screened to be physically and psychologically healthy with no medical or drug treatment, as verified by physical examination, blood chemistry, urinalysis, and questionnaires. They reported good habitual sleep, between 6 and 10 hours in duration and habitually getting up between 06:00 and 09:00, and were no extreme morning- or evening-types as assessed by questionnaire (Composite Scale of Morningness). They showed no evidence of any sleep or circadian disorders as assessed by nocturnal polysomnography (1) and validated questionnaires (Pittsburgh Sleep Quality Index, Sleep Disorders Questionnaire, Epworth Sleepiness Scale). They had no history of drug or alcohol abuse, were free of traces of alcohol and drugs as assessed by drug screen and breathalyzer, and did not smoke. They were not involved in shift work within three months of entering the study, and did not travel across time zones within one month of entering the study. Women were not pregnant as assessed by blood-based assay.

Participants maintained a regular sleep/wake schedule in the week prior to the in-laboratory experiment, with bedtimes and wake times within 30 minutes from their self-reported habitual schedule. This was confirmed by means of wrist actigraphy, sleep diary, and participants calling a time-stamped voice mail recorder upon waking and before going to bed. In the week prior to the study, participants were requested to abstain from alcohol and caffeine.

Targeted metabolomics analysis. Although targeted metabolomics does not provide a complete assessment of the entire metabolome, it covers important metabolite classes, and the results obtained are quantifiable and highly reproducible across laboratories (2). Targeted metabolomics is also well suited for high throughput of large number of samples as generated by time-series circadian studies.

Metabolites were quantified in the plasma samples collected at 3-h intervals during the 24-h constant routine using the Absolute[®] IDQ p180 targeted metabolomics kit (Biocrates Life Sciences AG, Innsbruck, Austria) and a Waters Xevo TQ-S mass spectrometer coupled to an Acquity UPLC system (Waters Corporation, Milford, MA, USA). Plasma samples (10 μ l) were prepared according to the manufacturer's instructions adding several stable isotope-labeled standards to the samples prior to the derivatization and extraction steps. Using LC/MS (liquid chromatography/mass spectrometry), 184 metabolites from 5 different compound classes (acylcarnitines, amino acids, biogenic amines, glycerophospholipids, and sphingolipids) were quantified.

The samples were run on 2 $\times$ 96-well plates. Sample order was randomized and three levels of quality control (QC) were run on each plate. Data were normalized between the plates using the

results of quality control level 2 (QC2) repeats across the plate ($n=4$) and between plates ($n=2$) using Biocrates METIDQ software (QC2 correction). Metabolites where >25% samples were below the limit of detection, below the lower limit of quantification, above the upper limit of quantification, or blank out of range, or where the QC2 coefficient of variance was >30%, were excluded. This was the case for 52 metabolites. The remaining 132 quantified metabolites comprised 10 acylcarnitines, 20 amino acids, 7 biogenic amines, 81 glycerophospholipids, and 14 sphingolipids.

Plasma melatonin. Melatonin levels were measured in the plasma samples collected hourly at baseline (18:30–21:30) and during the constant routine (18:30–01:30) using RIA (IB88111, IBL, Minneapolis, MN, USA) performed in duplicate by KMI Diagnostics, Inc. (Minneapolis, MN, USA).

Plasma cortisol. Cortisol levels were measured in the plasma samples collected at 3-h intervals during the 24-h constant routine using ELISA (ADI-900-097, Enzo Life Sciences, Farmingdale, NY, USA) following the manufacturer's instructions. Assays were performed in triplicate. Standards were used as per the kit manual. Analyses were performed using MyAssays software as recommended ([https://www.myassays.com/corticosterone-\(enzo\).assay](https://www.myassays.com/corticosterone-(enzo).assay)).

PER3 expression. *PER3* transcript levels were measured in the plasma samples collected at 3-h intervals during the 24-h constant routine using nCounter multiplexed assay (NanoString Technologies, Seattle, WA, USA). RNA was measured directly with no amplification or other enzymatic processing. 100 ng of total RNA was used for the assay. Analysis was performed using nSolver 3.0 software (NanoString Technologies, Seattle, WA, USA). Genes with an expectancy of less than 10 counts with 90% occurrence or more were removed. Background values were subtracted and data were normalized with overall geometric mean of internal control genes.

Statistical analysis. Cosinor analysis to investigate 24-h rhythmicity in all of the metabolites, cortisol, and *PER3* expression, was performed across all participants in both conditions using linear mixed-effects regression (3). Regression coefficients for mesor (center level), acrophase (timing of peak), and amplitude (difference between mesor and level at acrophase) were assessed (Table S1) and used for statistical testing. Rhythm significance in each of the two conditions was determined by testing amplitude against zero using t test, with a one-sided type I error threshold of 0.05. 95% confidence intervals for acrophase were computed using the delta method. Differences between conditions in acrophase, amplitude and mesor were evaluated using t test, with a two-sided type I error threshold of 0.05.

The cosinor analyses for metabolites were repeated after removal of data from the first 3 h of the 24-h constant routine period, in order to verify robustness to any transient effects from physiological adjustment to the constant routine procedures. This resulted in minor differences in acrophase estimates (mean $\pm$ SD: 38 $\pm$ 34 min) and did not substantively affect any of the findings. Separately, the cosinor analyses for metabolites were repeated with time awake added as a regression term. Out of the 132 metabolites analyzed, 115 did not show a significant effect of time awake. For the 17 metabolites that did show a significant effect of time awake, the levels of 7 metabolites decreased and the levels of 10 metabolites increased across the 24-h constant

routine. In all cases, the total change over time was small relative to the 24-h overall average. The constant routine procedure and the increasing sleep pressure associated with 24-h sustained wakefulness did not produce any substantive confounds in the metabolites' temporal profiles.

The timing of dim light melatonin onset (DLMO) was analyzed with non-linear mixed-effects regression of a Taylor series approximation of the melatonin curve (Fig. S2). Differences between conditions were evaluated using t test. Differences between baseline and constant routine were evaluated using paired-sample t test. Although this methodology does not require the definition of a threshold to estimate timing differences, we used a conventional 10 pg/ml threshold (4) to define the DLMO.

Principal component analysis (PCA) was based on scree plot to determine how many factors to retain, and used varimax rotation to assess factor loadings. All statistical analyses were implemented in SAS version 9.4.

Pathway analyses were performed for the day shift and night shift conditions separately (Tables S3, S4) using the MetaboAnalyst 3.0 database (5). Enriched pathways were identified using a false discovery rate (FDR) threshold of 0.05.

Table S1. Statistical results of cosinor analyses. Statistically significant differences from zero ($p < 0.05$) are indicated by bold font for amplitude (orange, purple) and for difference between conditions in amplitude (black), mesor (gray, italicized), and phase (red).

<i>Metabolite</i>	<i>Day Shift Condition</i>			<i>Night Shift Condition</i>			<i>Difference between Conditions</i>		
	<i>Amplitude ± SE</i>	<i>Mesor ± SE</i>	<i>Acrophase ± SE</i>	<i>Amplitude ± SE</i>	<i>Mesor ± SE</i>	<i>Acrophase ± SE</i>	<i>Amplitude Δ ± SE</i>	<i>Mesor Δ ± SE</i>	<i>Acrophase Δ ± SE</i>
PC aa C30:0	0.283 ± 0.054	1.446 ± 0.126	11:20 ± 00:42	0.222 ± 0.054	1.397 ± 0.126	23:44 ± 00:53	-0.062 ± 0.076	-0.049 ± 0.178	-11:36 ± 01:08
PC ae C34:3	0.387 ± 0.143	4.012 ± 0.390	13:02 ± 01:22	0.331 ± 0.143	3.904 ± 0.389	23:29 ± 01:35	-0.056 ± 0.203	-0.108 ± 0.551	10:26 ± 02:06
PC aa C36:6	0.035 ± 0.014	0.357 ± 0.041	13:44 ± 01:29	0.049 ± 0.014	0.374 ± 0.041	23:43 ± 01:01	0.015 ± 0.020	0.017 ± 0.058	09:59 ± 01:48
PC aa C32:1	0.507 ± 0.161	3.910 ± 0.506	12:51 ± 01:11	1.054 ± 0.161	4.373 ± 0.506	00:44 ± 00:33	0.547 ± 0.228	0.463 ± 0.715	11:52 ± 01:18
PC ae C34:0	0.146 ± 0.039	0.918 ± 0.066	11:53 ± 00:59	0.091 ± 0.039	0.985 ± 0.066	01:35 ± 01:35	-0.055 ± 0.055	0.068 ± 0.093	-10:17 ± 01:52
PC ae C32:1	0.068 ± 0.040	1.169 ± 0.085	13:48 ± 02:13	0.056 ± 0.040	1.195 ± 0.085	23:27 ± 02:36	-0.011 ± 0.057	0.026 ± 0.120	09:39 ± 03:25
PC ae C34:2	0.572 ± 0.229	6.642 ± 0.422	13:03 ± 01:29	0.410 ± 0.228	6.341 ± 0.422	01:22 ± 02:03	-0.162 ± 0.323	-0.301 ± 0.597	-11:41 ± 02:32
PC ae C34:1	0.244 ± 0.160	4.708 ± 0.261	13:08 ± 02:27	0.406 ± 0.161	4.766 ± 0.260	00:36 ± 01:27	0.162 ± 0.227	0.058 ± 0.368	11:28 ± 02:51
PC aa C34:3	0.614 ± 0.318	9.415 ± 0.675	12:28 ± 01:55	1.183 ± 0.317	8.647 ± 0.675	01:24 ± 00:59	0.569 ± 0.449	-0.768 ± 0.954	-11:03 ± 02:10
PC aa C34:4	0.166 ± 0.036	1.043 ± 0.085	12:52 ± 00:48	0.171 ± 0.037	0.955 ± 0.085	00:26 ± 00:47	0.005 ± 0.052	-0.088 ± 0.120	11:33 ± 01:07
PC aa C32:0	0.930 ± 0.291	7.324 ± 0.463	10:56 ± 01:10	0.748 ± 0.290	7.614 ± 0.463	01:38 ± 01:26	-0.182 ± 0.410	0.290 ± 0.655	-09:17 ± 01:51
PC ae C36:2	0.490 ± 0.337	10.310 ± 0.602	16:13 ± 02:40	0.511 ± 0.333	9.905 ± 0.602	04:40 ± 02:33	0.021 ± 0.473	-0.405 ± 0.852	-11:32 ± 03:41
PC ae C38:6	0.174 ± 0.122	3.185 ± 0.273	14:57 ± 02:40	0.194 ± 0.122	3.709 ± 0.273	22:04 ± 02:21	0.020 ± 0.172	0.524 ± 0.387	07:07 ± 03:33
PC ae C36:5	0.455 ± 0.239	6.485 ± 0.634	13:21 ± 01:57	0.547 ± 0.239	7.193 ± 0.634	23:30 ± 01:36	0.092 ± 0.338	0.707 ± 0.897	10:08 ± 02:32
PC ae C36:1	0.242 ± 0.235	6.938 ± 0.410	15:56 ± 03:45	0.396 ± 0.239	7.426 ± 0.410	01:34 ± 02:14	0.154 ± 0.335	0.489 ± 0.580	09:37 ± 04:22
PC ae C36:0	0.038 ± 0.018	0.444 ± 0.031	09:45 ± 01:47	0.011 ± 0.017	0.460 ± 0.031	06:12 ± 06:16	-0.027 ± 0.025	0.016 ± 0.044	-03:32 ± 06:32
PC ae C32:2	0.019 ± 0.011	0.330 ± 0.022	15:23 ± 02:11	0.021 ± 0.011	0.353 ± 0.022	22:56 ± 01:54	0.002 ± 0.015	0.024 ± 0.031	07:32 ± 02:54
PC aa C32:3	0.035 ± 0.008	0.250 ± 0.013	11:49 ± 00:53	0.035 ± 0.008	0.244 ± 0.013	23:32 ± 00:53	0.000 ± 0.012	-0.006 ± 0.018	11:42 ± 01:15
SM C18:0	1.869 ± 0.939	23.392 ± 1.664	12:52 ± 01:52	2.286 ± 0.939	26.502 ± 1.663	00:38 ± 01:30	0.417 ± 1.328	3.111 ± 2.352	11:46 ± 02:24
PC ae C36:3	0.237 ± 0.141	4.173 ± 0.255	14:27 ± 02:15	0.237 ± 0.143	4.057 ± 0.254	00:04 ± 02:12	0.000 ± 0.201	-0.116 ± 0.360	09:36 ± 03:09
PC aa C34:1	3.983 ± 3.303	103.063 ± 5.529	16:54 ± 03:14	8.304 ± 3.321	107.107 ± 5.525	03:08 ± 01:31	4.321 ± 4.683	4.044 ± 7.816	10:13 ± 03:35
SM C18:1	0.895 ± 0.421	10.741 ± 0.782	13:06 ± 01:45	0.975 ± 0.421	11.770 ± 0.782	00:44 ± 01:35	0.081 ± 0.595	1.030 ± 1.106	11:38 ± 02:22
PC aa C40:6	0.774 ± 0.551	14.210 ± 1.873	17:52 ± 02:47	0.920 ± 0.566	18.167 ± 1.873	23:49 ± 02:15	0.146 ± 0.790	3.958 ± 2.649	05:57 ± 03:35
PC aa C38:6	1.961 ± 1.526	38.695 ± 4.470	20:02 ± 03:00	1.624 ± 1.557	48.038 ± 4.469	00:25 ± 03:31	-0.337 ± 2.180	9.343 ± 6.321	04:22 ± 04:38
PC ae C30:0	0.019 ± 0.007	0.204 ± 0.014	14:03 ± 01:22	0.021 ± 0.007	0.201 ± 0.014	22:54 ± 01:14	0.002 ± 0.010	-0.003 ± 0.019	08:50 ± 01:50
SM C16:0	5.082 ± 4.232	110.256 ± 7.735	13:30 ± 03:07	4.851 ± 4.244	116.946 ± 7.730	00:38 ± 03:13	-0.231 ± 5.994	6.689 ± 10.935	11:07 ± 04:29
PC ae C38:0	0.056 ± 0.037	1.021 ± 0.112	22:11 ± 02:31	0.035 ± 0.037	1.107 ± 0.112	01:52 ± 04:00	-0.021 ± 0.053	0.087 ± 0.158	03:41 ± 04:44
PC aa C38:0	0.065 ± 0.066	1.642 ± 0.199	14:43 ± 03:54	0.089 ± 0.065	1.964 ± 0.199	20:23 ± 02:50	0.025 ± 0.093	0.321 ± 0.281	05:40 ± 04:49
PC ae C42:2	0.004 ± 0.011	0.312 ± 0.025	17:29 ± 10:28	0.009 ± 0.011	0.338 ± 0.025	02:42 ± 04:37	0.005 ± 0.016	0.026 ± 0.036	09:13 ± 11:27
SM (OH) C22:1	1.127 ± 1.087	26.956 ± 1.742	13:45 ± 03:37	1.572 ± 1.091	30.504 ± 1.741	00:43 ± 02:33	0.445 ± 1.540	3.548 ± 2.463	10:58 ± 04:25
SM (OH) C16:1	0.203 ± 0.137	3.415 ± 0.228	14:06 ± 02:32	0.267 ± 0.138	3.859 ± 0.228	00:25 ± 01:54	0.064 ± 0.194	0.444 ± 0.322	10:19 ± 03:10
SM (OH) C22:2	1.406 ± 1.066	28.123 ± 1.764	15:12 ± 02:54	1.817 ± 1.082	30.791 ± 1.762	00:25 ± 02:11	0.411 ± 1.518	2.668 ± 2.493	09:12 ± 03:38
PC aa C36:0	0.323 ± 0.108	0.945 ± 0.190	09:25 ± 01:15	0.389 ± 0.109	1.648 ± 0.190	00:48 ± 01:01	0.065 ± 0.153	<i>0.704 ± 0.269</i>	-08:57 ± 01:37
SM C16:1	0.688 ± 0.603	16.426 ± 0.970	13:55 ± 03:17	0.594 ± 0.606	16.004 ± 0.969	00:30 ± 03:45	-0.094 ± 0.855	-0.422 ± 1.371	10:35 ± 04:59
PC ae C40:1	0.012 ± 0.033	0.851 ± 0.091	08:55 ± 10:08	0.035 ± 0.033	0.838 ± 0.091	09:37 ± 03:35	0.022 ± 0.047	-0.012 ± 0.129	00:41 ± 10:45
SM (OH) C14:1	0.275 ± 0.216	5.576 ± 0.357	14:03 ± 02:57	0.254 ± 0.218	5.794 ± 0.357	23:43 ± 03:08	-0.020 ± 0.307	0.218 ± 0.505	09:39 ± 04:19
PC aa C36:1	1.447 ± 1.323	32.326 ± 2.741	19:18 ± 03:34	1.589 ± 1.355	31.253 ± 2.739	11:34 ± 03:08	0.142 ± 1.894	-1.074 ± 3.875	-07:44 ± 04:45
PC aa C36:5	0.495 ± 0.243	6.735 ± 0.627	15:53 ± 01:54	0.895 ± 0.246	7.804 ± 0.627	01:53 ± 01:01	0.400 ± 0.346	1.069 ± 0.886	10:00 ± 02:09
Tyr	1.358 ± 1.956	58.837 ± 2.659	10:59 ± 05:19	2.573 ± 1.887	59.846 ± 2.659	06:03 ± 02:54	1.214 ± 2.718	1.009 ± 3.760	-04:55 ± 06:03
PC aa C36:3	2.551 ± 2.542	81.641 ± 4.062	20:02 ± 03:51	3.936 ± 2.497	78.492 ± 4.059	05:41 ± 02:31	1.384 ± 3.563	-3.149 ± 5.742	09:38 ± 04:36
PC aa C36:4	3.047 ± 3.576	112.319 ± 4.458	15:39 ± 04:31	8.412 ± 3.581	118.737 ± 4.452	02:49 ± 01:37	5.365 ± 5.061	6.419 ± 6.301	11:09 ± 04:48
PC ae C40:6	0.106 ± 0.094	2.414 ± 0.190	16:06 ± 03:25	0.138 ± 0.096	2.995 ± 0.190	22:51 ± 02:33	0.032 ± 0.134	0.581 ± 0.269	06:44 ± 04:16
PC aa C36:2	4.188 ± 5.069	114.921 ± 5.231	09:10 ± 04:36	15.580 ± 5.040	116.477 ± 5.221	02:56 ± 01:14	11.393 ± 7.148	1.555 ± 7.390	-06:14 ± 04:46
PC aa C42:6	0.004 ± 0.008	0.184 ± 0.015	17:52 ± 08:06	0.006 ± 0.008	0.214 ± 0.015	01:43 ± 04:46	0.002 ± 0.011	0.030 ± 0.021	07:50 ± 09:24

Metabolite	Day Shift Condition			Night Shift Condition			Difference between Conditions		
	Amplitude $\pm$ SE	Mesor $\pm$ SE	Acrophase $\pm$ SE	Amplitude $\pm$ SE	Mesor $\pm$ SE	Acrophase $\pm$ SE	Amplitude $\Delta \pm$ SE	Mesor $\Delta \pm$ SE	Acrophase $\Delta \pm$ SE
PC aa C28:1	0.064 $\pm$ 0.046	1.534 $\pm$ 0.088	14:46 $\pm$ 02:45	0.052 $\pm$ 0.047	1.495 $\pm$ 0.088	00:04 $\pm$ 03:19	-0.012 $\pm$ 0.066	-0.040 $\pm$ 0.125	09:18 $\pm$ 04:19
SM C24:0	0.714 $\pm$ 1.024	26.268 $\pm$ 2.074	12:05 $\pm$ 05:19	0.743 $\pm$ 1.008	26.950 $\pm$ 2.073	02:43 $\pm$ 05:09	0.029 $\pm$ 1.437	0.682 $\pm$ 2.932	-09:22 $\pm$ 07:24
PC aa C38:3	1.903 $\pm$ 0.984	29.542 $\pm$ 3.120	18:42 $\pm$ 02:01	1.608 $\pm$ 1.003	32.467 $\pm$ 3.120	01:48 $\pm$ 02:19	-0.295 $\pm$ 1.406	2.925 $\pm$ 4.412	07:06 $\pm$ 03:05
LysoPC a C28:1	0.018 $\pm$ 0.010	0.305 $\pm$ 0.023	16:45 $\pm$ 02:01	0.019 $\pm$ 0.010	0.308 $\pm$ 0.023	22:30 $\pm$ 01:55	0.000 $\pm$ 0.014	0.002 $\pm$ 0.033	05:45 $\pm$ 02:47
PC aa C34:2	8.425 $\pm$ 7.822	134.105 $\pm$ 6.959	07:55 $\pm$ 03:36	23.568 $\pm$ 7.873	140.496 $\pm$ 6.942	02:36 $\pm$ 01:15	15.143 $\pm$ 11.098	6.391 $\pm$ 9.830	-05:18 $\pm$ 03:49
SM C20:2	0.064 $\pm$ 0.023	0.550 $\pm$ 0.033	12:21 $\pm$ 01:19	0.057 $\pm$ 0.023	0.551 $\pm$ 0.032	00:36 $\pm$ 01:27	-0.006 $\pm$ 0.032	0.001 $\pm$ 0.046	-11:44 $\pm$ 01:57
PC ae C42:1	0.015 $\pm$ 0.010	0.262 $\pm$ 0.023	11:22 $\pm$ 02:36	0.015 $\pm$ 0.010	0.259 $\pm$ 0.023	02:46 $\pm$ 02:33	0.000 $\pm$ 0.014	-0.003 $\pm$ 0.032	-08:35 $\pm$ 03:38
Lys	15.622 $\pm$ 4.876	153.876 $\pm$ 8.735	12:25 $\pm$ 01:08	4.336 $\pm$ 4.838	145.122 $\pm$ 8.735	22:09 $\pm$ 04:10	-11.286 $\pm$ 6.869	-8.754 $\pm$ 12.353	09:43 $\pm$ 04:19
PC ae C38:2	0.064 $\pm$ 0.027	0.646 $\pm$ 0.080	15:32 $\pm$ 01:39	0.032 $\pm$ 0.027	0.464 $\pm$ 0.080	05:41 $\pm$ 03:24	-0.032 $\pm$ 0.038	-0.182 $\pm$ 0.113	-09:51 $\pm$ 03:47
PC ae C30:2	0.003 $\pm$ 0.002	0.062 $\pm$ 0.002	15:41 $\pm$ 03:14	0.002 $\pm$ 0.002	0.064 $\pm$ 0.002	21:45 $\pm$ 03:19	0.000 $\pm$ 0.003	0.002 $\pm$ 0.003	06:04 $\pm$ 04:39
C9	0.001 $\pm$ 0.002	0.024 $\pm$ 0.002	05:56 $\pm$ 12:06	0.007 $\pm$ 0.002	0.028 $\pm$ 0.002	02:10 $\pm$ 01:18	0.006 $\pm$ 0.003	0.003 $\pm$ 0.002	-03:45 $\pm$ 12:11
C3-DC (C4-OH)	0.003 $\pm$ 0.005	0.027 $\pm$ 0.005	08:55 $\pm$ 05:16	0.013 $\pm$ 0.005	0.033 $\pm$ 0.005	04:41 $\pm$ 01:28	0.009 $\pm$ 0.007	0.006 $\pm$ 0.007	-04:13 $\pm$ 05:28
C14:2	0.001 $\pm$ 0.002	0.017 $\pm$ 0.001	06:20 $\pm$ 06:17	0.003 $\pm$ 0.002	0.020 $\pm$ 0.001	04:13 $\pm$ 01:59	0.002 $\pm$ 0.002	0.003 $\pm$ 0.002	-02:06 $\pm$ 06:35
LysoPC a C20:4	0.974 $\pm$ 0.228	5.755 $\pm$ 0.489	20:24 $\pm$ 00:54	0.073 $\pm$ 0.224	6.080 $\pm$ 0.488	16:51 $\pm$ 12:10	-0.902 $\pm$ 0.320	0.325 $\pm$ 0.691	-03:33 $\pm$ 12:12
LysoPC a C17:0	0.123 $\pm$ 0.057	1.373 $\pm$ 0.078	19:16 $\pm$ 01:48	0.079 $\pm$ 0.059	1.511 $\pm$ 0.077	00:13 $\pm$ 02:42	-0.044 $\pm$ 0.082	0.138 $\pm$ 0.110	04:57 $\pm$ 03:15
PC ae C38:4	0.396 $\pm$ 0.288	7.835 $\pm$ 0.507	15:36 $\pm$ 02:47	0.398 $\pm$ 0.291	9.105 $\pm$ 0.507	01:33 $\pm$ 02:43	0.001 $\pm$ 0.409	1.270 $\pm$ 0.717	09:56 $\pm$ 03:54
C0	0.842 $\pm$ 1.045	30.552 $\pm$ 1.708	11:30 $\pm$ 04:34	0.705 $\pm$ 1.008	32.497 $\pm$ 1.708	05:06 $\pm$ 05:39	-0.137 $\pm$ 1.452	1.945 $\pm$ 2.416	-06:23 $\pm$ 07:16
Leu	7.872 $\pm$ 3.622	110.720 $\pm$ 4.755	19:48 $\pm$ 01:47	4.403 $\pm$ 3.594	111.318 $\pm$ 4.755	05:32 $\pm$ 03:14	-3.470 $\pm$ 5.102	0.597 $\pm$ 6.725	09:43 $\pm$ 03:42
Ile	6.308 $\pm$ 2.210	70.260 $\pm$ 2.481	20:16 $\pm$ 01:21	5.073 $\pm$ 2.207	68.619 $\pm$ 2.481	08:06 $\pm$ 01:41	-1.235 $\pm$ 3.123	-1.640 $\pm$ 3.508	11:49 $\pm$ 02:10
LysoPC a C20:3	0.464 $\pm$ 0.083	2.013 $\pm$ 0.144	20:24 $\pm$ 00:41	0.042 $\pm$ 0.082	1.976 $\pm$ 0.143	19:18 $\pm$ 07:40	-0.422 $\pm$ 0.117	-0.037 $\pm$ 0.203	-01:05 $\pm$ 07:41
PC ae C40:4	0.065 $\pm$ 0.054	1.480 $\pm$ 0.078	14:46 $\pm$ 03:07	0.081 $\pm$ 0.054	1.710 $\pm$ 0.078	00:42 $\pm$ 02:27	0.016 $\pm$ 0.076	0.230 $\pm$ 0.110	09:56 $\pm$ 03:58
PC aa C38:4	2.191 $\pm$ 2.239	68.228 $\pm$ 4.628	17:52 $\pm$ 04:00	4.498 $\pm$ 2.251	77.889 $\pm$ 4.625	03:22 $\pm$ 01:55	2.307 $\pm$ 3.175	9.661 $\pm$ 6.543	09:30 $\pm$ 04:27
Val	10.897 $\pm$ 6.738	227.412 $\pm$ 8.512	13:51 $\pm$ 02:18	6.083 $\pm$ 6.620	209.350 $\pm$ 8.512	03:41 $\pm$ 04:12	-4.814 $\pm$ 9.446	-18.063 $\pm$ 12.037	-10:09 $\pm$ 04:48
LysoPC a C16:0	4.658 $\pm$ 2.638	66.578 $\pm$ 3.512	18:36 $\pm$ 02:13	3.444 $\pm$ 2.707	69.452 $\pm$ 3.508	00:44 $\pm$ 02:53	-1.214 $\pm$ 3.780	2.875 $\pm$ 4.963	06:08 $\pm$ 03:39
PC ae C38:5	0.524 $\pm$ 0.335	9.572 $\pm$ 0.485	14:10 $\pm$ 02:24	0.531 $\pm$ 0.338	10.038 $\pm$ 0.484	23:47 $\pm$ 02:20	0.007 $\pm$ 0.476	0.466 $\pm$ 0.685	09:36 $\pm$ 03:21
LysoPC a C18:0	1.571 $\pm$ 0.780	19.623 $\pm$ 1.346	19:24 $\pm$ 01:56	0.686 $\pm$ 0.798	20.393 $\pm$ 1.345	00:45 $\pm$ 04:17	-0.885 $\pm$ 1.116	0.770 $\pm$ 1.903	05:21 $\pm$ 04:42
PC aa C38:5	1.304 $\pm$ 0.998	27.671 $\pm$ 1.821	18:49 $\pm$ 02:59	1.797 $\pm$ 1.005	31.887 $\pm$ 1.820	03:00 $\pm$ 02:08	0.493 $\pm$ 1.417	4.216 $\pm$ 2.574	08:11 $\pm$ 03:40
Phe	3.636 $\pm$ 1.834	59.819 $\pm$ 1.771	17:58 $\pm$ 02:00	1.469 $\pm$ 1.872	57.943 $\pm$ 1.771	02:56 $\pm$ 04:51	-2.167 $\pm$ 2.620	-1.875 $\pm$ 2.505	08:58 $\pm$ 05:15
PC ae C36:4	0.613 $\pm$ 0.319	8.794 $\pm$ 0.527	13:29 $\pm$ 01:56	0.631 $\pm$ 0.320	9.430 $\pm$ 0.526	23:57 $\pm$ 01:51	0.018 $\pm$ 0.452	0.637 $\pm$ 0.745	10:28 $\pm$ 02:41
PC ae C40:5	0.099 $\pm$ 0.087	2.372 $\pm$ 0.120	15:30 $\pm$ 03:22	0.130 $\pm$ 0.089	2.798 $\pm$ 0.120	00:21 $\pm$ 02:30	0.031 $\pm$ 0.125	<i>0.426 $\pm$ 0.170</i>	08:50 $\pm$ 04:12
Trp	2.420 $\pm$ 1.859	56.493 $\pm$ 2.664	22:01 $\pm$ 02:52	4.208 $\pm$ 1.871	56.037 $\pm$ 2.664	01:02 $\pm$ 01:38	1.788 $\pm$ 2.638	-0.455 $\pm$ 3.768	03:00 $\pm$ 03:18
Kynurenine	0.118 $\pm$ 0.055	1.646 $\pm$ 0.087	10:03 $\pm$ 01:43	0.099 $\pm$ 0.053	1.686 $\pm$ 0.087	05:09 $\pm$ 02:07	-0.019 $\pm$ 0.076	0.040 $\pm$ 0.123	-04:54 $\pm$ 02:44
His	4.665 $\pm$ 2.318	78.016 $\pm$ 2.460	15:08 $\pm$ 01:54	0.881 $\pm$ 2.334	77.704 $\pm$ 2.460	02:26 $\pm$ 10:00	-3.784 $\pm$ 3.289	-0.312 $\pm$ 3.478	11:17 $\pm$ 10:11
LysoPC a C18:1	2.545 $\pm$ 0.558	14.465 $\pm$ 0.648	21:27 $\pm$ 00:49	1.158 $\pm$ 0.561	13.529 $\pm$ 0.647	13:25 $\pm$ 01:47	-1.387 $\pm$ 0.791	-0.936 $\pm$ 0.916	-08:01 $\pm$ 01:58
PC aa C40:4	0.087 $\pm$ 0.090	2.603 $\pm$ 0.282	16:34 $\pm$ 04:03	0.148 $\pm$ 0.091	2.844 $\pm$ 0.282	02:44 $\pm$ 02:20	0.061 $\pm$ 0.128	0.240 $\pm$ 0.399	10:09 $\pm$ 04:41
C18:2	0.002 $\pm$ 0.002	0.030 $\pm$ 0.002	18:09 $\pm$ 02:55	0.002 $\pm$ 0.002	0.032 $\pm$ 0.002	00:31 $\pm$ 02:32	0.000 $\pm$ 0.002	0.002 $\pm$ 0.002	06:21 $\pm$ 03:52
PC ae C44:6	0.038 $\pm$ 0.026	0.734 $\pm$ 0.046	16:20 $\pm$ 02:38	0.032 $\pm$ 0.027	0.841 $\pm$ 0.046	23:39 $\pm$ 03:01	-0.006 $\pm$ 0.037	0.108 $\pm$ 0.066	07:18 $\pm$ 04:00
PC aa C40:5	0.262 $\pm$ 0.211	5.692 $\pm$ 0.512	17:46 $\pm$ 03:09	0.461 $\pm$ 0.215	6.984 $\pm$ 0.512	01:59 $\pm$ 01:44	0.199 $\pm$ 0.301	1.292 $\pm$ 0.724	08:13 $\pm$ 03:36
PC ae C42:5	0.052 $\pm$ 0.040	1.007 $\pm$ 0.046	16:47 $\pm$ 02:58	0.052 $\pm$ 0.040	1.195 $\pm$ 0.045	22:26 $\pm$ 02:52	0.000 $\pm$ 0.057	<i>0.187 $\pm$ 0.064</i>	05:39 $\pm$ 04:07
PC ae C38:3	0.173 $\pm$ 0.121	3.599 $\pm$ 0.232	17:27 $\pm$ 02:44	0.210 $\pm$ 0.123	3.967 $\pm$ 0.232	01:26 $\pm$ 02:11	0.037 $\pm$ 0.173	0.368 $\pm$ 0.328	07:59 $\pm$ 03:29
C2	0.216 $\pm$ 0.129	3.388 $\pm$ 0.159	22:11 $\pm$ 02:14	0.478 $\pm$ 0.129	3.970 $\pm$ 0.158	10:43 $\pm$ 01:00	0.262 $\pm$ 0.182	<i>0.582 $\pm$ 0.224</i>	-11:27 $\pm$ 02:27
Met	0.872 $\pm$ 0.837	22.893 $\pm$ 0.844	13:30 $\pm$ 03:34	1.029 $\pm$ 0.821	24.527 $\pm$ 0.844	20:17 $\pm$ 03:05	0.157 $\pm$ 1.172	1.635 $\pm$ 1.194	06:47 $\pm$ 04:43
LysoPC a C16:1	0.150 $\pm$ 0.070	1.792 $\pm$ 0.096	18:57 $\pm$ 01:49	0.131 $\pm$ 0.072	1.930 $\pm$ 0.096	00:39 $\pm$ 02:01	-0.019 $\pm$ 0.100	0.139 $\pm$ 0.135	05:41 $\pm$ 02:43
PC ae C44:5	0.038 $\pm$ 0.032	0.880 $\pm$ 0.057	16:36 $\pm$ 03:16	0.040 $\pm$ 0.032	1.018 $\pm$ 0.057	23:02 $\pm$ 03:01	0.002 $\pm$ 0.045	0.138 $\pm$ 0.080	06:26 $\pm$ 04:27
SDMA	0.005 $\pm$ 0.015	0.460 $\pm$ 0.020	22:58 $\pm$ 10:36	0.021 $\pm$ 0.015	0.454 $\pm$ 0.020	22:20 $\pm$ 02:39	0.016 $\pm$ 0.022	-0.006 $\pm$ 0.028	-00:38 $\pm$ 10:55
LysoPC a C18:2	6.531 $\pm$ 1.579	40.562 $\pm$ 1.745	19:44 $\pm$ 00:56	4.109 $\pm$ 1.615	33.358 $\pm$ 1.742	11:56 $\pm$ 01:26	-2.422 $\pm$ 2.258	<i>-7.204 $\pm$ 2.466</i>	-07:47 $\pm$ 01:43
PC aa C42:4	0.005 $\pm$ 0.006	0.161 $\pm$ 0.011	01:03 $\pm$ 04:35	0.007 $\pm$ 0.006	0.160 $\pm$ 0.011	11:31 $\pm$ 03:10	0.002 $\pm$ 0.009	-0.001 $\pm$ 0.016	10:28 $\pm$ 05:34
Sarcosine	1.103 $\pm$ 0.175	4.727 $\pm$ 0.288	20:50 $\pm$ 00:36	1.381 $\pm$ 0.176	4.913 $\pm$ 0.288	21:47 $\pm$ 00:28	0.279 $\pm$ 0.248	0.186 $\pm$ 0.407	00:57 $\pm$ 00:46

Metabolite	Day Shift Condition			Night Shift Condition			Difference between Conditions		
	Amplitude $\pm$ SE	Mesor $\pm$ SE	Acrophase $\pm$ SE	Amplitude $\pm$ SE	Mesor $\pm$ SE	Acrophase $\pm$ SE	Amplitude Δ $\pm$ SE	Mesor Δ $\pm$ SE	Acrophase Δ $\pm$ SE
Pro	35.570 $\pm$ 7.014	203.241 $\pm$ 13.280	11:51 $\pm$ 00:43	16.491 $\pm$ 6.994	174.900 $\pm$ 13.280	22:54 $\pm$ 01:34	-19.079 $\pm$ 9.905	-28.341 $\pm$ 18.781	11:02 $\pm$ 01:43
Creatinine	3.609 $\pm$ 8.006	126.698 $\pm$ 9.725	02:28 $\pm$ 08:23	6.581 $\pm$ 7.809	134.485 $\pm$ 9.725	06:02 $\pm$ 04:42	2.972 $\pm$ 11.184	7.786 $\pm$ 13.754	03:33 $\pm$ 09:37
LysoPC a C24:0	0.005 $\pm$ 0.005	0.122 $\pm$ 0.006	19:05 $\pm$ 03:27	0.003 $\pm$ 0.005	0.130 $\pm$ 0.006	21:09 $\pm$ 05:18	-0.002 $\pm$ 0.006	0.008 $\pm$ 0.009	02:03 $\pm$ 06:19
LysoPC a C28:0	0.015 $\pm$ 0.006	0.150 $\pm$ 0.010	16:25 $\pm$ 01:35	0.011 $\pm$ 0.006	0.161 $\pm$ 0.010	22:51 $\pm$ 01:59	-0.003 $\pm$ 0.009	0.011 $\pm$ 0.014	06:25 $\pm$ 02:32
C5-DC (C6-OH)	0.000 $\pm$ 0.001	0.010 $\pm$ 0.001	15:28 $\pm$ 05:48	0.002 $\pm$ 0.001	0.011 $\pm$ 0.001	05:13 $\pm$ 01:37	0.001 $\pm$ 0.001	0.001 $\pm$ 0.001	-10:15 $\pm$ 06:01
C14:1	0.002 $\pm$ 0.002	0.031 $\pm$ 0.002	19:23 $\pm$ 03:43	0.001 $\pm$ 0.002	0.034 $\pm$ 0.002	06:02 $\pm$ 04:51	0.000 $\pm$ 0.002	0.003 $\pm$ 0.002	10:38 $\pm$ 06:07
LysoPC a C26:1	0.011 $\pm$ 0.004	0.102 $\pm$ 0.004	18:27 $\pm$ 01:23	0.008 $\pm$ 0.004	0.116 $\pm$ 0.004	00:20 $\pm$ 01:56	-0.003 $\pm$ 0.006	0.013 $\pm$ 0.006	05:52 $\pm$ 02:23
C7-DC	0.001 $\pm$ 0.002	0.016 $\pm$ 0.002	14:21 $\pm$ 07:48	0.003 $\pm$ 0.002	0.016 $\pm$ 0.002	08:15 $\pm$ 02:19	0.002 $\pm$ 0.002	0.001 $\pm$ 0.002	-06:05 $\pm$ 08:08
LysoPC a C26:0	0.023 $\pm$ 0.008	0.176 $\pm$ 0.011	18:05 $\pm$ 01:20	0.027 $\pm$ 0.008	0.194 $\pm$ 0.011	23:10 $\pm$ 01:05	0.004 $\pm$ 0.011	0.018 $\pm$ 0.015	05:05 $\pm$ 01:43
Gly	15.780 $\pm$ 8.286	259.371 $\pm$ 17.728	13:50 $\pm$ 01:57	4.999 $\pm$ 8.306	271.632 $\pm$ 17.728	13:31 $\pm$ 06:10	-10.781 $\pm$ 11.732	12.261 $\pm$ 25.071	-00:18 $\pm$ 06:28
Asn	1.589 $\pm$ 2.247	58.917 $\pm$ 3.473	22:03 $\pm$ 05:17	4.095 $\pm$ 2.252	64.240 $\pm$ 3.473	10:19 $\pm$ 02:02	2.506 $\pm$ 3.181	5.323 $\pm$ 4.911	-11:44 $\pm$ 05:40
PC aa C42:0	0.016 $\pm$ 0.014	0.334 $\pm$ 0.027	16:27 $\pm$ 03:14	0.017 $\pm$ 0.014	0.427 $\pm$ 0.027	20:54 $\pm$ 03:01	0.001 $\pm$ 0.019	0.093 $\pm$ 0.039	04:27 $\pm$ 04:25
Arg	8.037 $\pm$ 3.211	92.811 $\pm$ 7.771	18:33 $\pm$ 01:35	6.480 $\pm$ 3.330	98.089 $\pm$ 7.771	12:42 $\pm$ 01:53	-1.557 $\pm$ 4.626	5.278 $\pm$ 10.990	-05:51 $\pm$ 02:28
Thr	8.757 $\pm$ 4.405	122.990 $\pm$ 6.769	11:09 $\pm$ 01:51	3.478 $\pm$ 4.263	147.150 $\pm$ 6.769	19:15 $\pm$ 04:49	-5.279 $\pm$ 6.130	24.160 $\pm$ 9.573	08:05 $\pm$ 05:10
PC aa C42:1	0.007 $\pm$ 0.007	0.185 $\pm$ 0.017	17:52 $\pm$ 03:57	0.008 $\pm$ 0.007	0.231 $\pm$ 0.017	18:44 $\pm$ 03:48	0.000 $\pm$ 0.010	0.047 $\pm$ 0.024	00:52 $\pm$ 05:29
Ser	3.685 $\pm$ 3.420	99.101 $\pm$ 7.197	21:51 $\pm$ 03:29	5.626 $\pm$ 3.415	112.155 $\pm$ 7.197	09:39 $\pm$ 02:17	1.940 $\pm$ 4.833	13.054 $\pm$ 10.178	11:48 $\pm$ 04:10
PC ae C40:2	0.052 $\pm$ 0.035	0.981 $\pm$ 0.075	15:36 $\pm$ 02:37	0.061 $\pm$ 0.036	1.130 $\pm$ 0.075	22:53 $\pm$ 02:09	0.009 $\pm$ 0.050	0.149 $\pm$ 0.106	07:17 $\pm$ 03:23
Gln	56.291 $\pm$ 20.540	659.548 $\pm$ 36.599	15:30 $\pm$ 01:24	28.488 $\pm$ 20.662	674.291 $\pm$ 36.599	14:55 $\pm$ 02:45	-27.803 $\pm$ 29.134	14.743 $\pm$ 51.759	-00:35 $\pm$ 03:06
PC ae C42:3	0.008 $\pm$ 0.017	0.484 $\pm$ 0.036	16:40 $\pm$ 08:36	0.006 $\pm$ 0.017	0.508 $\pm$ 0.036	22:19 $\pm$ 09:51	-0.001 $\pm$ 0.024	0.024 $\pm$ 0.051	05:39 $\pm$ 13:04
SM C26:1	0.029 $\pm$ 0.018	0.400 $\pm$ 0.041	13:01 $\pm$ 02:21	0.033 $\pm$ 0.018	0.459 $\pm$ 0.041	02:41 $\pm$ 02:03	0.004 $\pm$ 0.025	0.059 $\pm$ 0.058	-10:20 $\pm$ 03:07
PC ae C44:3	0.000 $\pm$ 0.002	0.055 $\pm$ 0.004	13:10 $\pm$ 21:20	0.005 $\pm$ 0.002	0.061 $\pm$ 0.004	23:34 $\pm$ 01:50	0.004 $\pm$ 0.003	0.006 $\pm$ 0.005	10:24 $\pm$ 21:25
SM C26:0	0.003 $\pm$ 0.010	0.245 $\pm$ 0.019	12:01 $\pm$ 11:10	0.007 $\pm$ 0.010	0.261 $\pm$ 0.019	21:30 $\pm$ 05:53	0.003 $\pm$ 0.014	0.017 $\pm$ 0.026	09:29 $\pm$ 12:37
SM (OH) C24:1	0.061 $\pm$ 0.059	1.505 $\pm$ 0.099	14:31 $\pm$ 03:41	0.077 $\pm$ 0.060	1.684 $\pm$ 0.099	01:09 $\pm$ 02:52	0.016 $\pm$ 0.084	0.179 $\pm$ 0.140	10:37 $\pm$ 04:41
Orn	3.384 $\pm$ 1.525	47.645 $\pm$ 3.239	17:51 $\pm$ 01:47	4.780 $\pm$ 1.530	49.685 $\pm$ 3.239	07:06 $\pm$ 01:15	1.396 $\pm$ 2.161	2.040 $\pm$ 4.580	-10:44 $\pm$ 02:11
PC aa C42:2	0.022 $\pm$ 0.007	0.163 $\pm$ 0.013	23:54 $\pm$ 01:11	0.024 $\pm$ 0.007	0.166 $\pm$ 0.013	13:27 $\pm$ 01:06	0.002 $\pm$ 0.010	0.003 $\pm$ 0.018	-10:27 $\pm$ 01:37
PC ae C40:3	0.038 $\pm$ 0.028	0.873 $\pm$ 0.051	17:16 $\pm$ 02:53	0.042 $\pm$ 0.029	0.939 $\pm$ 0.051	23:06 $\pm$ 02:32	0.004 $\pm$ 0.041	0.067 $\pm$ 0.071	05:49 $\pm$ 03:50
SM C24:1	4.553 $\pm$ 4.120	105.360 $\pm$ 8.341	13:40 $\pm$ 03:23	6.606 $\pm$ 4.131	121.096 $\pm$ 8.337	00:55 $\pm$ 02:18	2.053 $\pm$ 5.835	15.736 $\pm$ 11.794	11:14 $\pm$ 04:06
Cit	0.676 $\pm$ 0.885	25.951 $\pm$ 1.634	19:11 $\pm$ 05:09	1.874 $\pm$ 0.911	28.562 $\pm$ 1.634	01:40 $\pm$ 01:48	1.198 $\pm$ 1.270	2.610 $\pm$ 2.311	06:28 $\pm$ 05:28
PC aa C42:5	0.006 $\pm$ 0.007	0.182 $\pm$ 0.014	15:21 $\pm$ 04:43	0.009 $\pm$ 0.007	0.210 $\pm$ 0.014	01:54 $\pm$ 03:01	0.003 $\pm$ 0.010	0.028 $\pm$ 0.019	10:32 $\pm$ 05:36
PC ae C44:4	0.010 $\pm$ 0.006	0.157 $\pm$ 0.013	17:39 $\pm$ 02:17	0.009 $\pm$ 0.006	0.191 $\pm$ 0.013	00:30 $\pm$ 02:32	-0.001 $\pm$ 0.009	0.034 $\pm$ 0.018	06:51 $\pm$ 03:25
PC aa C40:3	0.002 $\pm$ 0.012	0.328 $\pm$ 0.024	03:35 $\pm$ 05:15	0.009 $\pm$ 0.011	0.339 $\pm$ 0.024	16:58 $\pm$ 05:00	0.007 $\pm$ 0.016	0.011 $\pm$ 0.034	-10:37 $\pm$ 05:40
PC ae C42:4	0.021 $\pm$ 0.019	0.513 $\pm$ 0.027	15:44 $\pm$ 03:29	0.026 $\pm$ 0.020	0.571 $\pm$ 0.027	23:19 $\pm$ 02:48	0.004 $\pm$ 0.027	0.058 $\pm$ 0.039	07:35 $\pm$ 04:28
Ala	35.568 $\pm$ 14.124	372.478 $\pm$ 22.718	10:45 $\pm$ 01:28	11.676 $\pm$ 13.707	389.346 $\pm$ 22.718	19:21 $\pm$ 04:37	-23.892 $\pm$ 19.682	16.868 $\pm$ 32.128	08:35 $\pm$ 04:50
C18:1	0.012 $\pm$ 0.003	0.064 $\pm$ 0.002	20:58 $\pm$ 00:51	0.006 $\pm$ 0.003	0.075 $\pm$ 0.002	11:34 $\pm$ 01:39	-0.006 $\pm$ 0.004	0.010 $\pm$ 0.003	-09:23 $\pm$ 01:52
Taurine	18.702 $\pm$ 4.581	88.146 $\pm$ 5.696	10:56 $\pm$ 00:54	16.592 $\pm$ 4.520	88.797 $\pm$ 5.696	09:16 $\pm$ 01:02	-2.110 $\pm$ 6.435	0.650 $\pm$ 8.055	-01:39 $\pm$ 01:22
PC aa C40:2	0.054 $\pm$ 0.012	0.262 $\pm$ 0.021	00:14 $\pm$ 00:49	0.066 $\pm$ 0.012	0.211 $\pm$ 0.021	12:50 $\pm$ 00:39	0.012 $\pm$ 0.017	-0.051 $\pm$ 0.030	-11:24 $\pm$ 01:03
ADMA	0.003 $\pm$ 0.019	0.503 $\pm$ 0.020	14:51 $\pm$ 03:54	0.005 $\pm$ 0.019	0.485 $\pm$ 0.020	03:22 $\pm$ 14:20	0.002 $\pm$ 0.027	-0.018 $\pm$ 0.028	-11:28 $\pm$ 07:22
Serotonin	0.277 $\pm$ 0.055	0.538 $\pm$ 0.058	10:40 $\pm$ 00:44	0.175 $\pm$ 0.054	0.580 $\pm$ 0.058	08:46 $\pm$ 01:11	-0.102 $\pm$ 0.078	0.042 $\pm$ 0.082	-01:54 $\pm$ 01:24
Glu	3.478 $\pm$ 2.733	45.856 $\pm$ 3.217	06:41 $\pm$ 03:06	12.916 $\pm$ 2.756	57.897 $\pm$ 3.217	04:04 $\pm$ 00:49	9.437 $\pm$ 3.881	12.041 $\pm$ 4.549	-02:37 $\pm$ 03:13
PC aa C24:0	0.008 $\pm$ 0.004	0.052 $\pm$ 0.013	18:10 $\pm$ 01:41	0.006 $\pm$ 0.004	0.074 $\pm$ 0.013	23:43 $\pm$ 02:15	-0.002 $\pm$ 0.005	0.022 $\pm$ 0.019	05:33 $\pm$ 02:49

Table S2. Factor loadings from PCA.

<i>Metabolite</i>	<i>Cluster 1</i>	<i>Cluster 2</i>	<i>Cluster 3</i>	<i>Metabolite</i>	<i>Cluster 1</i>	<i>Cluster 2</i>	<i>Cluster 3</i>
PC aa C30:0	0.8518	0.1871	0.2281	Val	0.2820	0.7706	0.2088
PC ae C34:3	0.8342	0.3633	0.1602	lysoPC a C16:0	0.3401	0.7566	0.3287
PC aa C36:6	0.7950	0.0338	0.4794	PC ae C38:5	0.4991	0.7449	0.3058
PC aa C32:1	0.7771	0.1239	0.2063	lysoPC a C18:0	0.3910	0.7336	0.2591
PC ae C34:0	0.7743	0.3940	0.1596	PC aa C38:5	0.4294	0.7327	0.1785
PC ae C32:1	0.7708	0.2725	0.3604	Phe	0.3547	0.7179	0.3995
PC ae C34:2	0.7694	0.4099	0.3130	PC ae C36:4	0.5722	0.7163	0.2003
PC ae C34:1	0.7619	0.4193	0.4420	PC ae C40:5	0.4230	0.7104	0.3644
PC aa C34:3	0.7608	0.3060	0.3267	Trp	0.4416	0.7099	0.3124
PC aa C34:4	0.7437	0.4689	0.0047	Kynurenine	0.3481	0.7064	0.2498
PC aa C32:0	0.7379	0.2883	0.4098	His	0.2715	0.7023	0.5296
PC ae C36:2	0.7331	0.4612	0.3077	lysoPC a C18:1	0.1288	0.6988	0.3888
PC ae C38:6	0.7312	0.3603	0.4370	PC aa C40:4	0.5389	0.6968	-0.0272
PC ae C36:5	0.7272	0.5836	0.0472	C18:2	0.1301	0.6828	0.2898
PC ae C36:1	0.7160	0.5763	0.2829	PC ae C44:6	0.0024	0.6476	0.4994
PC ae C36:0	0.7129	0.3017	0.2942	PC aa C40:5	0.5144	0.6450	0.1565
PC ae C32:2	0.7086	0.2015	0.4913	PC ae C42:5	0.1487	0.6444	0.5004
PC aa C32:3	0.7044	0.4713	0.2549	PC ae C38:3	0.5709	0.6400	0.2987
SM C18:0	0.7040	0.3772	0.4558	C2	-0.0428	0.6349	0.2986
PC ae C36:3	0.7007	0.4249	0.4666	Met	0.3304	0.6123	0.4065
PC aa C34:1	0.6952	0.4040	0.2757	lysoPC a C16:1	0.2532	0.6080	0.5139
SM C18:1	0.6876	0.4463	0.3568	PC ae C44:5	-0.0678	0.5912	0.5636
PC aa C40:6	0.6852	0.1248	0.5070	SDMA	0.0753	0.5766	0.4849
PC aa C38:6	0.6771	0.0591	0.6163	lysoPC a C18:2	0.1529	0.5692	0.3447
PC ae C30:0	0.6765	0.4455	0.1348	PC aa C42:4	0.4164	0.5664	0.3682
SM C16:0	0.6719	0.3283	0.5753	Sarcosine	0.2643	0.4963	0.2836
PC ae C38:0	0.6568	0.0768	0.6182	Pro	-0.0636	0.4846	0.2859
PC aa C38:0	0.6536	0.0670	0.6482	Creatinine	0.1462	0.4673	-0.0016
PC ae C42:2	0.6526	0.3882	0.4630	lysoPC a C24:0	0.2961	0.4662	0.2215
SM (OH) C22:1	0.6415	0.4816	0.4380	lysoPC a C28:0	0.2359	0.3732	-0.0828
SM (OH) C16:1	0.6407	0.4038	0.4867	C5-DC (C6-OH)	0.2712	0.3677	0.1028
SM (OH) C22:2	0.6398	0.4895	0.4906	C14:1	0.3511	0.3515	0.3229
PC aa C36:0	0.6364	-0.1855	0.1928	lysoPC a C26:1	0.2674	0.3429	0.0106
SM C16:1	0.6325	0.4272	0.5032	C7-DC	0.1548	0.2932	0.0932
PC ae C40:1	0.6224	0.2105	0.4994	lysoPC a C26:0	0.0894	0.2112	-0.0397
SM (OH) C14:1	0.6059	0.4065	0.4829	Gly	0.1471	0.2560	0.8531
PC aa C36:1	0.6038	0.4676	0.2980	Asn	0.1228	0.2160	0.8246
PC aa C36:5	0.6006	0.4545	0.1752	PC aa C42:0	0.2630	0.2063	0.8094
Tyr	0.5937	0.5115	0.4079	Arg	0.1752	0.0219	0.7967
PC aa C36:3	0.5929	0.5389	0.3012	Thr	0.0952	0.2863	0.7950
PC aa C36:4	0.5864	0.5849	0.1162	PC aa C42:1	0.3999	0.2064	0.7844
PC ae C40:6	0.5835	0.3392	0.5614	Ser	0.2149	0.1890	0.7754
PC aa C36:2	0.5752	0.1542	0.0777	PC ae C40:2	0.5535	0.1970	0.7526
PC aa C42:6	0.5705	0.4315	0.4773	Gln	0.2074	0.3683	0.7501
PC aa C28:1	0.5585	0.5120	0.3395	PC ae C42:3	0.5508	0.2333	0.7270
SM C24:0	0.5489	0.4493	0.4599	SM C26:1	0.5956	0.0428	0.7198
PC aa C38:3	0.5359	0.5314	0.1815	PC ae C44:3	0.3615	0.3515	0.7115
lysoPC a C28:1	0.5358	0.3585	0.2409	SM C26:0	0.5380	0.1611	0.7081
PC aa C34:2	0.5352	0.0475	0.0478	SM (OH) C24:1	0.5193	0.2893	0.7012
SM C20:2	0.5285	0.4055	0.4675	Orn	0.0616	0.2104	0.6993
PC ae C42:1	0.5183	0.4020	0.3981	PC aa C42:2	0.3804	0.1259	0.6988
Lys	0.5147	0.5114	0.1668	PC ae C40:3	0.5572	0.3702	0.6665
PC ae C38:2	0.5067	0.2276	0.1580	SM C24:1	0.5633	0.2955	0.6659
PC ae C30:2	0.4774	0.4564	0.3445	Cit	0.1145	0.4092	0.6645
C9	0.4332	0.1441	-0.0103	PC aa C42:5	0.5529	0.3062	0.6595
C3-DC (C4-OH)	0.3010	0.0349	-0.0235	PC ae C44:4	0.0064	0.4185	0.6519
C14:2	0.2665	0.1879	0.1665	PC aa C40:3	0.5093	0.3241	0.6490
lysoPC a C20:4	-0.0101	0.8838	0.0602	PC ae C42:4	0.1840	0.5706	0.6283
lysoPC a C17:0	0.2864	0.8296	0.2469	Ala	0.4101	0.3311	0.5538
PC ae C38:4	0.3753	0.8175	0.1354	C18:1	0.0213	0.4960	0.5286
C0	0.3445	0.8027	0.0215	Taurine	0.0607	0.0395	0.4872
Leu	0.2036	0.7949	0.1873	PC aa C40:2	0.3014	0.1923	0.4706
Ile	0.2252	0.7934	0.2380	ADMA	0.1413	0.4010	0.4461
lysoPC a C20:3	0.1669	0.7794	0.1466	Serotonin	0.1649	-0.1272	0.3241
PC ae C40:4	0.3375	0.7766	0.3024	Glu	0.1356	0.2405	0.2728
PC aa C38:4	0.4443	0.7762	0.0559	PC aa C24:0	-0.2173	0.1859	-0.2533

Table S3. Pathway analysis for the simulated day shift schedule.

Pathway	Total	Expected	Hits	p	$-\log(p)$	Holm p	FDR	Impact
Aminoacyl-tRNA biosynthesis	75	0.467	8	$3.30 \cdot 10^{-9}$	19.53	$2.64 \cdot 10^{-7}$	$2.64 \cdot 10^{-7}$	0.113
Nitrogen metabolism	39	0.243	5	$2.29 \cdot 10^{-6}$	12.99	$1.81 \cdot 10^{-4}$	$9.16 \cdot 10^{-5}$	0.008
Alanine, aspartate and glutamate metabolism	24	0.150	4	$9.66 \cdot 10^{-6}$	11.55	$7.53 \cdot 10^{-4}$	$2.58 \cdot 10^{-4}$	0.486
Arginine and proline metabolism	77	0.480	5	$6.87 \cdot 10^{-5}$	9.59	$5.29 \cdot 10^{-3}$	$1.37 \cdot 10^{-3}$	0.312
Cyanoamino acid metabolism	16	0.100	3	0.0001	9.17	$7.94 \cdot 10^{-3}$	$1.67 \cdot 10^{-3}$	0
D-Arginine and D-ornithine metabolism	8	0.050	2	0.0010	6.91	0.075	0.013	0
Glutathione metabolism	38	0.237	3	0.0015	6.54	0.107	0.017	0.011
D-glutamine and D-glutamate metabolism	11	0.069	2	0.0019	6.25	0.141	0.019	0.139
Glycine, serine and threonine metabolism	48	0.299	3	0.0029	5.86	0.206	0.025	0.420
Taurine and hypotaurine metabolism	20	0.125	2	0.0065	5.04	0.458	0.052	0.363
Sphingolipid metabolism	25	0.156	2	0.0100	4.60	0.701	0.073	0.010
Methane metabolism	34	0.212	2	0.0181	4.01	1.000	0.121	0.018
Porphyrin and chlorophyll metabolism	104	0.648	3	0.0244	3.71	1.000	0.150	0
Primary bile acid biosynthesis	47	0.293	2	0.0333	3.40	1.000	0.191	0.016
Cysteine and methionine metabolism	56	0.349	2	0.0460	3.08	1.000	0.245	0.012
Linoleic acid metabolism	15	0.093	1	0.0898	2.41	1.000	0.449	0
Sulfur metabolism	18	0.112	1	0.1068	2.24	1.000	0.489	0
Purine metabolism	92	0.573	2	0.1100	2.21	1.000	0.489	0
Selenoamino acid metabolism	22	0.137	1	0.1290	2.05	1.000	0.543	0
Thiamine metabolism	24	0.150	1	0.1399	1.97	1.000	0.560	0
Valine, leucine and isoleucine biosynthesis	27	0.168	1	0.1561	1.86	1.000	0.595	0
Alpha-linolenic acid metabolism	29	0.181	1	0.1667	1.79	1.000	0.606	0
Glycerophospholipid metabolism	39	0.243	1	0.2179	1.52	1.000	0.743	0.101
Butanoate metabolism	40	0.249	1	0.2228	1.50	1.000	0.743	0
Histidine metabolism	44	0.274	1	0.2424	1.42	1.000	0.776	0.001
Lysine degradation	47	0.293	1	0.2567	1.36	1.000	0.790	0
Pyrimidine metabolism	60	0.374	1	0.3160	1.15	1.000	0.928	0
Arachidonic acid metabolism	62	0.386	1	0.3247	1.12	1.000	0.928	0
Tryptophan metabolism	79	0.492	1	0.3947	0.93	1.000	1.000	0.057

Table S4. Pathway analysis for the simulated night shift schedule.

Pathway	Total	Expected	Hits	p	$-\log(p)$	Holm p	FDR	Impact
Aminoacyl-tRNA biosynthesis	75	0.561	10	$1.68 \cdot 10^{-11}$	24.81	$1.35 \cdot 10^{-9}$	$1.35 \cdot 10^{-9}$	0.056
Nitrogen metabolism	39	0.292	4	0.0002	8.78	0.012	$4.85 \cdot 10^{-3}$	0
Arginine and proline metabolism	77	0.576	5	0.0002	8.61	0.014	$4.85 \cdot 10^{-3}$	0.365
Valine, leucine and isoleucine biosynthesis	27	0.202	3	0.0009	6.99	0.071	0.018	0.027
D-Arginine and D-ornithine metabolism	8	0.060	2	0.0014	6.54	0.109	0.023	0
Taurine and hypotaurine metabolism	20	0.150	2	0.0093	4.68	0.695	0.124	0.363
Alanine, aspartate and glutamate metabolism	24	0.179	2	0.0132	4.33	0.979	0.151	0.264
Glycerophospholipid metabolism	39	0.292	2	0.0332	3.40	1.000	0.310	0.104
Valine, leucine and isoleucine degradation	40	0.299	2	0.0348	3.36	1.000	0.310	0.022
Glycine, serine and threonine metabolism	48	0.359	2	0.0486	3.02	1.000	0.389	0.146
Biotin metabolism	11	0.082	1	0.0794	2.53	1.000	0.529	0
D-glutamine and D-glutamate metabolism	11	0.082	1	0.0794	2.53	1.000	0.529	0.027
Linoleic acid metabolism	15	0.112	1	0.1068	2.24	1.000	0.657	0
Tryptophan metabolism	79	0.591	2	0.1160	2.15	1.000	0.663	0.092
Selenoamino acid metabolism	22	0.165	1	0.1528	1.88	1.000	0.815	0
Sphingolipid metabolism	25	0.187	1	0.1719	1.76	1.000	0.828	0.010
Phenylalanine, tyrosine and tryptophan biosynthesis	27	0.202	1	0.1844	1.69	1.000	0.828	0.001
Beta-alanine metabolism	28	0.209	1	0.1905	1.66	1.000	0.828	0
Alpha-linolenic acid metabolism	29	0.217	1	0.1967	1.63	1.000	0.828	0
Lysine biosynthesis	32	0.239	1	0.2148	1.54	1.000	0.859	0.100
Glutathione metabolism	38	0.284	1	0.2498	1.39	1.000	0.952	0
Histidine metabolism	44	0.329	1	0.2834	1.26	1.000	0.959	0.140
Phenylalanine metabolism	45	0.337	1	0.2889	1.24	1.000	0.959	0.119
Primary bile acid biosynthesis	47	0.351	1	0.2997	1.21	1.000	0.959	0.008
Lysine degradation	47	0.351	1	0.2997	1.21	1.000	0.959	0.147
Cysteine and methionine metabolism	56	0.419	1	0.3464	1.06	1.000	1.000	0
Pyrimidine metabolism	60	0.449	1	0.3662	1.00	1.000	1.000	0
Arachidonic acid metabolism	62	0.464	1	0.3759	0.98	1.000	1.000	0
Purine metabolism	92	0.688	1	0.5054	0.68	1.000	1.000	0
Porphyrin and chlorophyll metabolism	104	0.778	1	0.5497	0.60	1.000	1.000	0

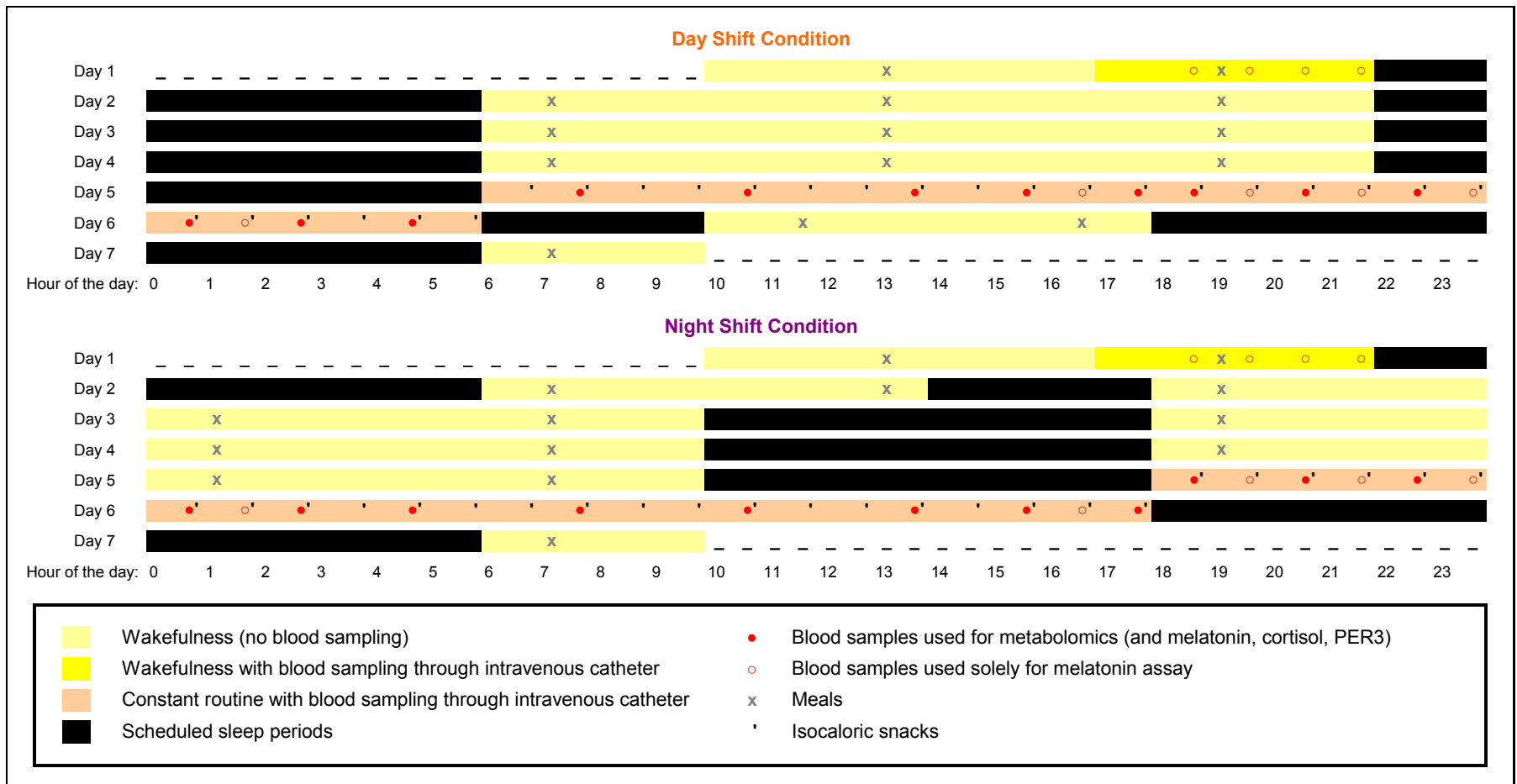


Fig. S1. In-laboratory study protocol comprising an adaptation period, 3 days on a simulated day shift or night shift schedule, 24 h under constant routine – sustained wakefulness in constant ambient temperature and dim light, fixed posture, and hourly, identical snacks (which were all consumed) – and a recovery period.

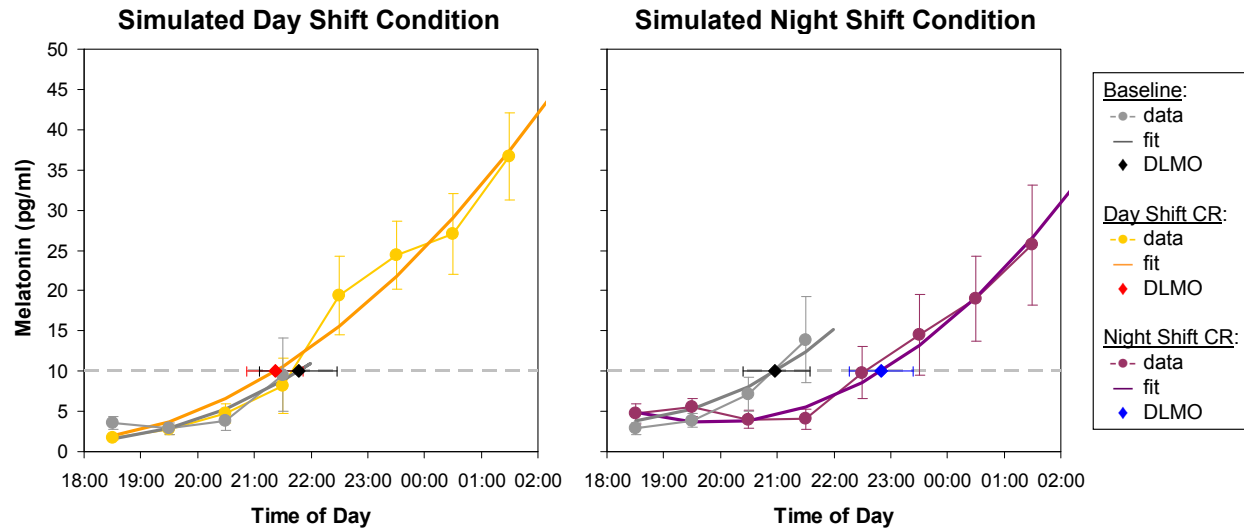


Fig. S2. Plasma melatonin and dim light melatonin onset (DLMO) at baseline and during the constant routine (CR) after simulated day shift work (left) and night shift work (right). For the day shift condition, the threshold of 10 pg/ml was crossed during baseline at 21:47 (± 41 min) and during the constant routine at 21:22 (± 30 min) – indicating a phase difference (advance) of -25 min (± 37 min), which was not statistically significant ($t_6 = -0.66$, $p = 0.53$). For the night shift condition, the threshold was crossed during baseline at 20:58 (± 37 min) and during the constant routine at 22:50 (± 34 min) – indicating a phase difference (delay) of 112 min (± 32 min), which was statistically significant ($t_6 = 3.53$, $p = 0.012$). There was no significant difference in the baseline phase of the DLMO between the two groups ($t_{12} = -1.23$, $p = 0.24$); but during the constant routine, the timing of the DLMO was significantly later by 88 min (± 32 min) in the night shift condition ($t_{12} = 2.72$, $p = 0.019$). Gray/black: baseline. Orange/red: constant routine after simulated day shift condition. Purple/blue: constant routine after simulated night shift condition. Light tinted circles: group means ($\pm$ SE). Dark tinted curves: Taylor series approximation fits. Dashed line: 10 pg/ml threshold for DLMO. Diamonds: timing of DLMO ($\pm$ SE).

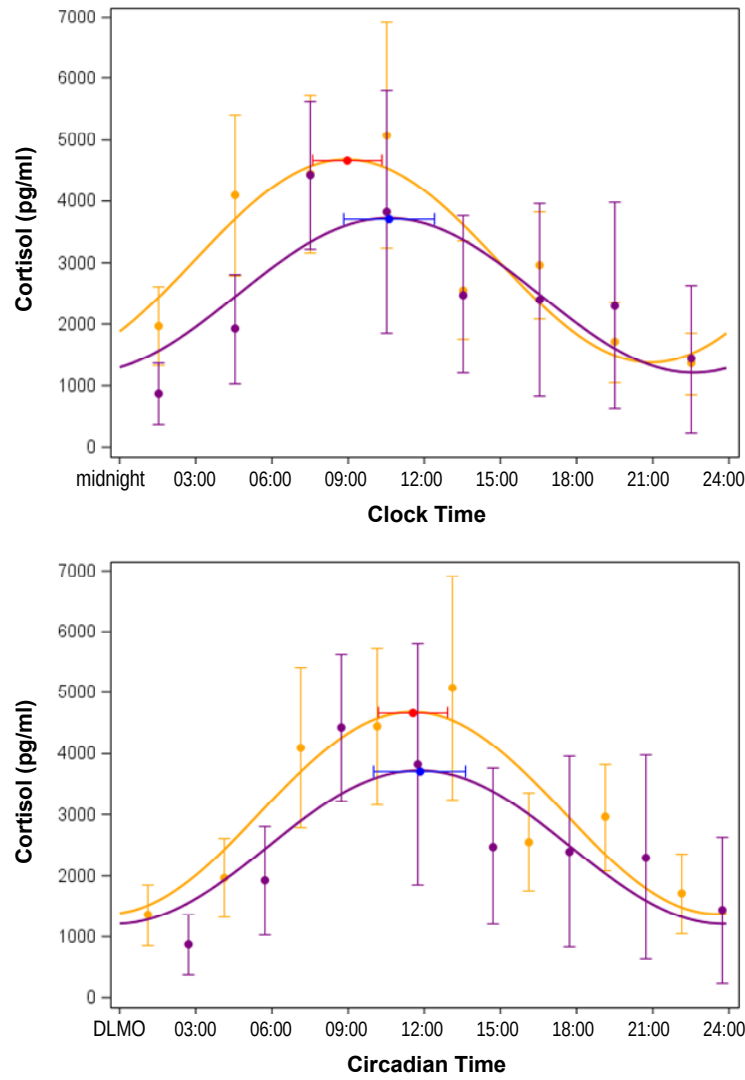


Fig. S3. Plasma cortisol during constant routine after simulated day shift work (orange) and night shift work (purple), plotted against time of day (top) and against circadian time relative to DLMO (bottom). For the day shift condition, there was a significant 24-h rhythm ($t_6=5.60$, $p<0.001$), and the acrophase occurred at 08:55 (± 40 min). For the night shift condition, there was also a significant 24-h rhythm ($t_6=4.26$, $p=0.003$), and the acrophase occurred at 10:35 (± 53 min). The phase difference between the two groups during the constant routine involved a delay of 100 min (± 67 min) in the night shift condition, which was not statistically significant ($t_{12}=1.48$, $p=0.16$), but was similar to the delay of 88 min (± 32 min) seen for the DLMO (see Fig. S2). Orange/red: constant routine after simulated day shift condition. Purple/blue: constant routine after simulated night shift condition. Circles: group means ($\pm$ SE). Curves: cosinor fits. Red and blue markers: timing of acrophase (and 95% confidence interval).

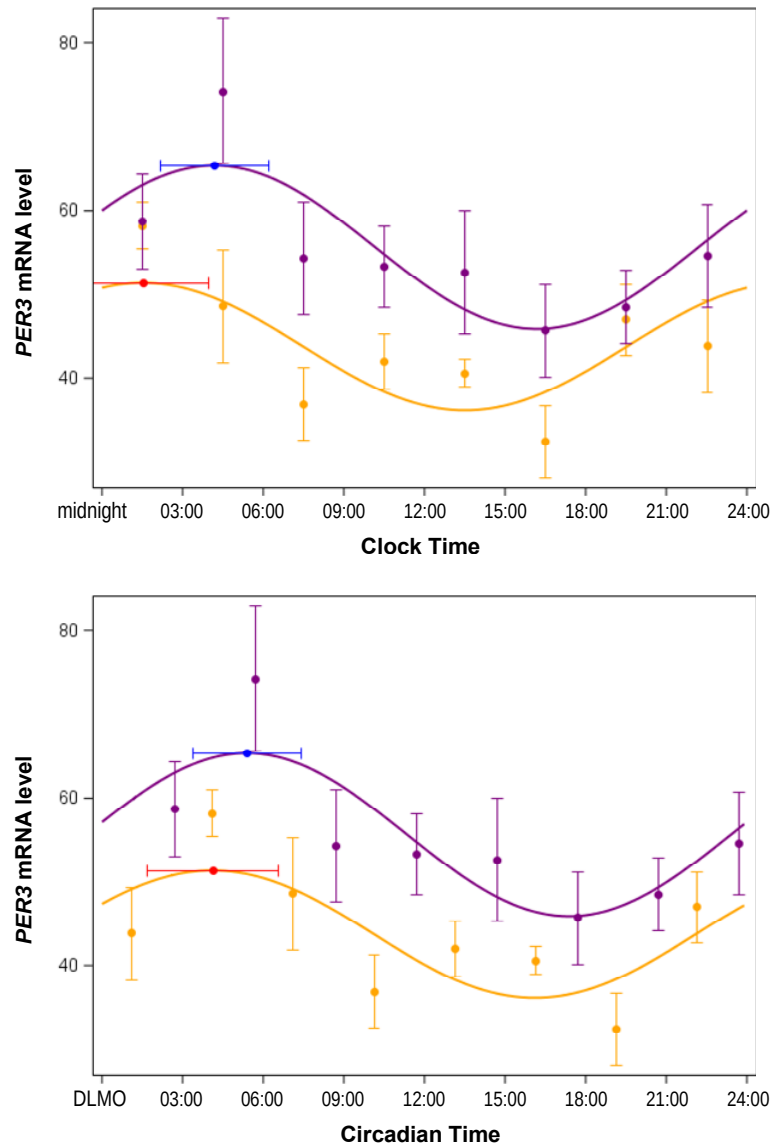


Fig. S4. Transcript levels of *PER3* gene expression during constant routine after simulated day shift work (orange) and night shift work (purple), plotted against time of day (top) and against circadian time relative to DLMO (bottom). For the day shift condition, there was a significant 24-h rhythm ($t_6=3.14$, $p=0.010$), and the acrophase occurred at 01:30 (± 73 min). For the night shift condition, there was also a significant 24-h rhythm ($t_6=3.93$, $p=0.004$), and the acrophase occurred at 04:11 (± 60 min). The phase difference between the two groups during the constant routine involved a delay of 160 min (± 76 min) in the night shift condition, which was not statistically significant ($t_{12}=1.70$, $p=0.12$) but was similar to the delay of 100 min (± 67 min) in the circadian rhythm of plasma cortisol (see Fig. S3). Orange/red: constant routine after simulated day shift condition. Purple/blue: constant routine after simulated night shift condition. Circles: group means ($\pm$ SE). Curves: cosinor fits. Red and blue markers: timing of acrophase (and 95% confidence interval).

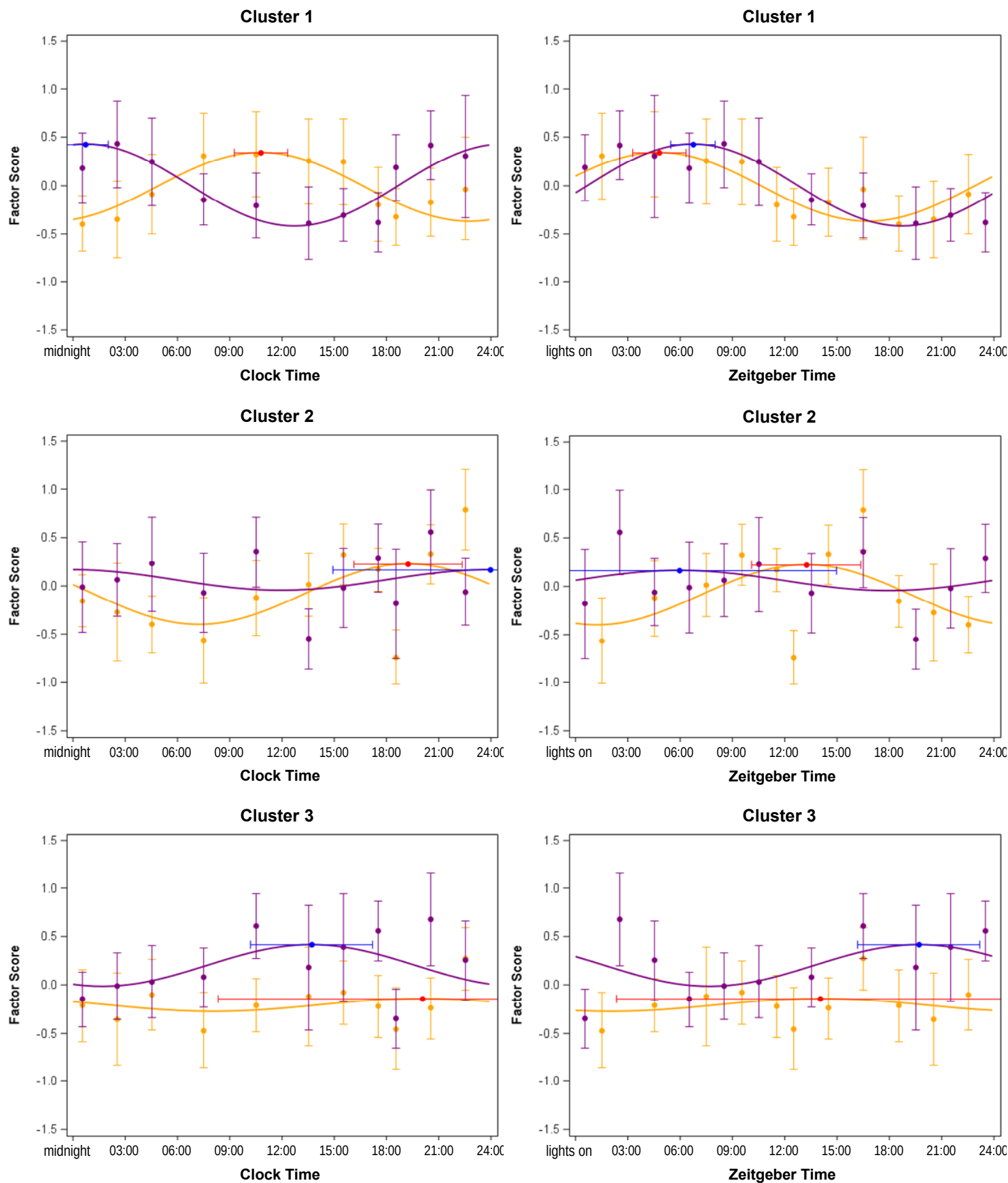


Fig. S5. Temporal profiles of the three principal component clusters of the metabolites measured during constant routine, plotted against clock time (time of day, left) and against zeitgeber time (time in constant routine since scheduled awakening, right). Orange/red: constant routine after simulated day shift schedule. Purple/blue: constant routine after simulated night shift schedule. Circles: group means ($\pm$ SE). Curves: cosinor fits. Red and blue markers: timing of acrophase (and 95% confidence interval).

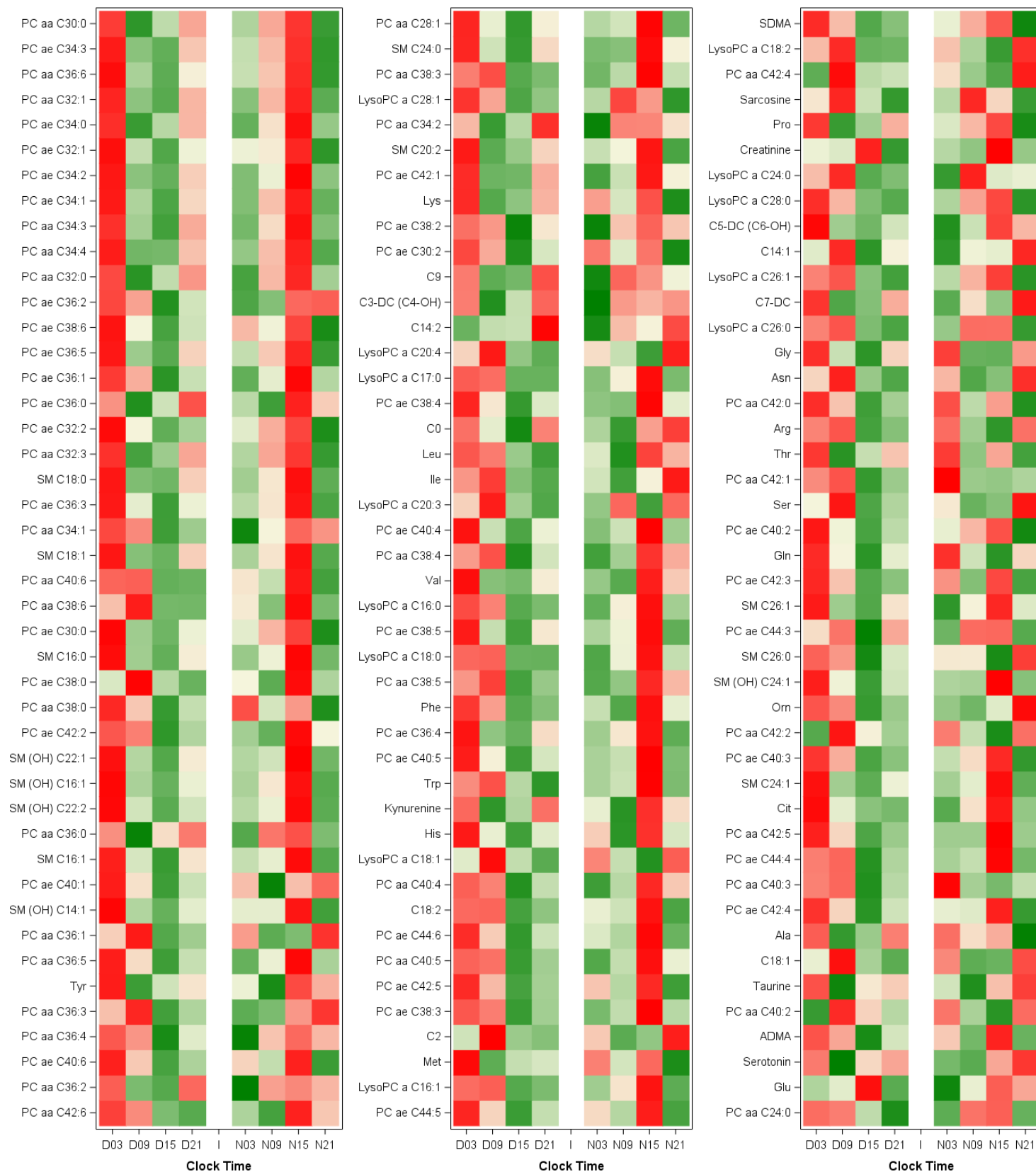


Fig. S6. Heat maps of metabolites during the 24-h constant routine, plotted as Z scores (standard deviations away from the mean) against clock time in 6-h blocks. The dominant response to the experiment was a complete reversal of 24-h rhythmicity following the simulated night shift schedule. Red/green continuum indicates Z score (see scale on top). Order of metabolites is based on factor loadings from PCA (Table S2). D = day shift condition; N = night shift condition. 03 = 00:00–06:00; 09 = 06:00–12:00; 15 = 12:00–18:00; 21 = 18:00–24:00.

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Cardiac autonomic activity during simulated shift work

Elena SKORNYAKOV^{1,2}, Shobhan GADDAMEEDHI^{1,3}, Gemma M. PAECH¹, Amy R. SPARROW^{1,4}, Briann C. SATTERFIELD^{1,5}, Nita L. SHATTUCK⁶, Matthew E. LAYTON^{1,4}, Ilia KARATSOREOS^{1,7} and Hans P. A. VAN DONGEN^{1,4*}

¹Sleep and Performance Research Center, Washington State University, USA

²Department of Physical Therapy, Eastern Washington University, USA

³Department of Pharmaceutical Sciences, College of Pharmacy and Pharmaceutical Sciences, Washington State University, USA

⁴Elson S. Floyd College of Medicine, Washington State University, USA

⁵Social, Cognitive, and Affective Neuroscience Laboratory, Department of Psychiatry, College of Medicine, University of Arizona, USA

⁶Naval Postgraduate School, USA

⁷Department of Integrative Physiology and Neuroscience, Washington State University, USA

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Abstract: Shift work leads to adverse health outcomes including increased risk of cardiovascular disease. Heart rate (HR) and heart rate variability (HRV) are measures of cardiac autonomic activity and markers of cardiovascular disease and mortality. To investigate the effects of shift work on cardiac autonomic activity, we assessed the influence of simulated night work on HR and HRV, and dissociated the direct effects of circadian misalignment from those of sleep displacement and altered physical activity patterns. A total of 29 subjects each participated in one of two in-laboratory, simulated shift work studies. In both studies, EKG was continuously monitored via Holter monitors to measure HR and the high frequency (HF) component of HRV (HF-HRV). We found endogenous circadian rhythmicity in HR and HF-HRV. Sleep and waking physical activity, both displaced during simulated night work, had more substantial, and opposite, effects on HR and HF-HRV. Our findings show systematic but complex, interacting effects of time of day, sleep/wake state, and physical activity on cardiac autonomic activity. These effects need to be taken into account when evaluating HR and HRV in shift work settings and when interpreting these measures of cardiac autonomic activity as markers of cardiovascular disease.

Key words: Night shift, Human sleep, Circadian misalignment, Parasympathetic nervous system, Sympathetic nervous system, Vagal tone, Heart rate variability

Introduction

Shift work has substantial negative effects on long-term health¹⁾. Shift work is associated with hypertension, myocardial infarction, diabetes, and obesity²⁾. Furthermore,

*To whom correspondence should be addressed.
E-mail: hvd@wsu.edu

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shift work increases the risk for cardiovascular disease^{3, 4)}—a leading cause of mortality in the United States⁵⁾.

The health consequences of shift work are partly due to the circadian misalignment associated with these work schedules^{6, 7)}. The circadian pacemaker, located in the suprachiasmatic nuclei (SCN) of the hypothalamus, functions as an internal biological clock, maintaining a wide range of biological processes on a (near-) 24-h rhythm⁸⁾. The SCN sends projections to other areas of the hypothalamus, including the subparaventricular zone and the dorsomedial nucleus of the hypothalamus. During the daytime hours, projections from these areas cause activation of the nuclei of the ascending arousal system, which promote wakefulness; and inhibition of the ventrolateral preoptic (VLPO) nucleus of the hypothalamus, which promotes sleep⁸⁾. As such, the circadian pacemaker exerts a drive for wakefulness during the daytime hours, which it withdraws during the nighttime hours, thereby promoting sleep⁹⁾. In night shift workers, who must be awake at night and sleep during the day, the behaviorally driven timing of wakefulness and sleep thus conflicts with the biologically driven timing of pressure for wakefulness and sleep. This conflict is central to understanding the health consequences of shift work¹⁰⁾.

Heart rate (HR) and heart rate variability (HRV) are measures of cardiac autonomic nervous system activity and markers of cardiovascular health and mortality¹¹⁾. Reduced parasympathetic activity, as indicated by higher HR and lower HRV, is associated with increased risk of cardiovascular disease, increased risk of all-cause mortality, and overall degraded health^{11, 12)}. Given the relationship between cardiac autonomic activity and cardiovascular disease on the one hand, and the association between shift work and cardiovascular disease on the other, studies in shift work settings have used HR and HRV to investigate the risk of cardiovascular disease associated with shift work^{13–17)}. However, HR and HRV are dynamically influenced by endogenous circadian rhythmicity^{18–23)} and by the timing of sleep^{19, 22, 23)}, as well as by waking physical activity, exercise, and posture^{24–26)}. Since shift work schedules produce misalignment between endogenous circadian rhythmicity and the timing of sleep and wakefulness, it is important to understand the impact of this misalignment on HR and HRV.

We set out to study these aspects of circadian misalignment on cardiac autonomic activity in two laboratory-based, simulated shift work studies. Study 1 aimed to dissociate the effects of endogenous circadian rhythmicity, sleep, waking physical activity, and exercise on HR and HRV. Study 2 aimed to provide an integrated view of the

factors dissociated in study 1.

Methods

Subjects

A total of 29 healthy young adults each participated in one of two laboratory-based, simulated shift work studies. In study 1, N=14 healthy young adults (ages 22–34 yr, 4 female) completed a seven-day, six-night laboratory study. Subjects were assigned to either a day shift condition or a night shift condition. In study 2, N=15 healthy young adult males (ages 18–29 yr) completed a six-day, five-night laboratory study. Subjects were assigned to one of four Naval shift schedules.

Subjects were physically and psychologically healthy as assessed by history, questionnaires, and physical examination. They had no sleep or circadian disorders as verified by history, questionnaires, and wrist actigraphy (Actiwatch-2; Respironics, Bend, OR); and, in study 1 only, by baseline polysomnography. Subjects were free of traces of drugs and alcohol as assessed by blood and urine chemistry, and were non-smokers. They did not travel across time zones within one month of entering the study, and were not exposed to shift work within three months of entering the study.

All subjects reported to be good sleepers, habitually sleeping between 6 and 10 h daily with regular bedtimes and typical wake times between 06:00 and 09:00. Subjects were asked to avoid napping and to maintain their habitual sleep schedules during the seven days before the laboratory experiment. Compliance with this part of the study was verified by means of wrist actigraphy and sleep/wake diary, and subjects reported their bedtimes and rising times on a time-stamped voice recorder. Subjects were also instructed to refrain from caffeine or alcohol consumption, and to avoid drugs (including tobacco products) during the seven days before the laboratory experiment. Compliance was verified with urine and breathalyzer tests immediately prior to entering the laboratory.

Experimental design

Study 1

Figure 1 shows a schematic of the experimental design for study 1. Subjects were in the laboratory continuously for seven days (six nights) with up to two other subjects in the laboratory at the same time. For each study run, subjects were assigned to either a day shift (DS) condition (n=7; ages 24.0 ± 2.2 yr) or to a night shift (NS) condition (n=7; ages 27.6 ± 3.2 yr). The total amount of scheduled sleep and wakefulness was the same for these two conditions.

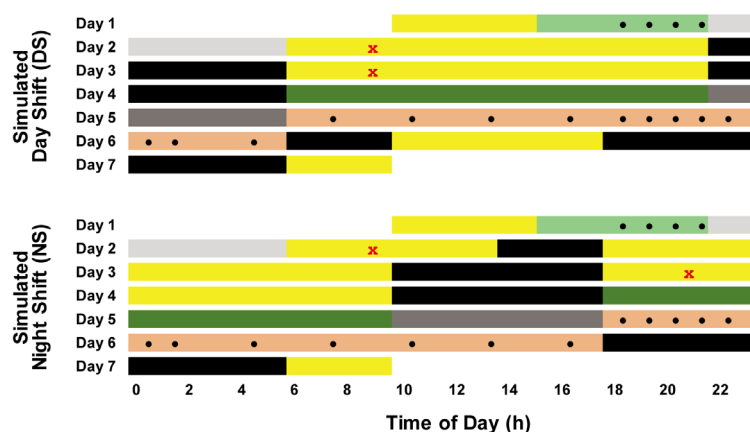


Fig. 1. Schematic of the design of study 1, showing the day shift (top) and night shift (bottom) conditions simulated in the laboratory. In each panel, days progress from top to bottom, and time of day progresses from left to right. Orange, 24-h constant routine period; dark green, wakefulness during third shift day used for analyses; dark gray, sleep opportunity during third shift day used for analyses; light green, baseline wakefulness period used for analyses; light gray, baseline sleep opportunity used for analyses; yellow, other scheduled wakefulness; black, other scheduled sleep opportunities. Red markings, stepping exercise; filled black circles, blood sampling times.

On the first day, subjects entered the laboratory at 10:00. Meals were provided at 13:00 and 19:00. This day included an 8-h nighttime sleep opportunity (22:00–06:00).

At 8:45 on the second day, shortly after awakening from baseline sleep, subjects completed an exercise protocol. This protocol encompassed a 15-min stepping exercise, which involved stepping on and off an 8-inch step bench to the sound of a beat (50 bpm). For 30 min before and after the stepping exercise, subjects were seated in a controlled posture (upright with feet flat on the floor, hands in their lap, and back flat against the back rest of the chair) while avoiding physical movements as much as possible.

Condition assignment (DS or NS) was announced at 11:50 on the second day. Time in the study up until condition announcement served as the baseline period.

Subjects assigned to the DS condition followed a simulated day shift schedule for three days, with daytime wakefulness (06:00–22:00) and nighttime sleep opportunities (22:00–06:00). Meals were provided at 07:00, 13:00 and 19:00 each simulated DS day. At 08:45 on the second simulated DS day, subjects again completed the exercise protocol described above.

Subjects assigned to the NS condition first received a 4-h prophylactic nap opportunity (14:00–18:00) on the second day in the laboratory, in order to transition to a simulated night shift schedule. They then followed the night shift schedule for three days, with nighttime wakefulness (18:00–10:00) and daytime sleep opportunities (10:00–18:00). Meals were provided at 19:00, 01:00 and 07:00 each simulated NS day. At 20:45 on the second

simulated NS day, subjects again completed the exercise protocol described above.

On the fifth day in the laboratory, all subjects were exposed to a 24-h constant routine protocol. This protocol allowed for measuring the endogenous circadian rhythm in HR and HRV^{18–20}). In the DS condition, the 24-h constant routine started at 06:00; in the NS condition, it started at 18:00. During the constant routine, subjects were kept awake at all times. They remained seated in a semi-reclined position, with the exception of brief bathroom breaks. They received hourly equicaloric snacks (80 calories per snack; 40% carbohydrate, 30% protein, 30% dietary fat). One subject in the DS condition did not consume the hourly snacks during the last 6 h of the constant routine; this subject's HR and HRV data recorded during this period were not used for analyses.

After the constant routine, subjects in the DS condition received a 4-h nap opportunity (06:00–10:00), followed by a 12-h nighttime recovery sleep period (18:00–06:00). Subjects in the NS condition had a 12-h nighttime recovery sleep period right after the constant routine. All subjects were discharged from the laboratory on the seventh day at 10:00.

Blood samples were collected at 1-h intervals across a 3-h period right before bedtime (18:30–21:30) on the baseline day. Blood samples were also collected at 3-h intervals throughout the 24-h constant routine, and at 1 h intervals during a 7-h portion of the constant routine (18:30–01:30; Fig. 1). Blood samples were analyzed for markers of endogenous circadian timing; melatonin levels

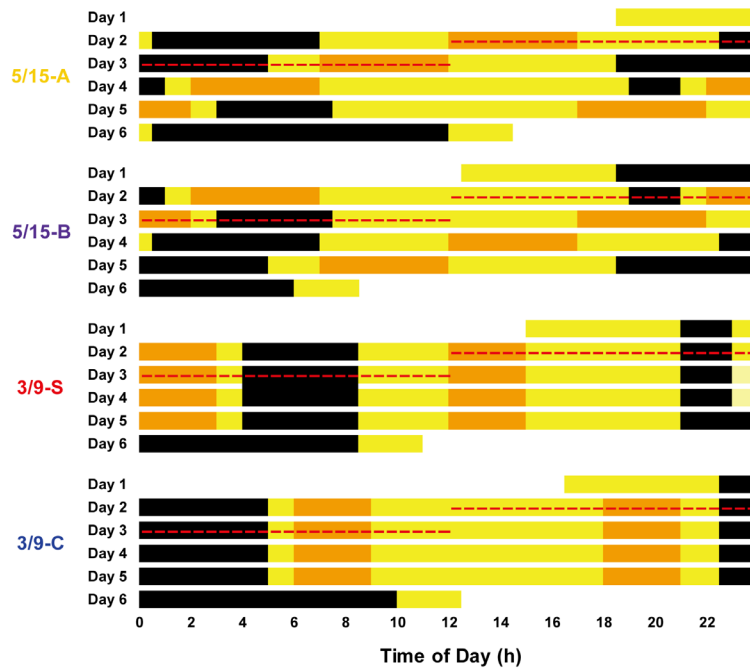


Fig. 2. Schematic of the design of study 2, showing each of the four watch sections simulated in the laboratory. In each panel, days progress from top to bottom and time of day progresses from left to right. Black, scheduled sleep opportunities; orange, watchstanding periods; yellow, other scheduled wakefulness periods. Red dotted lines, 24-h period used for analyses.

were quantified using RIA (IB88111, KMI Diagnostics Inc., Minneapolis, MN, USA), and cortisol levels were quantified using ELISA (ADI-900-097, Enzo Life Sciences, Farmingdale, NY, USA). During the baseline blood sampling period and throughout the 24-h constant routine, subjects were seated in a semi-reclined position.

In both conditions, sleep and nap opportunities were recorded with digital polysomnography (Nihon Kohden, Foothill Ranch, CA, USA). Activity levels were recorded continuously using wrist actigraphy (Actiwatch-2; Respironics, Bend, OR, USA).

Study 2

Figure 2 shows a schematic of the experimental design for study 2. Subjects were in the laboratory continuously for six days (five nights) with up to seven other subjects in the laboratory at the same time. Simulating around-the-clock Naval shift schedules (watch sections), subjects were assigned to one of four conditions as previously described²⁷⁾:

5/15-A: a “5/15” backward rotating watch section, with 6.5-h sleep opportunities beginning at 00:30 on Day 2, 22:30 on Day 2, 18:30 on Day 3, and split sleep at 19:00 (2 h) on Day 4 and 03:00 (4.5 h) on Day 5 ($n=4$; ages 25.0 ± 2.2 yr);

5/15-B: a “5/15” backward rotating watch section equivalent to the 5/15-A watch section, but shifted by two days in the four-day rotation cycle ($n=4$; ages 22.3 ± 3.8 yr);

3/9-S: a “3/9” non-rotating watch section, with 6.5-h split sleep opportunities beginning at 21:00 (2 h) and 4:00 (4.5 h) each day ($n=3$; ages 23.7 ± 1.5 yr);

3/9-C: a “3/9” non-rotating watch section, with 6.5-h consolidated sleep opportunities beginning at 22:30 each day ($n=4$; 24.0 ± 3.4 yr).

After four simulated watch section days, all subjects received an 11.5-h recovery sleep opportunity. Subjects were discharged from the laboratory on Day 6 (Fig. 2).

Subjects assigned to the 5/15-A and 5/15-B watch sections were in the laboratory at the same time. Likewise, subjects assigned to the 3/9-S and 3/9-C watch sections were in the laboratory at the same time. Condition assignment was announced at the beginning of the study. The total amount of scheduled sleep and wakefulness was the same for these four conditions.

Subjects slept in bunk beds in a shared sleeping area; they were instructed to try to sleep during scheduled sleep opportunities and to minimize the sleep disturbance of others. They received three meals and a snack each watch section day. Subjects were scheduled to stand simulated watch duties (i.e., simulated watchstanding) for an average of 6 h per watch section day (Fig. 2). During simulated

watchstanding, subjects performed continuous, cognitively demanding computer tasks while seated at a desk, including tests on psychomotor vigilance, reaction time, perseveration, memory, response inhibition, and decision-making processes. In all four conditions, activity levels were recorded continuously using wrist actigraphy (Actiwatch-2; Respironics, Bend, OR, USA) to assess sleep/wake patterns (reported elsewhere)²⁷⁾.

Both studies

In both studies, to enable experimental control over the simulated shift work conditions, subjects remained isolated from the outside world. They had no exposure to natural daylight and no visitors, phone calls, e-mail, internet access, live television, radio, or other contact with the external environment. Caffeine, alcohol, and tobacco were not allowed. During scheduled wakefulness, light exposure was fixed, with illuminance set below 50 lux in study 1 and below 100 lux in study 2. Ambient temperature was kept at 22 ± 1 °C (mean $\pm$ SD) during both studies, except during the constant routine in study 1 when it was 24 ± 1 °C.

Cognitive performance tests were administered at least every 2 h during scheduled wakefulness. Subjects performed the same types and the same number of performance tests regardless of condition assignment in study 1, and likewise in study 2. Between performance tests, meals, and sleep opportunities, subjects were allowed to read, watch movies, play games, and talk with other study participants and research staff. Beside the stepping exercise in study 1, subjects were not allowed to engage in vigorous physical activity. Trained research assistants carefully monitored the subjects 24 h per day and kept them awake during scheduled waking periods.

Both studies conformed with the Recommendations from the Declaration of Helsinki of 1983. The studies were approved by the Institutional Review Board of Washington State University. All subjects gave written, informed consent, and were financially compensated for their time.

Measurements

HR and HRV

In both studies, electrocardiography (EKG) was recorded at 4,096 Hz with a Holter monitor (DMS 300-3A; Bravo, Huntington Beach, CA, USA) using standard 5-lead electrode placement. The EKG was recorded continuously, with the exception of a portion of the second simulated shift day in study 1 (not relevant for data analyses) and brief periods around scheduled shower opportunities. The EKG was manually reviewed and ectopic

beats were removed. The EKG records were then analyzed using CardioScan software (version 11.4; Stateline, NV, USA). EKG data were binned into 5-min epochs. Epochs with movement artifact were removed.

For each epoch, the average HR and the high frequency (HF) component of the HRV power spectrum were calculated. The HF component of HRV (HF-HRV) included frequencies ranging from 0.15 to 0.40 Hz, as proposed by the American Heart Association²⁸⁾. There is broad consensus that HF-HRV represents parasympathetic activity²⁹⁾. We did not consider a low frequency (LF) component of the HRV power spectrum, previously believed to reflect mostly sympathetic activity³⁰⁾, as there is mounting uncertainty regarding the reliability of that interpretation^{29, 31)}.

In study 1, the EKG data from 15:00 to 22:00 on the first day in the laboratory were used to determine baseline HR and HF-HRV during wakefulness (Fig. 1, light green bars). The EKG data from 22:00 on the first day to 06:00 on the second day were used to determine baseline HR and HF-HRV during sleep (Fig. 1, light gray bars). The EKG data from the third simulated shift day were used to compare HR and HF-HRV between the simulated DS or NS schedules. Data from 06:00 to 22:00 in the DS condition and from 18:00 to 10:00 in the NS condition were used to determine HR and HF-HRV during simulated shift work when subjects were awake (Fig. 1, dark green bars). Data from 22:00 to 6:00 in the DS condition and from 10:00 to 18:00 in the NS condition were used to determine HR and HF-HRV during simulated shift work when subjects were scheduled to sleep (Fig. 1, dark gray bars). The EKG recordings obtained during the 24-h constant routine were used to assess the endogenous circadian rhythm in HR and HF-HRV. Epochs recorded during the constant routine that overlapped with neurobehavioral testing (15 min every 2 h, beginning 2 h after waking), intravenous (iv) catheter insertion or removal for blood sampling, or bathroom breaks (and 5 min intervals after bathroom breaks) were discarded.

In study 2, only the 24-h period from 12:00 on the second day until 12:00 on the third day was used for analysis of HR and HF-HRV in each of the four watch sections (Fig. 2, red dotted lines). This 24-h period is representative of the differences between the watch sections, and serves to illustrate the complex interactions of multiple factors influencing cardiac autonomic activity. Due to technical failure, the data from one subject in the 3/9-S watch section was lost. With regard to the EKG recordings, therefore, the sample size for study 2 was N=14.

Activity levels and sleep

Actigraphic data were analyzed using Actiware software (version 6.0; Respironics, Bend, OR, USA). The number of activity counts, recorded in 1-min epochs, was averaged into 5-min bins. For study 1, the 5-min bins from 15:00 until 22:00 on the first day in the laboratory were used as estimates of waking physical activity at baseline (Fig. 1, light green bars). The 5-min bins from the third simulated shift day were used as estimates of waking physical activity during shift work: from 06:00 to 22:00 in the DS condition, and from 18:00 to 10:00 in the NS condition (Fig. 1, dark green bars).

Polysomnographic recordings of sleep periods in study 1 were scored according to the criteria of the American Academy of Sleep Medicine³². Total sleep time (TST) was assessed for the baseline night (Fig. 1, light gray bars) and for the sleep period of the third simulated shift day (Fig. 1, dark gray bars).

Statistical analysis

Statistical analyses were performed using SAS (version 9.3; SAS Institute, Inc., Cary, NC, USA). Unless noted otherwise, data were analyzed with mixed-effects analysis of variance³³ (ANOVA). For study 1, subject-specific baseline values for wake (average over 15:00 to 22:00 on day 1; Fig. 1, light green bars) and sleep (average over 22:00 day 1 to 06:00 day 2; Fig. 1, light gray bars) were included as a covariate in analyses of HR and HF-HRV for wakefulness and sleep, respectively, during simulated shift work. Analyses focused on physical activity included the 5-min averages of activity counts from actigraphy as covariate. For study 2 analyses, watch section (5/15-A, 5/15-B, 3/9-S, 3/9-C) was included as a covariate. All mixed-effects analyses included a random effect on the intercept over subjects to account for idiosyncratic inter-individual differences in the magnitude of the signals analyzed. Estimates are provided as marginal mean $\pm$ SE (unless otherwise noted). Figures show raw hourly means and SEs by condition.

Circadian rhythmicity was analyzed with a non-linear, mixed-effects regression implementation of cosinor analysis³⁴; the 5% data with the most extreme residuals were excluded. Rhythm parameters, which included amplitude, acrophase (timing of the peak), and mesor (center value), were tested and compared between conditions with *t* tests embedded in the cosinor analysis. Statistical testing for an effect of time awake was done using linear mixed-effects regression; this analysis was applied to the residuals of the cosinor analysis across the two conditions in order to

avoid colinearity in parameter estimation.

HR and HF-HRV data were analyzed based on 5-min epochs. However, for data from the stepping exercise in study 1, the three 5-min epochs covering each exercise session were averaged into a single 15-min bin, and the data collected prior to each exercise session were also averaged into 15-min bins, beginning 15 min after scheduled awakening (in order to exclude potential confounds due to sleep inertia³⁵). Reactivity to the stepping exercise was quantified as the difference between the 15-min bin containing the exercise session and the 15-min bin immediately pre-exercise.

Results

Effects of simulated shift work on HR and HF-HRV during constant routine

The constant routine protocol in study 1 allowed for measuring the endogenous circadian rhythms of HR and HRV. Before focusing on the HR and HF-HRV data, we considered the effect of the simulated shift work that preceded the constant routine protocol (Fig. 1) on the timing of the circadian pacemaker. We found that markers of the circadian pacemaker, melatonin and cortisol, did not show a substantial shift in timing comparing DS to NS³⁶.

Despite the constant conditions under which the HR and HF-HRV data were measured, these data showed pronounced rhythms in both conditions (Fig. 3). Regardless of condition, HR was high during the afternoon hours and low during the nighttime hours. HF-HRV peaked earlier in the day than HR—especially in the NS condition, which showed an HF-HRV rhythm that was approximately inverse to the HR rhythm. Cosinor analysis confirmed significant 24-h rhythmicity in HR in the DS condition ($t_{13}=6.67$, $p<0.001$) and the NS condition ($t_{13}=19.77$, $p<0.001$). The amplitude of the 24-h rhythm was 1.0 bpm (± 0.2 bpm) for the DS condition and 3.0 bpm (± 0.2 bpm) for the NS condition. The difference between conditions of 2.0 bpm was statistically significant ($t_{12}=9.27$, $p<0.001$). The mesor (center value) was 64.6 bpm (± 3.4 bpm) in the DS condition and 64.4 bpm (± 3.4 bpm) in the NS condition, which was not significantly different ($t_{12}=0.03$, $p=0.97$). The acrophase (peak) of the 24-h rhythm in HR occurred at 14:34 (± 34 min) in the DS condition and at 16:43 (± 10 min) in the NS condition. The 129 min delay in the NS condition relative to the DS condition was statistically significant ($t_{12}=3.61$, $p=0.004$). After accounting for 24-h rhythmicity, there was no evidence of an effect of time awake in the HR data of the two conditions ($t_{13}=0.37$, $p=0.72$).

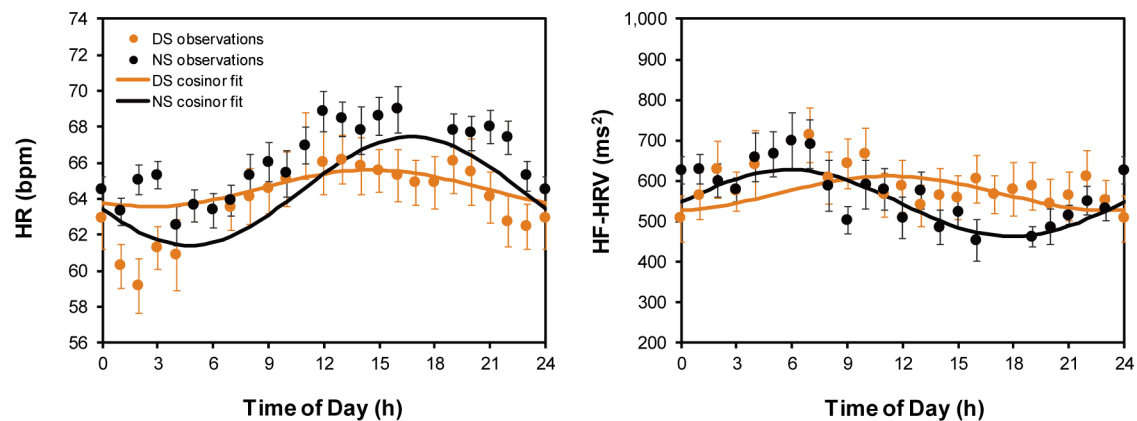


Fig. 3. HR (left) and HF-HRV (right) during the 24-h constant routine for the day shift (DS) and night shift (NS) conditions. Dots represent observed means; error bars indicate ± 1 standard error. Curves represent fitted 24-h rhythms. Data and curves are projected onto a 24-h axis from midnight to midnight.

Cosinor analysis also confirmed significant 24-h circadian rhythmicity in HF-HRV in the DS condition ($t_{13}=4.81$, $p=0.001$) and the NS condition ($t_{13}=8.32$, $p<0.001$). The amplitude of the 24-h rhythm was 42.4 ms^2 ($\pm 8.8 \text{ ms}^2$) for the DS condition and 82.2 ms^2 ($\pm 9.9 \text{ ms}^2$) for the NS condition. The difference between conditions of 39.8 ms^2 was statistically significant ($t_{12}=3.01$, $p=0.011$). The mesor (center value) was 569.5 ms^2 ($\pm 117.9 \text{ ms}^2$) in the DS condition and 545.3 ms^2 ($\pm 117.9 \text{ ms}^2$) in the NS condition, which was not significantly different ($t_{12}=0.15$, $p=0.89$). The acrophase (peak) of the 24-h rhythm of HF-HRV occurred at $11:16$ ($\pm 53 \text{ min}$) in the DS condition and at $05:53$ ($\pm 24 \text{ min}$) in the NS condition. The 323 min advance in the NS condition relative to the DS condition was statistically significant ($t_{12}=5.50$, $p<0.001$). The difference in the acrophase is substantial, but visual inspection of the data (Fig. 3) suggests that some outliers that remained in the data may have skewed the cosinor fit in the DS condition, resulting in an apparent delay of the estimate of the acrophase of HF-HRV in that condition. Potentially connected, after accounting for 24-h rhythmicity, there was a small but statistically significant effect of time awake in the HF-HRV data ($t_{13}=2.21$, $p=0.046$), with HF-HRV decreasing by 1.6 ms^2 ($\pm 0.7 \text{ ms}^2$) for every hour awake.

Effects of simulated shift work on HR and HF-HRV during wakefulness and sleep

The simulated shift work period preceding the constant routine protocol in study 1 allowed for measuring the effects of shifted wakefulness and sleep periods on HR and HRV. Before investigating the effects of wakefulness and sleep, we examined the polysomnographic records of

nighttime baseline sleep (Fig. 1, light gray bars) and nighttime or daytime sleep at the end of the three-day simulated shift work period (Fig. 1, dark gray bars). Baseline TST was 416.1 min ($\pm 15.5 \text{ min}$) for the DS condition and 431.4 min ($\pm 15.5 \text{ min}$) for the NS condition, which was not significantly different ($F_{1,12}=0.49$, $p=0.50$). TST for the third simulated shift day was 441.1 min ($\pm 16.6 \text{ min}$) in the DS condition (i.e., nighttime sleep) and 392.4 min ($\pm 16.6 \text{ min}$) in the NS condition (i.e., daytime sleep). Thus, daytime sleep in the NS condition was 48.7 min ($\pm 23.5 \text{ min}$) shorter than nighttime sleep in the DS condition; the difference approached statistical significance ($F_{1,12}=4.32$, $p=0.060$).

The temporal profiles of HR and HF-HRV during the baseline day and night (Fig. 1, light green and light gray bars, respectively) and during the wakefulness and sleep periods of the third simulated shift day (Fig. 1, dark green and dark gray bars, respectively) are shown in Fig. 4. Mixed-effects ANOVA of the HR data during baseline wakefulness, as a function of condition and time of day, showed no significant main effect of condition ($F_{1,986}=0.01$, $p=0.92$). There was, however, a significant main effect of time of day ($F_{83,986}=13.64$, $p<0.001$), with substantial changes in HR over time in both conditions. HR was lowest around hours 17:00 and 18:00, when subjects were mostly seated for baseline blood sampling procedures. The interaction of condition by time of day was also significant ($F_{83,986}=1.45$, $p=0.007$). HR was slightly greater in the NS condition around hour 15:00. Overall, HR during baseline wakefulness was comparable between the two conditions.

For scheduled sleep at baseline, there was no significant main effect of condition on HR ($F_{1,1067}=1.85$, $p=0.17$),

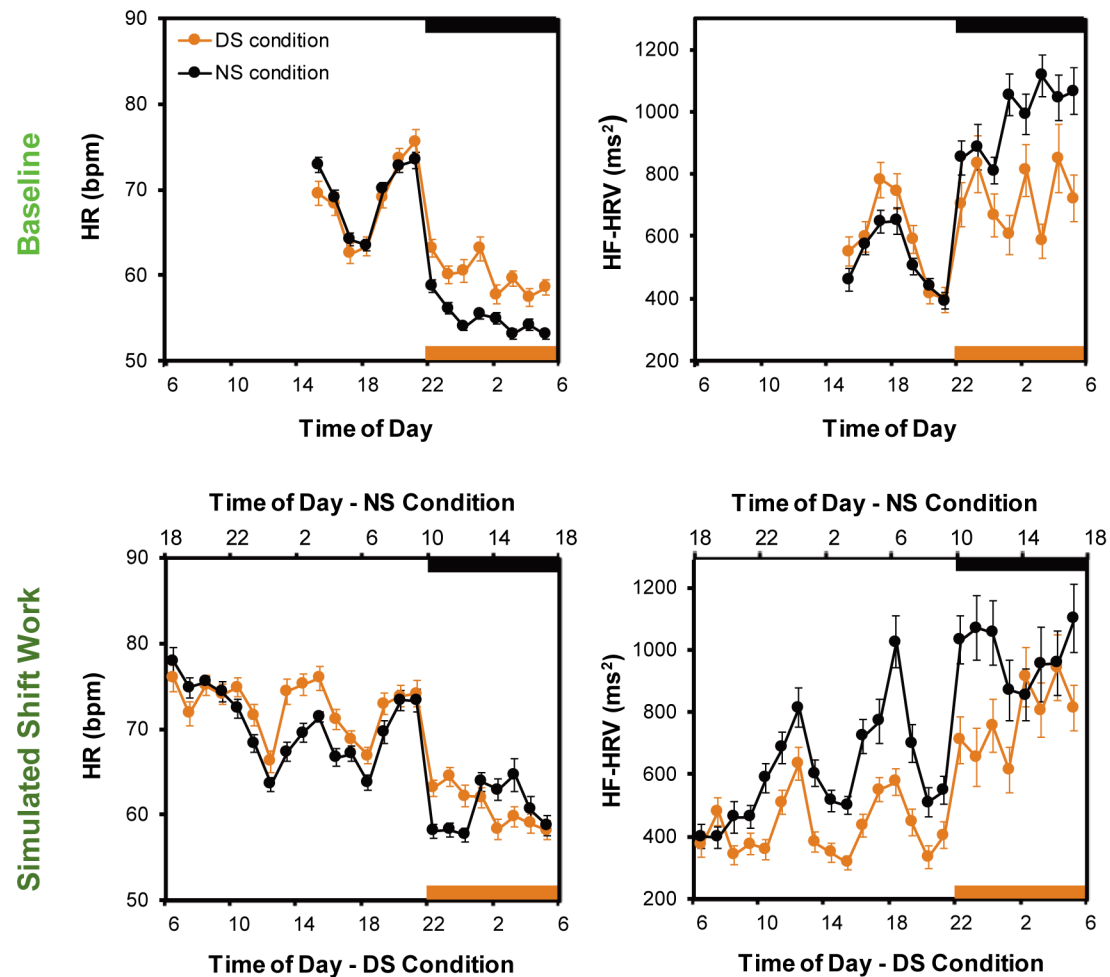


Fig. 4. HR (left panels) and HF-HRV (right panels) for the day shift (DS; orange) and night shift (NS; black) conditions at baseline (top panels) and during simulated shift work (bottom panels). For the bottom panels, the top axis indicates time of day for the night shift condition, and the bottom axis indicates time of day for the day shift condition. Dots represent observed means; error bars indicate ± 1 standard error. Orange horizontal bar, scheduled sleep opportunity for the DS condition; black horizontal bar, scheduled sleep opportunity for the NS condition.

but there was a significant main effect of time in bed ($F_{95,1067}=3.82$, $p<0.001$), with HR gradually decreasing over time in bed. The interaction of condition by time in bed was also significant ($F_{95,1067}=1.30$, $p=0.032$). The NS condition displayed a greater decrease in HR than the DS condition as time in bed progressed (Fig. 4, top left).

During wakefulness on the third day of simulated shift work, there was a trend for a main effect of condition on HR after controlling for baseline ($F_{1,2173}=3.15$, $p=0.076$). HR was greater in the DS condition (73.2 ± 1.5 bpm) than in the NS condition (69.5 ± 1.5 bpm). There was also a significant main effect of time awake ($F_{191,2173}=10.10$, $p<0.001$). As during baseline, there were substantial changes in HR over time that were common to both conditions. The interaction of condition by time awake was also significant ($F_{190,2173}=1.59$, $p<0.001$). The DS condition

had greater HR than the NS condition about halfway through the simulated work day.

For scheduled sleep during the third day of simulated shift work, there was a trend for a main effect of condition on HR after controlling for baseline ($F_{1,1055}=3.01$, $p=0.083$). There was also a significant main effect of time in bed ($F_{95,1055}=1.28$, $p=0.043$) and a significant interaction of condition by time in bed ($F_{95,1055}=2.15$, $p<0.001$). HR decreased across the nighttime sleep period in the DS condition, whereas it initially increased and then decreased during the daytime sleep period in the NS condition (Fig. 4, bottom left).

The HF-HRV data were essentially a mirror image of the HR data. Mixed-effects ANOVA of the HF-HRV data during baseline wakefulness, as a function of condition and time of day, showed no significant main effect of con-

dition on HF-HRV ($F_{1,986}=0.15$, $p=0.70$). There was, however, a significant main effect of time of day ($F_{83,986}=4.24$, $p<0.001$), with substantial changes in HF-HRV over time in both conditions. HF-HRV was highest around hours 17:00 and 18:00, when subjects were mostly seated for baseline blood sampling procedures. The interaction of condition by time of day was not significant ($F_{83,986}=0.81$, $p=0.89$). HF-HRV during baseline wakefulness was comparable between conditions.

For HF-HRV during scheduled sleep at baseline, there was no significant main effect of condition ($F_{1,1067}=0.54$, $p=0.46$) and no significant main effect of time in bed ($F_{95,1067}=0.86$, $p=0.82$). There was, however, a significant interaction of condition by time in bed ($F_{95,1067}=1.41$, $p=0.008$). The NS condition displayed a greater increase in HF-HRV than the DS condition as time in bed progressed (Fig. 4, top right).

During wakefulness on the third day of simulated shift work, there was a significant main effect of condition on HF-HRV after controlling for baseline ($F_{1,2174}=5.32$, $p=0.021$) and a significant main effect of time awake ($F_{191,2174}=4.83$, $p<0.001$). As during baseline, there were substantial changes in HF-HRV over time that were common to both conditions. The interaction of condition by time awake was also significant ($F_{190,2174}=1.62$, $p<0.001$). The DS condition had lower HF-HRV than the NS condition for the larger part of the simulated shift day, beginning a few hours after awakening.

For scheduled sleep during the third day of simulated shift work, there was no significant main effect of condition on HF-HRV after controlling for baseline ($F_{1,1055}=0.18$, $p=0.67$). There was also no significant main effect of time in bed ($F_{95,1055}=0.82$, $p=0.89$) and no significant interaction of condition by time in bed ($F_{95,1055}=0.87$, $p=0.80$). Despite the lack of statistical significance when accounting for baseline differences, the pattern of HF-HRV during sleep on the third shift day was similar (but mirrored) to that of HR for both conditions (Fig. 4, bottom right).

Effects of physical activity on HR and HF-HRV

Figure 5 shows the average number of activity counts per minute during wakefulness for the DS and NS conditions, at baseline (Fig. 1, light green bars) and during simulated shift work (Fig. 1, dark green bars). Mixed-effects ANOVA of the activity data during baseline wakefulness, as a function of condition and time of day, showed no significant main effect of condition ($F_{1,996}=2.42$, $p=0.12$). There was, however, a significant main effect of time of day ($F_{83,996}=15.11$, $p<0.001$) and a significant interaction

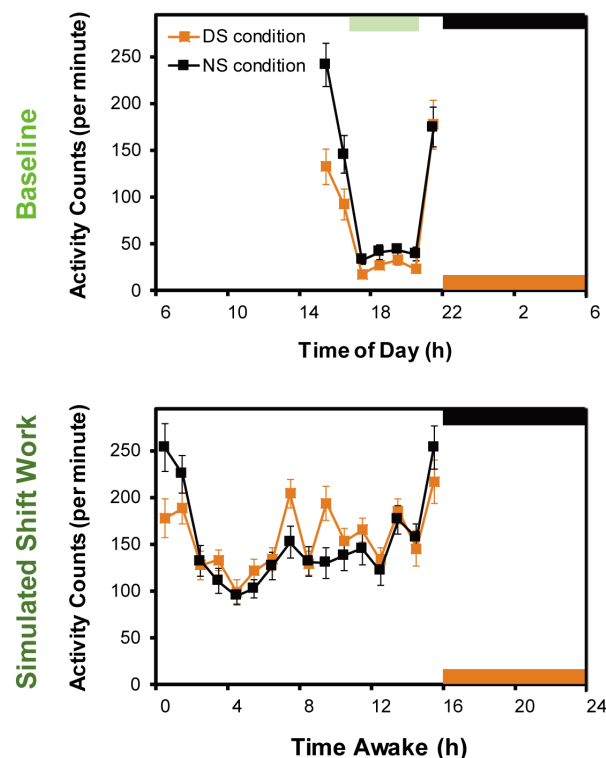


Fig. 5. Mean number of activity counts for the day shift (DS; orange) and night shift (NS; black) conditions at baseline (top) and during simulated shift work (bottom). Squares represent observed means; error bars indicate ± 1 standard error. Orange horizontal bar, scheduled sleep opportunity for the DS condition; black horizontal bar, scheduled sleep opportunity for the NS condition; light green horizontal bar, blood sampling period requiring subjects to be seated most of the time.

of condition by time of day ($F_{83,996}=1.33$, $p=0.029$). During wakefulness on the third day of simulated shift work, there was likewise no significant main effect of condition ($F_{1,2101}=0.02$, $p=0.89$). There was, however, a significant main effect of time awake ($F_{191,2101}=4.43$, $p<0.001$), as well as a significant interaction of condition by time awake ($F_{191,2101}=1.40$, $p<0.001$). The DS condition exhibited greater activity than the NS condition halfway through the simulated shift day (Fig. 5, bottom panel). Overall, the differences in activity between the two conditions were small.

Mixed-effects ANOVA with average activity counts from wrist actigraphy as a covariate revealed that baseline activity was a significant covariate of both baseline HR ($F_{1,985}=233.47$, $p<0.001$) and baseline HF-HRV ($F_{1,985}=25.35$, $p<0.001$). An increase of one activity count was associated with an increase of HR by 0.022 bpm (± 0.001 bpm) and a decrease of HF-HRV by 0.43 ms²

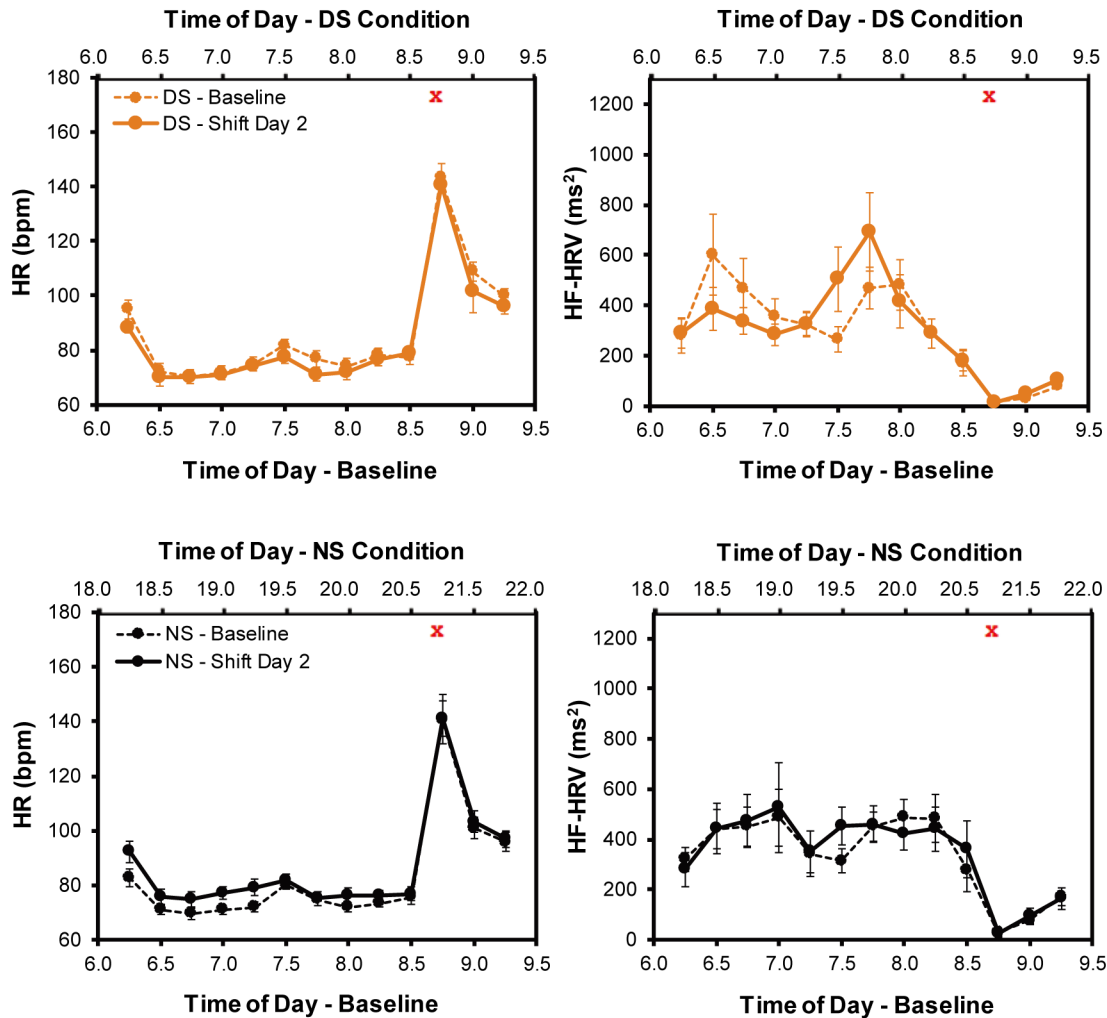


Fig. 6. HR (left panels) and HF-HRV (right panels) for the stepping exercise in the day shift (DS; orange) and night shift (NS; black) conditions, at baseline (dotted lines) and during simulated shift work (solid lines). Data are shown for 150 min (10 data points) before exercise, 15 min (1 data point) during exercise, and 30 min (2 data points) after exercise. Dots represent observed means; error bars indicate ± 1 standard error. Red markings, stepping exercise.

(± 0.09 ms²). Activity during the third day of simulated shift work was also a significant covariate of both HR ($F_{1,1983}=399.15$, $p<0.001$) and HF-HRV ($F_{1,1983}=57.17$, $p<0.001$) during the simulated shift work day. An increase of one activity count was associated with an increase of HR by 0.020 bpm (± 0.001 bpm) and a decrease of HF-HRV by 0.40 ms² (± 0.05 ms²)—very similar to what was found for baseline.

Effects of exercise during simulated shift work on HR and HF-HRV

The study 1 protocol contained two stepping exercise sessions, scheduled at 2 h and 45 min of scheduled wakefulness at baseline and on the second shift day (Fig. 1). The stepping exercise served as a controlled procedure to

measure the cardiac autonomic activity response to more intense physical activity. Figure 6 shows HR and HF-HRV pre-exercise, during exercise, and immediately post-exercise at baseline and on the second day of simulated shift work in the DS or NS conditions.

There were no differences between conditions in pre-exercise HR ($F_{1,124}=0.08$, $p=0.78$) on the second day of simulated shift work. Mixed-effects ANOVA of exercise reactivity in HR, as a function of condition (DS vs. NS) and session (baseline day vs. second simulated shift work day), showed no significant effects of condition ($F_{1,7}<0.01$, $p=0.97$), session ($F_{1,7}<0.01$, $p=0.97$), or their interaction ($F_{1,7}=0.51$, $p=0.50$). Similarly, there were no differences between conditions in pre-exercise HF-HRV ($F_{1,124}=0.08$, $p=0.78$). Mixed-effects ANOVA of exercise reactivity in

HF-HRV also showed no significant effects of condition ($F_{1,7}=0.42$, $p=0.54$), session ($F_{1,7}=2.11$, $p=0.19$), or their interaction ($F_{1,7}=1.15$, $p=0.32$).

Combined effects of endogenous circadian rhythm, sleep/wake state, and physical activity on HR and HF-HRV

In study 2, which involved laboratory-based shift work schedules simulating real-world, around-the-clock Naval operations (Fig. 2), we set out to assess the combined and interacting effects of the circadian pacemaker, sleep/wake state, and physical activity on HR and HF-HRV. Figure 7 shows mean HR and HF-HRV for each watch section across time of day, from 12:00 on the second day until 12:00 on the third day.

Mixed-effects ANOVA of HR, as a function of time of day and state (scheduled sleep versus wake vs. simulated watchstanding), with watch section as a covariate, showed a significant main effect of time of day ($F_{287,3173}=4.20$, $p<0.001$) and a significant main effect of state ($F_{2,3173}=639.63$, $p<0.001$). There was also a significant interaction of time of day by state ($F_{358,3173}=2.83$, $p<0.001$). There was no significant effect of watch section as a covariate ($F_{3,3173}=1.98$, $p=0.12$).

Mixed-effects ANOVA of HF-HRV showed no significant main effect of time of day ($F_{287,3173}=1.10$, $p=0.12$). There was, however, a significant main effect of state ($F_{2,3173}=85.01$, $p<0.001$) and a significant interaction of time of day by state ($F_{358,3173}=1.29$, $p<0.001$). There was no significant effect of watch section as a covariate ($F_{3,3173}=2.16$, $p=0.090$).

Discussion

As has been demonstrated previously, cardiac autonomic activity is dynamically influenced by endogenous circadian rhythmicity^{18–21} and by the timing of sleep^{19, 23}, as well as by waking physical activity, exercise, and posture^{22, 24–26}. However, how these factors combine and interact under conditions of shift work, when there is misalignment between endogenous circadian rhythmicity and the timing of sleep and wakefulness, is not well documented. We investigated this issue in two laboratory-based, simulated shift work studies of HR and HRV, with study 1 (Fig. 1) dissociating the effects of endogenous circadian rhythmicity, sleep, waking physical activity, and exercise, and study 2 (Fig. 2) illustrating their interactions.

The constant routine procedure in study 1 permitted an assessment of the effect of simulated shift work on the endogenous circadian rhythm in HR and HF-HRV,

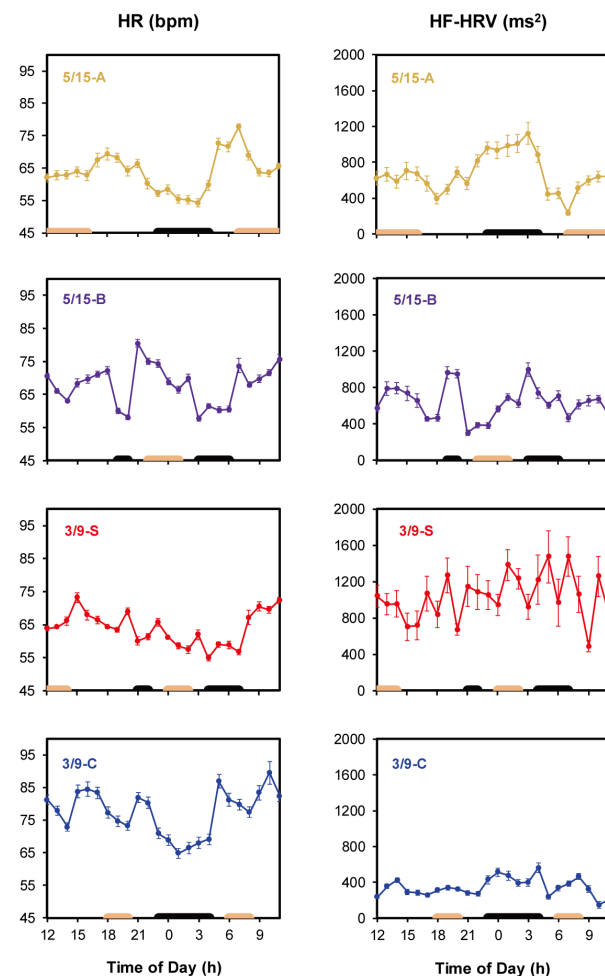


Fig. 7. HR (left panels) and HF-HRV (right panels) for the 5/15-A (yellow), 5/15-B (purple), 3/9-S (red), and 3/9-C (blue) watch sections. Dots represent observed means; error bars indicate ± 1 standard error. Black horizontal bars, scheduled sleep opportunities; orange horizontal bars, scheduled watchstanding.

while eliminating confounds known to influence cardiac autonomic activity, including sleep, food intake, physical activity, and posture. In line with previous field research that showed a lack of adaptation in circadian timing, even among permanent night shift workers³⁷, we found that the timing of endogenous circadian markers (melatonin and cortisol) after exposure to three days of simulated shift work remained *similar* for the DS and NS conditions³⁶. The HR and HF-HRV data collected under constant routine showed significant 24-h rhythmicity that was congruent with the well-established circadian rhythm in cardiac autonomic activity^{18–21, 38}, and also *similar* for the DS and NS conditions (Fig. 3). It follows that the HR and HF-HRV rhythms were not produced by the preceding shift schedule, but rather reflected endogenous rhythmicity

driven by the circadian pacemaker.

The simulated shift days in study 1 permitted an assessment of the effects of wakefulness versus sleep, and temporal displacement of sleep, on HR and HF-HRV. During wakefulness on the third simulated shift day, the NS condition exhibited somewhat lower HR and higher HF-HRV than the DS condition, whereas there were no such differences between conditions at baseline (Fig. 4). This is consistent with a previous study that measured HR in simulated shift schedules, which also found lower waking HR in a night shift schedule as compared to a day shift schedule³⁹. The negligible shifting of endogenous circadian timing in the NS condition indicates that this modulation may be influenced by the circadian rhythmicity of autonomic activity itself, potentially via projections from the SCN to the paraventricular nucleus (PVN) of the hypothalamus⁴⁰. Also, during nighttime hours, activity in the nuclei of the ascending arousal system, including the locus coeruleus, is reduced, and is further inhibited by the VLPO nucleus of the hypothalamus⁸. Inhibition of the locus coeruleus, the major noradrenergic center of the brain, leads to disinhibition of parasympathetic nuclei⁴¹, consistent with our findings of lower HR and higher HF-HRV during nighttime wakefulness in the NS condition.

The magnitude of changes in HR and HF-HRV over waking time was considerable (Fig. 4), especially when compared to the amplitude of the endogenous circadian rhythm (Fig. 3). This implies that there was substantial modulation of cardiac autonomic activity by other factors, such as physical activity and posture. Our actigraphy findings indicate that the systematic fluctuations in HR and HF-HRV across waking time (Fig. 4) could be largely explained by systematic variations in activity levels (Fig. 5). The relatively minor difference in activity levels between the DS and NS conditions halfway through the simulated shift day (Fig. 5, bottom), which is also reflected in HR (Fig. 4, bottom left), may be related to the opposite effect of the circadian pacemaker for the two conditions. That is, during this time in the simulated shift work protocol, the circadian pacemaker would have exerted a drive for wakefulness (and potentially more physical activity) in the DS condition and a drive for sleep (and potentially more sedentary behavior) in the NS condition. It should be noted, however, that in both conditions the overall level of physical activity, and the effect thereof on cardiac autonomic activity, was modest. This is corroborated by the results of the stepping exercise (Fig. 6), which increased HR and decreased HF-HRV regardless of condition to a much greater extent than the variations seen in response to regular waking physical

activity (Fig. 4).

The overall impact of sleep on cardiac autonomic activity was about the same for the DS and NS conditions after correcting for baseline differences (Fig. 4), and similar to what has been found in previous work^{39, 42}. However, the temporal dynamics of HR and HF-HRV across the sleep period were not the same between the two conditions. The stages of sleep are distributed differently in daytime sleep compared to nighttime sleep^{43–45}, and there are well-studied relationships between different sleep stages and cardiac autonomic activity^{46, 47}. While beyond the scope of this paper, the different dynamics of HR and HF-HRV during the sleep period could thus be due to differences in sleep architecture between nighttime and daytime sleep. It is also possible that the effect of sleep on cardiac autonomic activity is modulated by endogenous circadian rhythmicity directly.

Our findings in study 1 indicate that behavioral factors, such as sleep, posture, and physical activity, may dominate temporal changes in cardiac autonomic activity relative to endogenous circadian rhythmicity. This was confirmed in study 2, which allowed for an integrated view of the cardiac autonomic activity modulators that were dissociated in study 1. In study 2, we found that regardless of the time of day, HR was lowest and HF-HRV was highest during scheduled sleep, and vice versa, during scheduled wakefulness (Fig. 7). The magnitude of change between scheduled sleep and scheduled wakefulness was larger than the magnitude of change between sedentary simulated watchstanding periods and other waking periods. Thus, in the laboratory-based, simulated shift schedules of study 2, sleep was the dominant driver of HR and HRV.

Limitations

Our studies have some limitations that warrant consideration. Subjects were healthy young adults, free from clinically significant medical conditions including sleep disorders such as obstructive sleep apnea (OSA). OSA, which typically increases in severity during daytime sleep⁴⁸, modifies cardiac autonomic activity⁴⁹. As such, our results do not generalize to shift workers with OSA. Additionally, caffeine use was not permitted in our studies, though caffeine is commonly consumed by real-world shift workers⁵⁰ as a fatigue countermeasure. We did not address whether or how stimulants or other medications modulate cardiac autonomic activity in shift work settings. Eating habits—or even a single meal—can also alter HR and HRV⁵¹. Our studies were not designed to assess the impact of meal timing or meal composition on cardiac au-

tonomic activity, and any such effects are therefore intertwined with other factors modulating HR and HRV (especially in comparisons between waking and sleep). Further, we did not study the effects of chronic exposure to shift work, which over time may trigger allostatic mechanisms that modify autonomic activity to maintain homeostasis in the face of the recurring stress of shift work⁵²). This could ultimately result in allostatic overload, potentially leading to cardiovascular disease⁵³).

Conclusion

Our simulated shift work studies investigated the separate and combined effects of various factors affecting cardiac autonomic activity. We found that sleep, physical activity, and exercise are powerful modulators of HR and HRV, whereas the effect of endogenous circadian rhythmicity is comparatively small. In the published literature, some field studies measuring cardiac autonomic activity showed a decrease in parasympathetic activity and/or an increase in sympathetic activity during night shift work^{15, 16, 54, 55}). Other studies found the opposite^{13, 17}) or no difference between day and night shift schedules^{14, 56}). These field studies, however, did not systematically account for the effects of activity, posture, stress, workload, use of stimulants such as caffeine, and/or presence of medical conditions affecting autonomic activity. In field research, these effects may be intertwined and act as confounds, which may explain some of the discrepancies in the published literature. Without measuring and controlling or accounting for such factors, therefore, the results of field studies of cardiac autonomic activity must be interpreted carefully—and conclusions regarding cardiovascular disease or risk based on measures of cardiac autonomic activity should be drawn with caution.

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Sleep pressure regulates mushroom body neural-glial interactions in *Drosophila*

William M Vanderheyden, Hans P A Van Dongen, Marcos G Frank, Jason R Gerstner

Biomedical Sciences, Washington State University - Elson S. Floyd College of Medicine; Sleep and Performance Research Center, Washington State University - Elson S. Floyd College of Medicine

✉ **Correspondence**
marcos.frank@wsu.edu
j.gerstner@wsu.edu

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Abstract

Sleep is a behavior that exists broadly across animal phyla, from flies to humans, and is necessary for normal brain function. Recent studies in both vertebrates and invertebrates have suggested a role for glial cells in sleep regulatory processes. Changes in neural-glial interactions have been shown to be critical for synaptic plasticity and circuit function. Here, we wanted to test the hypothesis that changes in sleep pressure alters neural-glial interactions. In the fruit fly, *Drosophila melanogaster*, sleep is known to be regulated by mushroom body (MB) circuits. We used the technique GFP Reconstitution Across Synaptic Partners (GRASP) to test whether changes in sleep pressure affect neural-glial interactions between MB neurons and astrocytes, a specialized glial cell type known to regulate sleep in flies and mammals. The MB-astrocyte GRASP signal was reduced after 24 h of sleep deprivation, whereas the signal returned to baseline levels following 72 h of recovery. Social enrichment, which increases sleep drive, similarly reduced the MB-astrocyte GRASP signal. We did not observe any changes in the MB-astrocyte GRASP signal over time-of-day, or following paraquat exposure or starvation. These data suggest that changes in sleep pressure are linked to dynamic changes in neural-glial interactions between astrocytes and neuronal sleep circuits, which are not caused by normal rest-activity cycles or stressors.

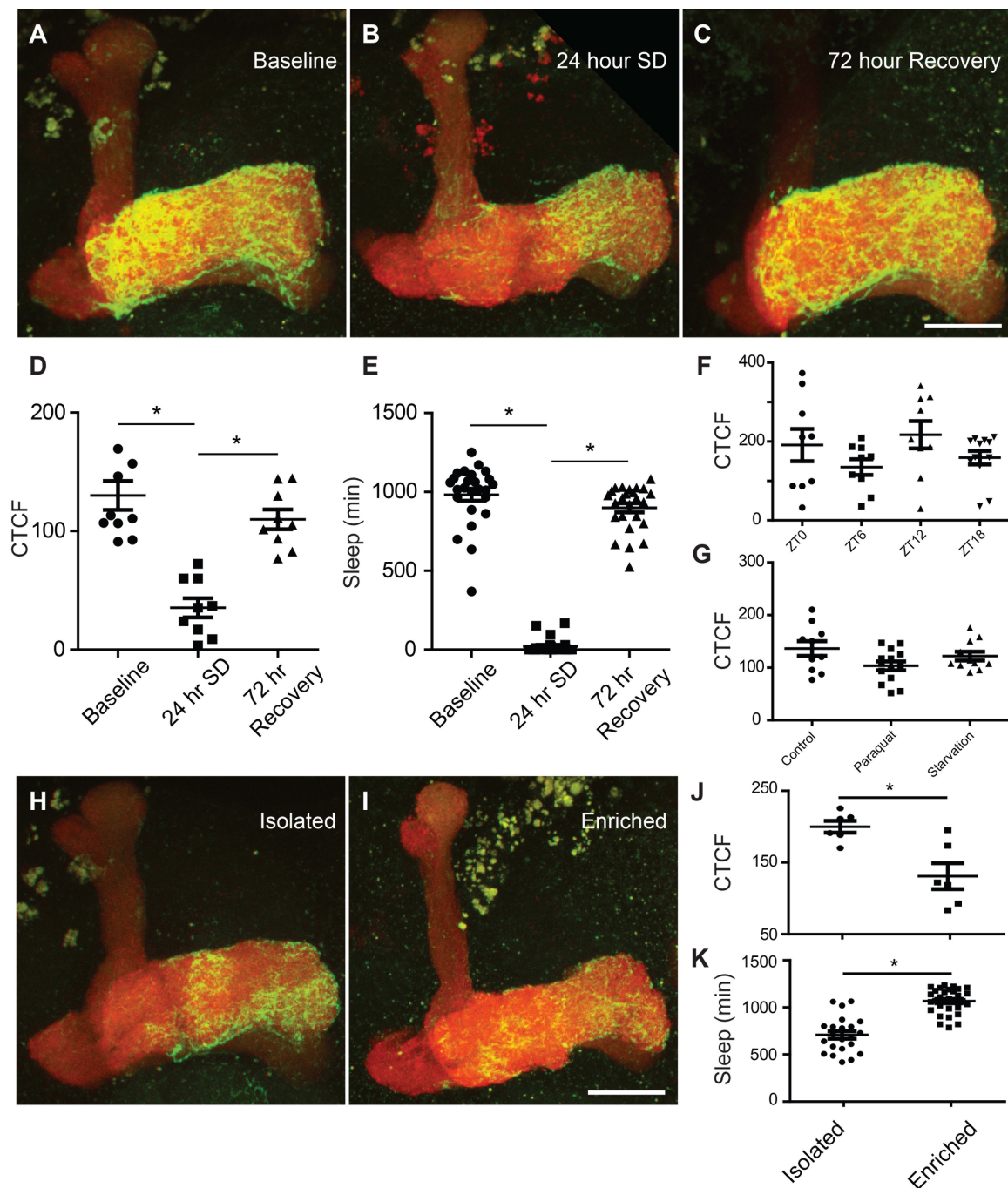
Introduction

Sleep is a ubiquitous behavior exhibited broadly throughout animal phyla, yet its functions remain enigmatic. Fundamental properties of sleep function may be revealed by determining phylogenetically conserved mechanisms associated with sleep behavior across evolutionarily distant species. Sleep is affected both by the amount of time spent awake, as well as experience-dependent changes in synaptic plasticity. Sleep regulatory processes have largely focused on the role of neurons; however, glial cells also play an important role in sleep, across invertebrates and vertebrates alike, including humans [1] [2] [3] [4] [5] [6] [7].

The fruit fly *Drosophila melanogaster* is a powerful model for exploring neural and glial processes that regulate sleep. For example, sleep in *Drosophila* has been shown to be regulated independently by mushroom body (MB) neural circuits [8] [9] as well as glial cells [1] [4] [6] [10] [11]. However, it is currently unclear how MB neurons and glial cells physically interact as a result of changes in sleep pressure. The GFP Reconstitution Across Synaptic Partners (GRASP) technique is a method that labels the membrane contact of two cell types by complementary fragments of the green fluorescent protein (GFP) molecule [12]. Here we use the GRASP technique to label interactions between MB neurons and astrocytes, a specific glial cell type known to regulate sleep in flies and mammals [1] [2] [5]. Determining that changes in neural-glial interactions are associated with sleep pressure would provide a new model system to test functional aspects of sleep-regulatory molecular events that may be conserved across species.

Objective

To determine whether changes in sleep pressure regulate mushroom body neural-glial interactions in flies.



a

Figure Legend

Figure 1. Increased sleep pressure decreases neural-glial interactions between mushroom body neurons and astrocytes in *Drosophila melanogaster*.

(A) Representative image of MB-astrocyte GRASP signal in baseline (non-sleep deprived) condition.

(B) Representative image of MB-astrocyte GRASP signal after 24 h of sleep deprivation (SD).

(C) Representative image of MB-astrocyte GRASP signal after 72 h of recovery following 24 h of SD. Scale bar 25 μ m.

(D) Average CTCF signal in groups from the 24 h of baseline (non-sleep deprived) condition, after 24 h of sleep deprivation (SD), and after 72 h of recovery following 24 h of SD. One-way ANOVA revealed a significant effect of sleep loss on GRASP signal ($P < 0.0001$). Tukey multiple comparisons test showed a significant reduction in GRASP signal after 24 h of SD when compared to both baseline ($*P < 0.001$) and after 72 h of recovery following 24 h of SD ($*P < 0.001$).

(E) Average sleep amount (min) per 24 h day in groups from the 24 h of baseline (non-sleep deprived) condition, during 24 h of sleep deprivation (SD), and for the final 24 h period after 72 h of recovery following 24 h of SD. One-way ANOVA confirmed a significant effect of sleep loss ($P < 0.0001$). Tukey multiple comparisons test showed a significant reduction in sleep during SD when compared to baseline ($*P < 0.001$) and during 72 h of recovery following 24 h of SD ($*P < 0.001$).

(F) Diurnal measures of MB-astrocyte GRASP signal in flies on a 12:12 light-dark cycle. One-way ANOVA indicated no significant changes across time-of-day ($P = 0.22$). ZTo (zeitgeber time 0) = lights on, ZT12 = lights off.

(G) Stress induced by 24 h of paraquat treatment (0.1 mM) or by 24 h of starvation did not affect MB-astrocyte GRASP signal compared to control flies. One-way ANOVA ($P = 0.08$); Tukey multiple comparisons tests among conditions (n.s.).

(H) Representative image of MB-astrocyte GRASP signal in control (isolated flies).

(I) Representative image of MB-astrocyte GRASP signal in flies following social enrichment (enriched flies). Scale bar 25 μm .

(J) Effect of social enrichment (enriched flies) on MB-astrocyte GRASP signal compared to control (isolated flies). T-test ($*P < 0.01$).

(K) Total sleep amount (min) in the 24 h day from MB-astrocyte GRASP flies following social enrichment (enriched flies) compared to control (isolated flies). T-test ($*P < 0.0001$).

Results & Discussion

Our GRASP studies utilized flies harboring mb247-splitGFP11 (specific to MB neurons) [13] [14] and the UAS-splitGFP1-10 expressed in glia, using the astrocyte-directed Alrm-GAL4 driver [15]. MB neural-glial interactions are quantified by the presence of a GFP fluorescent signal, which is triggered upon contact of the individual GRASP components [12]. MB-astrocyte GRASP flies also express Ds-Red under control of the mb247 MB neuronal promoter, which labels the whole MB region of the fly brain. MB-astrocyte GRASP flies were subjected to 24 h of mechanical sleep deprivation [16] and brains were harvested and examined for changes in GFP signal compared to control (undisturbed) flies using confocal microscopy (Fig. 1A–C). All flies were examined at the same time-of-day (ZTo, lights-on). MB-astrocyte GRASP flies showed a significant reduction in GFP signal (Corrected Total Cell Fluorescence, see methods) following sleep deprivation compared to control flies (Fig. 1D). Following 72 h of recovery after 24 h of sleep deprivation, we observed that the GFP signal returned to control levels (Fig. 1D). This MB-astrocyte GRASP response to sleep deprivation and recovery closely resembled the amount of sleep observed under these conditions (Fig. 1E).

To determine whether the changes in MB-astrocyte GRASP signal may have been influenced by the normal sleep-wake cycle, we performed brain dissections on MB-astrocyte GRASP flies at multiple times-of-day. We did not find any differences in the diurnal profile of GFP signal (Fig. 1F), indicating that the observed differences in MB-astrocyte GRASP signal were due to changes in sleep pressure, and not normal sleep-wake cycles. To rule out the possibility that the differences in GFP signal were caused by stress effects, we examined MB-astrocyte GRASP flies for changes in GFP signal following paraquat treatment and starvation stressors. We did not observe any differences in GFP signal in stressor-treated MB-astrocyte GRASP flies compared to control flies (Fig. 1G). To determine whether the decreases in MB-astrocyte GRASP signal were due to increases in sleep pressure, and not a nonspecific artifact of mechanical sleep deprivation, we tested

flies following a social enrichment paradigm, which is known to increase sleep drive in flies [17]. Compared to control (isolated flies), MB-astrocyte GRASP flies subjected to social enrichment (enriched flies) showed a significant reduction in GFP signal (Fig. 1H–J) in tandem with a significant increase in sleep (Fig. 1K), pointing to sleep pressure as the specific driver of the changes in MB-astrocyte GRASP signal.

Sleep deprivation is detrimental to cognitive functioning [18], including learning and memory [19], as well as overall health [20]. Yet, we lack a fundamental understanding of sleep function [21]. The fly model is a powerful tool to understand sleep regulatory processes and functions [22]. Here, we used the GRASP technique to show that increases in sleep pressure decrease neural-glial interactions between MB neurons and astrocytes. Dynamic changes in neural-glial interactions may influence sleep homeostasis through glial uptake of neurotransmitters, efficiency of gliotransmission, and glial processes underlying metabolic support of neurons. Future studies examining phylogenetically conserved molecular pathways in regulating the dynamic relationship of sleep pressure with sleep deprivation- and experience-dependent changes in neural-glial interactions will help to better understand the functional roles for sleep behavior.

Conclusions

This study shows that changes in sleep pressure regulate MB neural-glial interactions in flies.

Limitations

We used *Drosophila melanogaster* to test whether changes in sleep pressure regulate changes in neural-glial interactions. The current studies are limited to MB neurons and astrocytes, and we have not determined whether other sleep circuits or other glial cells are responsive to changes in sleep pressure. Our studies are also limited to the GRASP technique, and alternative strategies, such as immunohistochemistry against neural-glial extra-cellular matrix proteins or cell adhesion molecules [23] or electron microscopy-based morphological studies [24] may provide alternative means to examine sleep-dependent changes in neural-glial interactions. More research is needed to fully understand the time constants of the changes at the neural-glial interface. These changes may take place at time scales ranging from milliseconds to hours, and perhaps even days. Our study was limited to assessing the effects of acute (24 h) sleep deprivation. Our studies are also limited to the fly model, and testing vertebrate models is desirable in order to determine whether the observed changes in neural-glial interactions are phylogenetically conserved. Recent studies demonstrated sleep-dependent changes in the astrocyte glutamate transporter, GLT1, apposition to hypothalamic neurons in mice [25]. However, these studies did not conclude whether the changes were due to a redistribution of GLT1 protein in astrocytes, or to structural changes of astrocyte processes (e.g., extension/retraction) onto these neurons.

Alternative Explanations

Conjectures

Future studies using, e.g., RNAi-based strategies to knock down cell type-specific target proteins involved in cell growth or morphology or the maintenance of the extracellular matrix in our model will be needed to determine mechanisms underlying sleep-dependent changes in neural-glial interactions. In addition, since the MB is an important brain region for learning and memory processes in flies [26], testing whether changes in neural-glial interactions are important for cognitive function would be a worthwhile direction for future studies.

Additional Information

Methods

Fly stocks

Alrm-Gal4 stocks were obtained from the Bloomington Drosophila Stock Center (Indiana University). The mb247-DsRed; mb247-splitGFP¹¹, UAS-splitGFP¹⁻¹⁰/TM3sb flies were obtained from T. Riemensperger and A. Fiala (University of Göttingen).

Fly husbandry

Flies were cultured at 25°C, 60% humidity, maintained on a 12:12 Light:Dark cycle, on Nutri-fly Bloomington Formulation fly food (Genesee Scientific, San Diego, CA). Newly eclosed virgin female flies were collected from culture vials daily under CO₂ anesthesia and housed in groups of approximately 30 prior to experimentation.

Sleep analysis

Female flies 4–7 days after eclosion were used for all sleep studies. Flies were mouth aspirated into 5 mm × 65 mm (outside diameter × length) polycarbonate recording tubes (Trikinetics, Waltham, MA) with food (Bloomington Nutri-fly formula) on one end and yarn plugs on the other. Sleep parameters were continuously evaluated using the Trikinetics Drosophila activity monitoring system (DAMS; Trikinetics, Waltham, MA) as described previously [27]. One acclimatization day was followed by 2 days of baseline sleep recording, one 24 h period of mechanical sleep deprivation, and 72 h of recovery sleep. Sleep deprivation was performed using a Sleep Nullifying Apparatus (SNAP), which produces waking without nonspecifically activating stress responses [16], as described previously [27].

Imaging

Drosophila brains were dissected in phosphate-buffered saline (0.9% NaCl, 10 mM NaH₂PO₄, pH 7.2) containing 0.3% Triton X-100 (PBS-T) and fixed in 4% paraformaldehyde, washed, and mounted on cover slips. Optical sections were collected with a Leica DMi8 laser scanning confocal microscope. For each experiment, calibration on the microscope was held constant by establishing a signal threshold value for the control group. GRASP intensity levels were measured using Corrected Total Cell Fluorescence (CTCF). The corrected total fluorescence = Integrated Fluorescence density – (Area of ROI multiplied by Mean Fluorescence of background) and was calculated in max projected image stacks with the region of interest (ROI) around the mushroom bodies.

Stress and starvation

Virgin female flies were collected as described above. 4–7 days after eclosion, animals were mouth aspirated into 5 mm × 65 mm (outside diameter × length) polycarbonate recording tubes (Trikinetics, Waltham, MA) containing 0.1 mM Paraquat in minimal media (2% agar, 5% sucrose in ddH₂O) or starvation food (2% agar in ddH₂O). Animals were housed for 24 h on these media and afterwards were rapidly dissected at ZT0 for imaging of GRASP signal.

Social enrichment

To standardize the environmental conditions during critical periods of brain development, virgin female flies were collected upon eclosion and maintained in same-sex vials containing approximately 30 flies for 2 days. This protocol kept environmental conditions constant between subsequently isolated and enriched flies for the first 2 days of adult life. 3 day old flies were then divided into a socially isolated group, in which flies were individually housed in 5 mm × 65 mm plastic tubes, and a socially enriched group, consisting of 50 female flies housed in a single vial. After 5 days of social enrichment/isolation, flies were placed into clean 5 mm × 65 mm plastic tubes and sleep was recorded for 3 days using the Trikinetics DAMS.

Data analysis

Statistics were calculated using Graphpad Prism software. Student's t-test, one-way ANOVA, two-way ANOVA, and Tukey post-hoc analysis were used for analyses. Sleep data were analyzed by averaging across multiple experiments. Flies that did not survive the entire experimental paradigm were removed from data analysis.

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Ethics Statement

Not Applicable.

Citations

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Computational cognitive modeling of the temporal dynamics of fatigue from sleep loss

Matthew M. Walsh¹ · Glenn Gunzelmann² · Hans P. A. Van Dongen^{3,4}

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Abstract Computational models have become common tools in psychology. They provide quantitative instantiations of theories that seek to explain the functioning of the human mind. In this paper, we focus on identifying deep theoretical similarities between two very different models. Both models are concerned with how fatigue from sleep loss impacts cognitive processing. The first is based on the diffusion model and posits that fatigue decreases the drift rate of the diffusion process. The second is based on the Adaptive Control of Thought – Rational (ACT-R) cognitive architecture and posits that fatigue decreases the utility of candidate actions leading to microlapses in cognitive processing. A biomathematical model of fatigue is used to control drift rate in the first account and utility in the second. We investigated the predicted response time distributions of these two integrated computational cognitive models for performance on a psychomotor vigilance test under conditions of total sleep deprivation, simulated shift work, and sustained sleep restriction. The models generated equivalent predictions

of response time distributions with excellent goodness-of-fit to the human data. More importantly, although the accounts involve different modeling approaches and levels of abstraction, they represent the effects of fatigue in a functionally equivalent way: in both, fatigue decreases the signal-to-noise ratio in decision processes and decreases response inhibition. This convergence suggests that sleep loss impairs psychomotor vigilance performance through degradation of the quality of cognitive processing, which provides a foundation for systematic investigation of the effects of sleep loss on other aspects of cognition. Our findings illustrate the value of treating different modeling formalisms as vehicles for discovery.

Keywords ACT-R · Biomathematical fatigue models · Cognitive architecture · Diffusion model · Leaky accumulator · Local sleep · Psychomotor vigilance test (PVT)

Introduction

Fatigue due to sleep loss is associated with a wide range of deficits in cognitive performance (Jackson & Van Dongen, 2011; Killgore, 2010; Lim & Dinges, 2010) and an increased risk of errors and accidents (e.g., Dinges, 1995). The effects of fatigue are particularly profound for tasks involving sustained attention (Lim & Dinges, 2008). However, the effects of fatigue on cognitive performance vary considerably across tasks (Jackson et al., 2013). This variability reflects in part the differential effects of fatigue on different cognitive processes (Tucker, Whitney, Belenky, Hinson, & Van Dongen, 2010). Therefore, to better understand the effects of fatigue from sleep loss, it is necessary to consider the range of cognitive processes evoked during task performance (Whitney & Hinson, 2010). One way to do so is through

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✉ Matthew M. Walsh
mmw188@gmail.com

¹ TiER1 Performance Solutions, Covington, KY, USA

² Air Force Research Laboratory, Dayton, OH, USA

³ Sleep and Performance Research Center, Washington State University, Spokane, WA, USA

⁴ Elson S. Floyd College of Medicine, Washington State University, Spokane, WA, USA

the use of computational cognitive models (Gunzelmann, Gross, Gluck, & Dinges, 2009; Gunzelmann et al., 2015; Jackson et al., 2013).

Computational cognitive models provide a way to examine task performance in terms of underlying processing mechanisms (Newell, 1990). Models vary in terms of their focus (e.g., linguistics, learning, perception, motor planning; see Gray, 2007) and in terms of the level of analysis or representation they employ (e.g., connectionist models, cognitive architectures, Bayesian models; see Sun, 2008). Despite the prevalence of computational models in psychological science, quantitative models that account for the effects of fatigue from sleep loss on cognitive processes have only recently appeared (e.g., Gunzelmann et al., 2009a; Gunzelmann, Gluck, Moore, & Dinges, 2012; Ratcliff & Van Dongen, 2009, 2011; Veksler & Gunzelmann, in press). This reflects a longstanding tendency for models developed in psychology to focus on empirical phenomena and data associated with favorable physiological and psychological states that are conducive to cognitive processing.

Representing the detrimental effects of fatigue in cognitive models remains a critical challenge for developing unified theories of cognition (Newell, 1990). Representing these effects in cognitive models also creates an opportunity to evaluate theories from the sleep and sleep deprivation literature. Computational models enhance the transparency of theories – including theories of fatigue – and enable quantitative predictions. Recent modeling work suggests that fatigue mainly affects central cognition rather than perceptual and motor processes (Gunzelmann et al., 2009a; Ratcliff & Van Dongen, 2011). Here we build on that work and examine how fatigue affects cognitive processes in two distinct computational models. We show that the quantitative predictions of both models correspond closely to human performance data. More importantly, we demonstrate that the models implement ostensibly different but actually similar theoretical accounts of fatigue, despite being realized in distinct and substantively different conceptual and computational frameworks. In this way, two disparate models of fatigue, implemented computationally, map onto one theory. The juxtaposition of models provides an opportunity to pursue broader understanding of how fatigue impacts cognition, and illustrates how convergence can be achieved across alternative modeling approaches.

Psychomotor vigilance deficits due to fatigue

In this paper, we focus on deficits in sustained attention, one of the most profound and extensively studied aspects of fatigue from sleep loss. These deficits are frequently measured with the psychomotor vigilance test (PVT), a performance task in which stimuli are presented with random inter-trial intervals (Dinges & Powell, 1985; Lim & Dinges, 2008). The most

commonly used version of the task is 10 min in duration and has inter-trial intervals ranging from 2 to 10 s.¹ Participants watch a blank computer monitor for the sudden onset of a visual millisecond counter after which they respond with a key press. The counter starts from zero and continuously increments until the participant responds, or until 30 s have passed. Elapsed time remains on the screen for 1 s after the participant responds, serving as performance feedback. Participants are instructed to respond as quickly as possible, but to avoid responding before the stimulus appears.

PVT responses are frequently divided into three categories. *False starts* occur before the stimulus appears or within 150 ms of stimulus presentation; *alert responses* occur from 150 ms to 500 ms after stimulus presentation; and *lapses* occur more than 500 ms after stimulus presentation.² A fourth category, *non-responses*, is sometimes included for cases when no response occurs before the trial automatically terminates after 30 s.

Increased performance instability is a hallmark effect of fatigue on PVT performance (Doran, Van Dongen, & Dinges, 2001). The distribution of response times on the PVT, which has a long right tail even when participants are well rested, becomes increasingly skewed as participants become more fatigued. Fatigued participants make more extremely slow responses (i.e., more lapses), and they respond before the counter appears more often (i.e., more false starts). The progressive increase in performance variability typified by extremely slow responses and premature responses, and the general slowing of responses with time awake, are standard effects of sleep deprivation on the PVT and other vigilance tasks (Dorrian, Rogers, & Dinges, 2005; Kleitman, 1963). This performance instability contributes to an elevated risk of errors and accidents in fatigued individuals (Van Dongen & Hursh, 2010).

The PVT is among the most widely used cognitive assays of fatigue from sleep loss. PVT performance is highly sensitive to acute total sleep deprivation, sustained sleep restriction, circadian rhythm, time on task, and a range of fatigue countermeasures (Dorrian, Rogers, & Dinges, 2005; Lim & Dinges, 2008). Aptitude and practice effects on the PVT are negligible, making the task suitable for repeated administration and comparisons both within and between individuals (Dorrian, Rogers, & Dinges, 2005; Horne & Wilkinson, 1985). PVT performance deficits due to fatigue from sleep loss vary systematically among participants, reflecting stable

¹ Though we focus on the 10-min PVT, our description of PVT results and the integrated cognitive models we present apply to the more recently developed 3-min PVT as well (Basner & Dinges, 2011; Basner, Mollicone, & Dinges, 2011).

² Various sources define false starts as responses within 100 ms, 130 ms, or 150 ms of stimulus onset. These slight variations did not impact the cognitive modeling results presented later.

inter-individual differences in vulnerability to sleep loss (Van Dongen, Baynard, Maislin, & Dinges, 2004).

Biomathematical models of the temporal dynamics of fatigue

Biomathematical models of fatigue describe and predict changes in the level of fatigue over the course of hours and days. Different models account for different sets of fatigue factors, but all instantiate two primary processes of sleep regulation (Hursh & Van Dongen, 2010; Mallis, Mejdal, Nguyen, & Dinges, 2004). A homeostatic process controls the increasing drive for sleep with continuous time awake, and a circadian process promotes wakefulness during the day and sleep at night (Borbély & Achermann, 1999). Together these two primary processes produce dynamic changes in the level of fatigue. The homeostatic process is modulated by chronic sleep restriction across days (Hursh et al., 2004; McCauley et al., 2009, 2013).

Biomathematical models of fatigue are not specifically concerned with cognitive mechanisms of task performance. Rather, model outputs are typically scaled to a generic summary measure of performance such as an effectiveness score, or a selected outcome measure such as the number of lapses on the PVT. The basic trends produced by the models are observed in a variety of tasks. However, because the outputs of biomathematical models are fitted to specific tasks and measures using existing data, their ability to predict performance in novel tasks is limited. In addition, biomathematical models of fatigue are generally silent about underlying changes in cognitive processing caused by sleep loss and circadian rhythmicity.

Computational cognitive models of fatigue

Two classes of computational models have recently been used to account for the cognitive effects of fatigue. The first is based on a diffusion process that simulates the accumulation of evidence during simple and two-alternative forced-choice tasks (Laming, 1968; Ratcliff & McKoon, 2008; Stone, 1960). In this model, evidence accumulates stochastically until reaching a decision threshold, at which time a response is initiated. By varying parameter values in the diffusion model, researchers have reproduced the effects of various experimental manipulations on choice accuracy and response time distributions (e.g., Ratcliff & McKoon, 2008).

Ratcliff and Van Dongen (2011) showed that fatigue may be simulated by adjusting a composite diffusion model parameter, drift rate divided by drift rate variability. Varying this composite parameter allowed the diffusion model to capture changes in the response time distribution for individuals performing the PVT with increasing time awake (Ratcliff & Van Dongen, 2011). The same approach accounted for the

effects of fatigue in a two-choice numerosity discrimination task (Ratcliff & Van Dongen, 2009).

The second class of models uses a cognitive architecture to account for how fatigue affects specific components of cognition (e.g., Gunzelmann et al., 2009a). Cognitive architectures are general theories of cognition that specify foundational information processing mechanisms and how they interact with one another (Gluck, 2010). In the cognitive architecture used here, Adaptive Control of Thought – Rational (ACT-R), information enters the system through perceptual modules, affects processing throughout a collection of internal modules, and ultimately causes the manual module to issue a motor response (Anderson, 2007).

Gunzelmann et al. (2009a) developed an account of how fatigue selectively impairs information processing mechanisms in ACT-R. Briefly, fatigue reduced the utility of candidate behaviors, causing them probabilistically to fall below the threshold for action (cf. Gartenberg et al., 2014). This integrated account captured changes in the complete PVT response time distribution, including false starts, alert responses, lapses, and sleep attacks (Gunzelmann et al., 2009a). The same account made realistic predictions of the effects of fatigue on dual-task performance (e.g., Gunzelmann, Byrne, Gluck, & Moore, 2009) and lane deviation in driving (Gunzelmann, Moore, Salvucci, & Gluck, 2011).

Overview

Despite the many experiments that have documented the effects of fatigue on cognitive performance, and the increasingly widespread use of biomathematical models of fatigue in real-world applications, computational accounts of how fatigue affects cognitive processing mechanisms remain limited (cf., Gunzelmann et al., 2015). Further, there has been no attempt at a comparative analysis of the few available computational cognitive models of fatigue. Several basic questions remain unresolved: How does fatigue impact cognitive processes? How do different cognitive models account for the effects of fatigue? And how do these models relate to one another and to theories of fatigue from the sleep research literature?

We developed and compared two computational cognitive accounts of the effects of fatigue on cognition – a diffusion model and an ACT-R model – and we used the PVT as a test bed for evaluating these accounts. The diffusion model is based on that of Ratcliff and Van Dongen (2011), which we augmented with a leaky accumulator (Usher & McClelland, 2001) to capture false starts. Additionally, we merged the diffusion model with a biomathematical model of fatigue (McCauley et al., 2013) to systematically vary parameters in the diffusion model that are affected by sleep loss. The ACT-R model is based on that of Gunzelmann et al. (2009a). We updated their model for the latest release of the architecture, ACT-R 7.0 (Anderson, 2007), and fitted it to new data sets.

The same biomathematical model (McCauley et al., 2013) was used to systematically vary parameters in the ACT-R model that are affected by fatigue.

To date, the two accounts are the only computational cognitive models that have been shown to predict the complete distribution of response times on the PVT. Yet, aside from this shared capability, the diffusion model and ACT-R have few obvious similarities. As such, the question arose whether the two would support a consistent picture of how fatigue affects psychomotor vigilance performance. The focus of the research described here is not to evaluate the viability of either ACT-R or diffusion models as theories of cognitive processes per se. Nor is the objective to declare one of the models superior in accounting for the effects of fatigue. Rather, we evaluate what each model tells us about how fatigue impacts cognitive processing. In this way, we take seriously McClelland's (2009) statement that models are "vehicles for scientific discovery" (p. 16) and employ the two models' different levels of abstraction to look for converging evidence about the nature of fatigue, not tied to a specific modeling formalism, in the context of sustained attention.

Integrated models

Diffusion and ACT-R models have previously been proposed to account for the cognitive effects of fatigue on PVT performance, but the models did not focus on the same observed deficits. We modified and expanded both in order to be able to compare them directly.

Diffusion model

The diffusion model is based on a random walk sequential sampling process (Ratcliff & McKoon, 2008). In the diffusion model, evidence is accumulated over time (Fig. 1). Incoming information drives the process toward one of two decision boundaries during two-alternative forced choice tasks, or one decision criterion (A) during one-choice reaction time tasks. The rate of evidence accumulation, called drift rate, varies across trials according to a normal distribution with mean V and standard deviation η . The process terminates when accumulated evidence reaches a decision criterion, at which point the decision is made and the response initiated. Decision time is the elapsed time from when the diffusion process begins until it reaches the decision criterion. Other, non-central cognitive processes involved in task performance, such as perceptual and motor processes, make up non-decision time, which is represented as a uniformly distributed variable with mean T_{ND} and spread S_T . Response time equals the sum of decision time and non-decision time.

The diffusion model is typically fitted to accuracy rates and response time distributions for correct and error

responses. The model parameters capture a wide range of empirical effects (Ratcliff, 2006; Ratcliff & McKoon, 2008). For example, mean drift rate (V) nominally corresponds to the signal-to-noise ratio in the evidence accumulation process. Low drift rates produce slower, less accurate responses, and high drift rates produce faster, more accurate responses. Variations in mean drift rate can account for the effects of stimulus quality on response time and accuracy (Ratcliff & McKoon, 2008; Voss, Rothermund, & Voss, 2004). The decision criterion (A) controls whether responses are conservative or liberal. When the decision criterion is high, responses are slower but more accurate, and when the decision criterion is low, responses are faster but less accurate. Variations in the decision criterion can capture, for example, the effects of incentives or instructions to prioritize speed versus accuracy on performance (Ratcliff & McKoon, 2008).

The diffusion model has been applied to performance on many different tasks, such as perceptual discrimination (Ratcliff & Rouder, 2000), signal detection (Ratcliff, Van Zandt, & McKoon, 1999), and lexical decision making (Ratcliff, Gomez, & McKoon, 2004). In the context of fatigue research, the model has been applied to numerosity discrimination and the PVT (Ratcliff & Van Dongen, 2009, 2011; Patanaik, Zagorodnov, Kwoh, & Chee, 2014). For our purposes, the diffusion model is particularly suitable for studying the effects of fatigue on the PVT because it predicts complete response time distributions, and because its parameters can be manipulated to produce continuous performance decrements due to fatigue.

Task model

Ratcliff and Van Dongen (2011) developed a diffusion model of the PVT. Because the PVT is a one-choice reaction time task, the model includes a single, positive decision criterion, A (Fig. 1). Although accumulated evidence could become negative during the accumulation process, the process terminates only upon reaching the positive decision criterion.

Ratcliff and Van Dongen (2011) fitted this diffusion model to data from participants who completed the PVT every 2 h while staying awake for 36 h. They found that sleep deprivation mainly affected evidence accumulation, whereas the decision criterion and non-decision time were only marginally influenced by fatigue. As fatigue increased, drift rate (V) decreased and between-trial variability in drift rate (η) increased. The temporal dynamics of the effect of fatigue on PVT performance could be described by changing a single (composite) diffusion model scaling parameter, the drift ratio V/η (Ratcliff & Van Dongen, 2011).

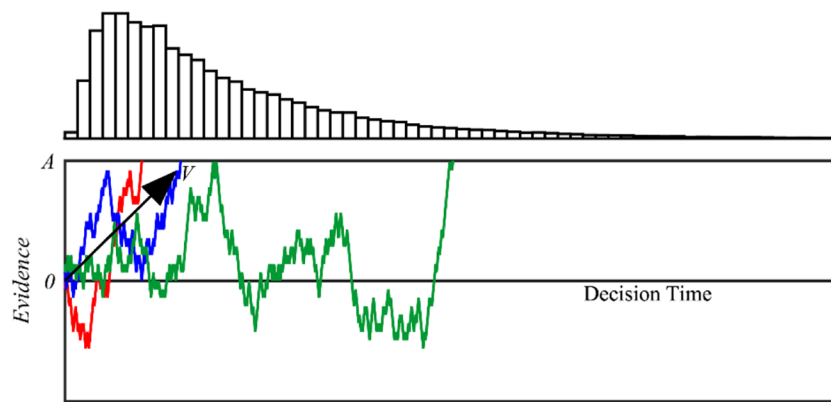


Fig. 1 Three sample trajectories from a one-criterion diffusion process with mean drift rate V . Evidence accumulation starts at 0 and terminates upon reaching criterion A . Histograms show example densities of response times

Task model extension

The model of Ratcliff and Van Dongen (2011) makes predictions about the complete response time distribution. However, because the model pertains to processing after the stimulus appears, it does not produce false starts. Increased numbers of false starts under conditions of sleep loss are an important phenomenon, as false starts indicate that fatigue-related performance impairments cannot be explained solely by general slowing or reduced motivation (Doran, Van Dongen, & Dinges, 2001). Here we expanded the diffusion model to also predict the proportion of false starts.

In a typical diffusion model, the decision process is initiated when a stimulus is presented. This is problematic because, in theory, it would necessitate a separate decision process to detect trial onset and to initiate the primary decision process associated with the trial. Further complicating matters, in tasks where different types of stimuli necessitate different decision processes (e.g., numerosity judgments vs. lexical decisions), the pre-trial decision process would need to include multiple boundaries associated with deciding which of the tasks to perform. To avoid this basic dilemma, we expanded the model so that the diffusion process began immediately after feedback from the preceding trial disappeared (i.e., in anticipation of the next stimulus). The diffusion process persisted throughout the pre-stimulus interval and after the stimulus appeared. Although this may seem counterintuitive, we believe that it represents a plausible characterization of decision processes. The change allows multiple processes to operate in parallel, with irrelevant processes remaining essentially dormant until the appropriate stimuli move their drift rates from zero.

Conceptually, the signal-to-noise ratio in the PVT should be zero during the pre-stimulus interval and greater than zero once the stimulus appears. To produce these dynamics, we allowed V to take on positive values once the

stimulus appeared, and we fixed it to zero during the pre-stimulus interval. Due to within-trial stochastic variability, the diffusion process is equally likely to move upward or downward at each point in time when V is zero. The noisy accumulation of evidence during the pre-stimulus interval allows the diffusion process to occasionally reach the decision criterion before the stimulus appears and thereby cause a false start.

Preliminary simulations with this model extension confirmed that stochasticity alone caused the diffusion process to nearly always reach the decision criterion prematurely, and the predicted number of false starts far exceeded what is typically seen. Therefore, we implemented an additional process based on the intrinsic decay present in neural integrator models (Abbott, 1991; Cain & Shea-Brown, 2012; Goldman, Compton, & Wang, 2009; Robinson, 1989; Smith & Ratcliff, 2009). We used the leaky competing accumulator model (LCA; Ossmy et al., 2013; Usher & McClelland, 2001), in which the diffusion process depends on two opposing forces: accumulation of evidence from a stimulus drives the process toward the decision criterion, while decay (or leakage) pulls the process back to zero with a certain decay rate, λ .

Decay can be seen as controlling response inhibition. When the value of λ is high, the diffusion process tends to return to zero and is thus more robust against noise (greater inhibition), whereas when the value of decay is low, the diffusion process is more sensitive to noise (less inhibition). Because decay rate depends on the simulation step size, we sometimes refer to the diffusion process's integration time constant instead, which does not depend on the simulation step size. The integration time constant is the time it takes for the diffusion process to reach $1 - 1/e$ of its final (asymptotic) value given a signal of constant intensity.

The frequency of false starts is jointly determined by the value of λ and by the decision criterion, A (Fig. 2). With the LCA process implemented, the diffusion model

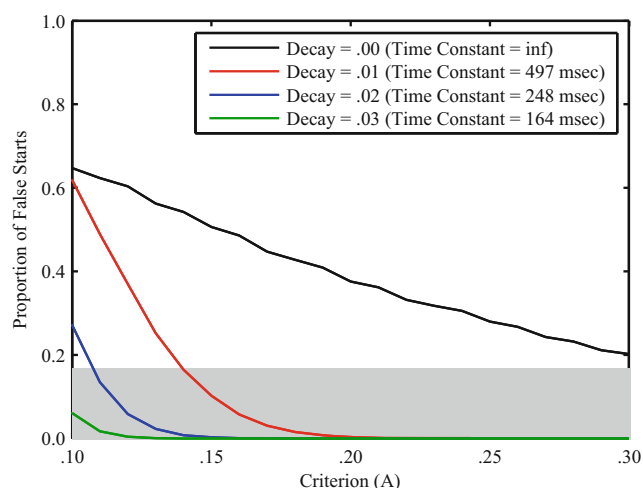


Fig. 2 Proportion of false starts in simulations as a function of leaky competing accumulator model (LCA) decay rate, λ , and diffusion model decision criterion, A . The gray band shows the range of the proportion of false starts committed by participants during the third day of total sleep deprivation (see Experiment 1 below)

of the PVT is able to produce false starts within the range of what is typically seen (Doran, Van Dongen, & Dinges, 2001).

The task model was implemented using a random walk approximation of the diffusion process with a step size $\tau = 5$ ms (Tuerlinckx, Maris, Ratcliff, & De Boeck, 2001). At each step j , a displacement Δ_j occurs with probability p , and a displacement $-\Delta_j$ occurs with probability $1-p$. The size of the displacement is determined by τ and the within-trial stochastic component of the accumulation process $s = 0.1$ (Tuerlinckx et al., 2001)³:

$$\Delta_j = s\sqrt{\tau}. \quad (1)$$

The probability of the positive displacement is given by:

$$p = \left(1 + \frac{V\sqrt{\tau}}{s}\right) / 2. \quad (2)$$

where V corresponds to drift rate. A within-trial stochastic component of the process is instantiated in Eq. 2, and a between-trial stochastic component is produced by drawing a value v from a normal distribution with a mean of V and a standard deviation of η for each trial.

To implement decay, we modified the displacement term in (1), as follows⁴:

$$\Delta_j = s\sqrt{\tau} - \lambda E_j, \quad (3)$$

³ Taking the square root of τ ensures that v meaningfully corresponds to drift rate in the continuous diffusion model and in a way not dependent on time-step size in its discrete approximation (Tuerlinckx et al., 2001).

⁴ For related expressions, see Goldman et al. (2009) and Usher and McClelland (2001).

where E_j is the evidence accumulated to that time in the diffusion process:

$$E_j = \sum_{k=1}^{j-1} \Delta_k, \quad (4)$$

with $E_0 = 0$. The first step of the diffusion process, $j = 1$, comes immediately after the offset of feedback from the preceding trial.

Biomathematical model of fatigue

We combined the extended diffusion model of the PVT with the biomathematical model of fatigue described by McCauley et al. (2013). This biomathematical model is based on the two-process model of sleep regulation (Borbély & Achermann, 1999), in which a homeostatic process increases the drive for sleep with time awake, and a circadian process promotes wakefulness during the day and sleep at night. The homeostatic and circadian processes interact in a non-linear manner such that the amplitude of the circadian process increases in sleep-deprived individuals (McCauley et al., 2013). A third process adjusts the set point of the homeostatic process in response to long-term sleep/wake history. The biomathematical model is sensitive to fatigue due to total sleep deprivation, circadian misalignment during shift work, and sustained sleep restriction (Fig. 3).⁵

Integration

We integrated the biomathematical model of fatigue with the diffusion model of the PVT. Ratcliff and Van Dongen (2011) showed that the dynamic changes in the response time distribution on the PVT across 36 h of total sleep deprivation were captured by varying the drift ratio V/η . Furthermore, they found a high correlation between the fitted values of V/η and the output of an earlier version of the biomathematical model of fatigue (McCauley et al., 2009). We captured this dynamic by fixing η across sessions and treating V as a linear function of the predictions of the biomathematical model of fatigue, F :

$$V = a_V F + b_V, \quad (5)$$

where a_V and b_V represent slope and intercept. When the slope term a_V is negative, drift rate decreases with fatigue, producing longer and more variable response times.

Dynamic changes in false starts could result from temporal changes in the decision criterion, A , or in the decay rate of the LCA process, λ . Ratcliff and Van Dongen

⁵ For a complete description of the model and its equations, see Table 1 of McCauley et al. (2013). A DOS executable of the model is available at <https://pounce.spokane.wsu.edu/data/public/9d87c1>

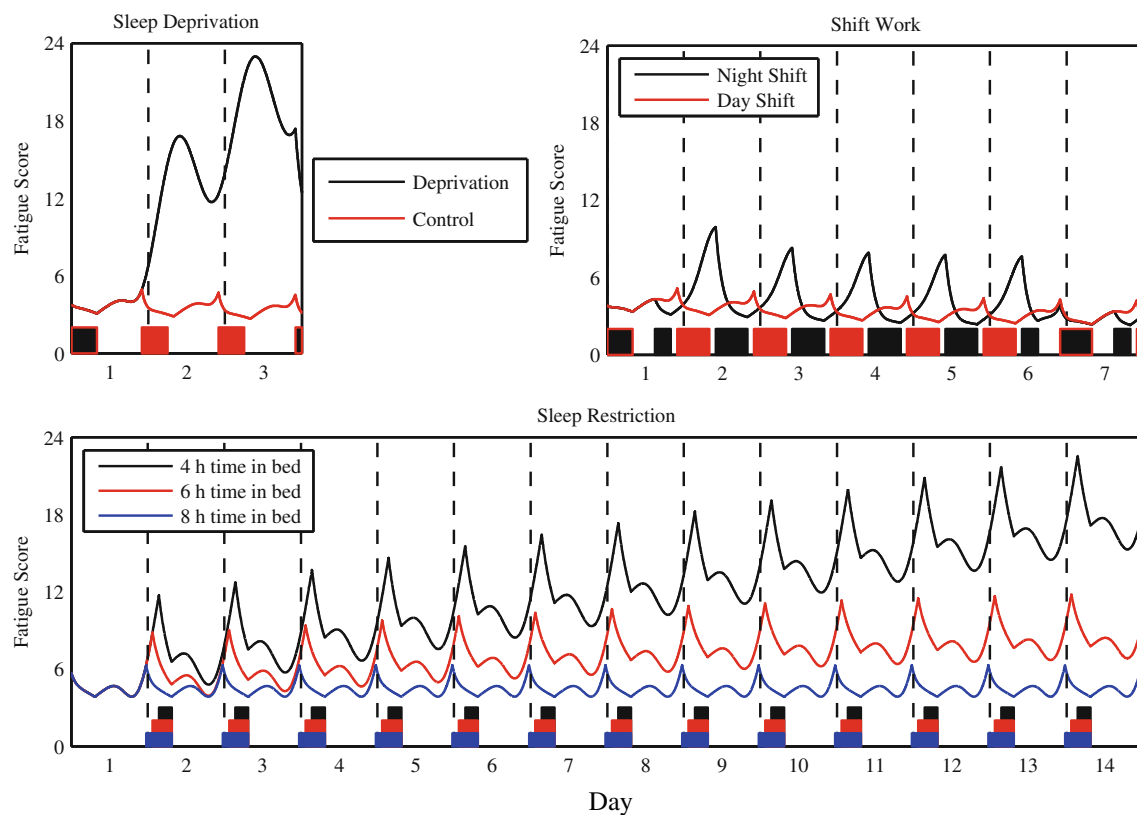


Fig. 3 Biomathematical model predictions of fatigue. **Top-left panel:** Predicted fatigue across 3 days of total sleep deprivation versus a control condition with daily time in bed (TIB) from 22:00 until 08:00. **Top-right panel:** Predicted fatigue across 5 days of a shift schedule with daily TIB from 22:00 until 08:00 (day shift) versus a shift schedule with daily TIB from 10:00 until 20:00 beginning on day 2 (night shift).

Bottom panel: Predicted fatigue across 14 days for schedules with 4 h, 6 h, or 8 h TIB daily, with TIB ending at 07:30 for all three conditions. Colored bars at the base of each panel show TIB for the corresponding conditions. In this model (McCauley et al., 2013), Fatigue Score is the predicted number of lapses in a 10-min Psychomotor Vigilance Test (PVT)

(2011) reported that A did not change significantly in response to sleep deprivation. We therefore fixed A , and treated λ as a linear function of the predictions of the biomathematical model of fatigue, F :

$$\lambda = a_{\lambda}F + b_{\lambda}, \quad (6)$$

where a_{λ} and b_{λ} represent slope and intercept.⁶ When the slope term a_{λ} is negative, the decay rate decreases with fatigue. This partially offsets the effect of fatigue on drift rate. However, this also offsets the dampening effect of decay during the pre-stimulus interval, which potentiates false starts.

In total, the extended, integrated diffusion model contained eight free, participant-specific parameters (Table 1). Ratcliff and Van Dongen (2011) reported that three diffusion model parameters (V , η , and A) were not uniquely determinable for the PVT. Rather, the two ratios A/V and V/η were approximately constant over different

model fits. In our extended model, the interplay between decay (λ) and drift rate make the values of all three parameters consequential. In our simulations, A and η were estimated for individuals and held constant across sessions, while V was estimated for individuals and allowed to vary across sessions by Eq. 5.

Table 1 Diffusion model parameters

Parameter	Definition
a_V	Drift rate scaling slope
b_V	Drift rate scaling intercept
a_{λ}	Decay rate scaling slope
b_{λ}	Decay rate scaling intercept
η	Drift rate variability
A	Decision criterion
T_{ND}	Mean of non-decision time
SD	Spread of non-decision time

Note. The first and second parameters (a_V , b_V) scale the effects of fatigue on drift rate, and the third and fourth parameters (a_{λ} , b_{λ}) scale the effects of fatigue on decay. The remaining parameters and corresponding processes are not involved in capturing fatigue in the model

⁶ In a later set of reported simulations, we examined the results of instead allowing A to vary with fatigue while holding λ constant. Although the fits were nearly as good, they were slightly better when λ was allowed to vary with fatigue.

Adaptive Control of Thought – Rational (ACT-R)

The cognitive architecture ACT-R (Anderson, 2007) contains a set of specialized information processing modules (Fig. 4). These include a visual module for locating and identifying objects in the visual field, a manual module for producing motor responses, a declarative module for storing and retrieving information in memory, an imaginal module for holding current problem representations, a goal module for maintaining information about context and intent, and a procedural module for coordinating other modules' behavior. Buffers allow information and commands to pass from the specialized information processing modules to the central procedural module and back.

In ACT-R, procedural knowledge is represented in the form of production rules. Each rule has a set of conditions that must be met for it to be selected, and a set of actions that modify the external world and the internal state of the architecture. Each rule also has real-valued utility, corresponding to the reward the rule is expected to lead to with respect to task performance and completion. Cognitive performance unfolds across a sequence of production cycles lasting on the order of tens of milliseconds. During each cycle, conditions for different productions are compared against the contents of the buffers, and the production with the highest utility is selected and enacted. The resulting state of the world and architecture, represented by the contents of the buffers, serves as the starting point for the next production cycle.

ACT-R has been used to model cognitive performance on dozens of laboratory tasks (see Anderson, 2007) and to

simulate complex skills such as air traffic control, algebra problem solving, and driving (Anderson et al., 2004; Salvucci, 2006). In the context of fatigue research, ACT-R has been applied to dual-tasking (Gunzelmann et al., 2009b), arithmetic retrieval (Gunzelmann et al., 2012), driving (Gunzelmann et al., 2011), flying (Gunzelmann & Gluck, 2009), and the PVT (Gunzelmann et al., 2009a). Like the diffusion model, ACT-R is particularly suitable for studying the effects of fatigue on the PVT because it predicts complete response time distributions, and because its parameters can be manipulated to produce continuous performance decrements due to fatigue.

Task model

Gunzelmann et al. (2009a) developed an ACT-R model of the PVT. The model contains four productions: (1) *wait* for the stimulus to appear, (2) *attend* to the stimulus, (3) *respond*, and (4) *press key*. Each production is eligible for selection in certain conditions. *Wait* is eligible when nothing is present on the screen, *attend* is eligible when the stimulus is present on the screen but has not yet been attended, *respond* is eligible when the stimulus is present on the screen and has been attended, and *press key* is always eligible. Thus, during each production cycle a choice is made between one of the first three productions, and the *press key* production. Logistically distributed noise is added to production utilities (U_i),

$$U'_i = U_i + \varepsilon_i, \quad (7)$$

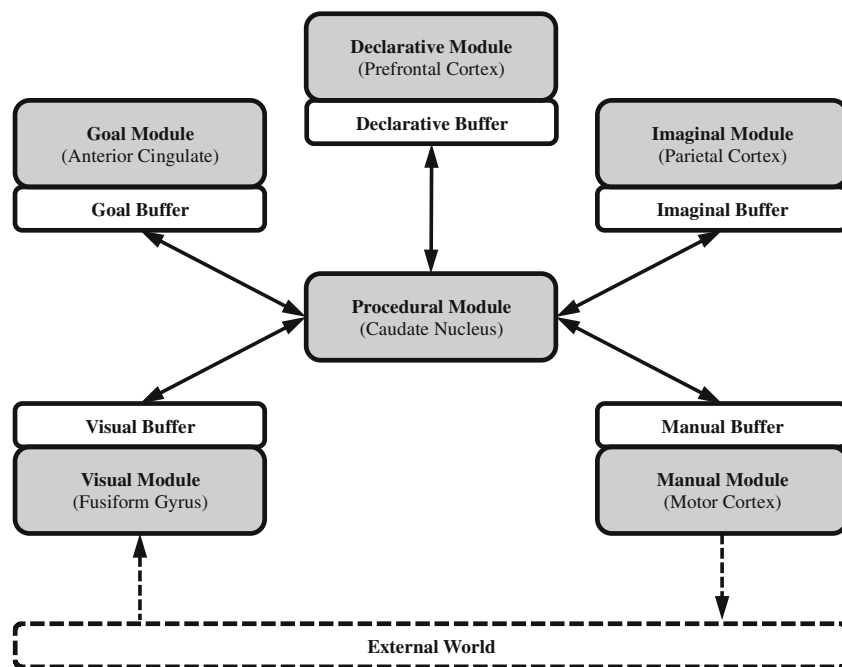


Fig. 4 Schematic representation of the modules and buffers of the Adaptive Control of Thought – Rational (ACT-R) cognitive architecture and their associations with brain regions

and the production with the greatest resulting utility value U'_i is selected. The occasional selection of *press key* before the stimulus appears permits false starts.

The production with the greatest value is enacted if its utility exceeds the threshold,

$$\text{Production} = \max(U'_i); \text{enacted if } \max(U'_i) > T. \quad (8)$$

When no production's utility exceeds the threshold, the model becomes briefly inactive before initiating the next production cycle – a microlapse. The period of inactivity equals the duration of one production cycle (i.e., tens of milliseconds).

Gunzelmann et al. (2009a) fitted this ACT-R model to data from participants who completed the PVT every 2 h while staying awake for 88 h. They found that sleep deprivation affected production utilities and the utility threshold; as time awake increased, production utilities and the utility threshold decreased. Changes in the duration of perceptual and motor processes, production execution time, and production noise were not needed to account for the effects of fatigue.

Task model update

Subsequent to the development of the ACT-R model of the PVT, a mechanism called *production partial matching* was introduced in ACT-R. With production partial matching, productions whose conditions are not perfectly met are eligible for selection, but their utility values are penalized:

$$U'_i = (U_i - MMP_i) + \varepsilon. \quad (9)$$

MMP_i is the mismatch penalty charged if the conditions for the production are not perfectly met. The production with the greatest value U'_i is selected and enacted provided its utility exceeds the threshold (Eq. 8). This is true even when the production with highest utility does not perfectly match the conditions, but exceeds the threshold.

The addition of production partial matching to ACT-R obviated the need for the *press key* production in the PVT model of Gunzelmann et al. (2009a); with this addition, *respond* can be selected at any time. Consequently, the updated model we advance contains a total of three productions: (1) *wait*, (2) *attend*, and (3) *respond* to the stimulus. When *respond* is selected before the stimulus appears, a false start occurs. However, because the utility of *respond* is penalized before the stimulus appears, this happens infrequently.

Productions' baseline utilities (U_i) were treated as a single free parameter – one value of U was estimated and used for all productions. U could be acquired from experience using ACT-R's procedural learning equation (Anderson, 2007; Fu & Anderson, 2006), but we disabled utility learning because learning effects on the PVT are negligible (Van Dongen et al., 2003). To simplify matters, the mismatch penalty (MMP , Eq. 9)

was set to the value of production utility. The resulting payoff matrix was symmetric with zero assigned to mismatches and U assigned to matches (see Eq. 9).⁷ The mean and standard deviation of the logistically distributed noise added to these values during each production cycle were set to the default ACT-R values of 0.0 and 0.453 (Anderson et al., 2004).

Integration

We integrated the biomathematical model of fatigue (McCauley et al., 2013) with the updated ACT-R model of the PVT. In the integrated model, the effects of fatigue play out through three component interactions. First, fatigue reduces productions' utility values (Fig. 5):

$$U''_i = FP \cdot (U_i - MMP_i) + \varepsilon_i, \quad (10)$$

where FP (i.e., *Fatigue in Procedural Knowledge*) is a linear function of the predictions of the biomathematical model of fatigue, F :

$$FP = a_P F + 1. \quad (11)$$

The parameter a_P is a slope parameter. In the absence of fatigue, FP equals one (i.e., utilities are unchanged). When the slope parameter a_P is negative, production utilities decrease with fatigue.⁸ Consequently, selections are increasingly driven by noise. Also, productions increasingly fall below the utility threshold, causing more microlapses.

Second, fatigue lowers the utility threshold, T (Fig. 5):

$$T' = FT \cdot T. \quad (12)$$

FT (i.e., *Fatigued Threshold*) is a linear function of the predictions of the biomathematical model of fatigue:

$$FT = a_T F + 1. \quad (13)$$

The parameter a_T is a slope parameter. In the absence of fatigue ($F = 0$), FT equals one. When the slope term a_T is negative, the utility threshold decreases with fatigue. This partially compensates for the effect of fatigue on utility values. However, this also reduces the inhibitive effect of the mismatch penalty on the *respond* production, allowing more false starts.

⁷ The mismatch penalty between the conditions for the *wait* and *respond* productions could conceivably be set to a different value than the mismatch penalty between the conditions for the *attend* and *respond* productions. However, such adjustments were not necessary to capture the results of the experiments modeled here.

⁸ For large negative values of a_P , FP could conceivably become negative, and U'' could become negative as well. Based on estimates of a_P from the reported simulations, however, FP did not approach negative values even after 62 h of total sleep deprivation. Future work could explore bounding FP at zero, or using a non-linear function to map the output of the biomathematical model to cognitive model parameter estimates to eliminate this possibility.

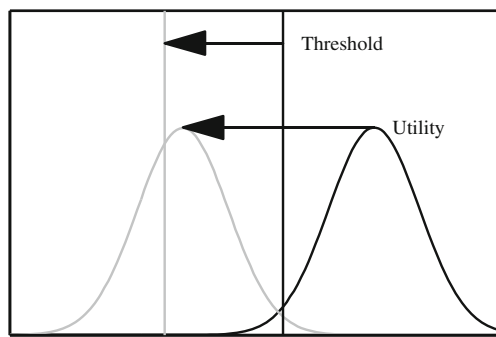


Fig. 5 In the integrated Adaptive Control of Thought – Rational (ACT-R) model of the Psychomotor Vigilance Test (PVT), fatigue reduces utility values (distributions), and to a lesser extent the utility threshold (vertical lines)

Third, when no production's utility exceeds the threshold and a microlapse occurs, FP is decreased by a small amount:

$$FP \leftarrow FP \cdot FP_{dec}, \quad (14)$$

where $0 < FP_{dec} < 1$. This small change makes it more likely that microlapses will occur in subsequent production cycles. Across such a series of cycles, the probability of responding progressively decreases, leading to behavioral lapses. The value of FP is restored when a stimulus next appears.

In total, the updated, integrated ACT-R model contained six free, participant-specific parameters (Table 2). The one parameter not yet discussed, *cycle time*, controls the amount of time to evaluate and select a production during each production cycle, and has a default value of 50 ms (Anderson, 2007). We allowed cycle time to vary across individuals, consistent with the notion that this parameter reflects stable differences in processing speed (Deary, Der, & Ford, 2001; Larson & Alderton, 1990). The interplay between these parameters and the biomathematical model of fatigue account for the complete RT distribution in the PVT, including false starts and lapses (Supplementary Fig. 1). Although the durations of events in the ACT-R model are on the order of tens of milliseconds, the summation of time across events and the

millisecond-level variability in event durations produces continuous reaction-time distributions.

Experiments and results

We investigated whether the integrated diffusion and ACT-R models could each account for the effects of fatigue stemming from total sleep deprivation, simulated shift work, and sustained sleep restriction on PVT performance. We compared simulations to observations from three experiments (Van Dongen, Belenky, & Vila, 2011; Van Dongen, Maislin, Mullington, & Dinges, 2003; Whitney, Hinson, Jackson, & Van Dongen, 2015).

Fitting procedure

In each of the experiments reported below, we collapsed data across multiple 10-min PVT sessions to form probability density functions. We binned response times corresponding to the 0.1-interval quantiles of responses that occurred after 150 ms for each participant. The 0.1 quantile contained the fastest 10% of responses after 150 ms, and the 1.0 quantile contained the slowest 10% of responses after 150 ms (including the few trials with no response after 30 s). We then calculated the overall proportion of responses that occurred before 150 ms (i.e., false starts), and the overall proportions of responses within the 10 quantiles.⁹ This provided 11 proportion values against which to compare the models for each participant.

We used the models to create corresponding expected probability density functions. To do so, we simulated participants' performance during each 10-min PVT session, and collapsed predictions across sessions as was done with the observations. We then calculated the proportion of predicted responses that occurred before 150 ms, and the proportions of responses within the 10 quantiles defined by boundaries derived from observed response times. Predictions were based on 1,000 simulations for each PVT session.

The observed and expected probability density functions were used to compute the likelihood ratio chi-square (G^2), which is asymptotically equivalent to the chi-square,

$$G^2 = 2 \sum_{i=1:day} \sum_{j=1:bin} N_{ij} \cdot \log \left(\frac{p_{ij}}{\pi_{ij}} \right). \quad (15)$$

N_{ij} is the observed number of responses in the j^{th} bin on the i^{th} day, p_{ij} is the predicted proportion of responses in that bin for that day, and π_{ij} is the observed proportion of responses (Smith & Ratcliff, 2009). A simplex search algorithm with

Table 2 ACT-R parameters

Parameter	Definition
U	Utility
a_P	Utility scaling slope
T	Threshold
a_T	Threshold scaling slope
FP_{dec}	Utility decrement after lapse
$Cycle$	Cycle time

Note. The second parameter (a_P) scales the effects of fatigue on production utilities, and the third parameter (a_T) scales the effects of fatigue on the utility threshold. The remaining parameters and corresponding processes are not involved in capturing fatigue in the model

⁹ Each quantile contained 10% of responses that occurred after 150 ms of stimulus onset. This is slightly less than 10% of all responses, which also include false starts (responses that occurred before or within 150 ms of stimulus onset).

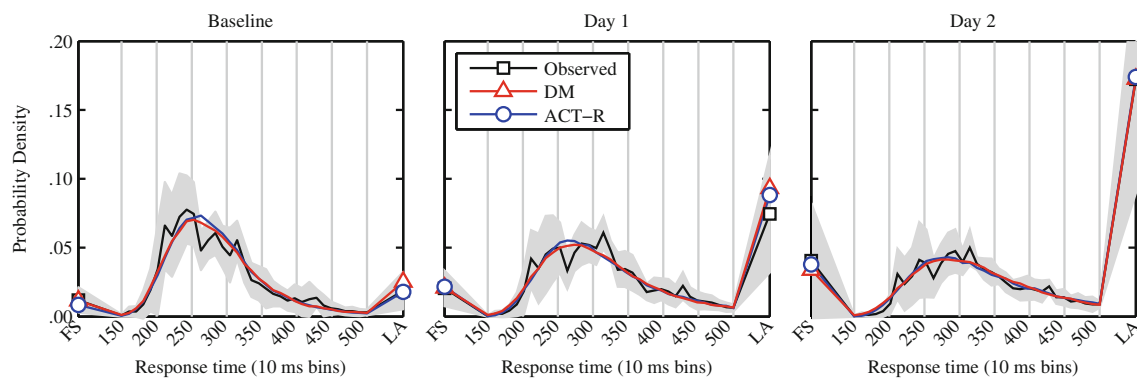


Fig. 6 Psychomotor Vigilance Test (PVT) response time distributions across 62 h of total sleep deprivation, aggregated over each day of Experiment 1. The first bin shows the proportion of false starts (FS), the final bin shows the proportion of lapses (LA), and the middle bins show the proportion of responses occurring in 10 ms intervals from 150–

500 ms. The gray area shows ± 1 SD around the mean for the observations. The red and blue curves show the predictions of the diffusion model (DM) and the Adaptive Control of Thought – Rational (ACT-R) model, respectively

multiple start points was used to find parameter values that minimized G^2 for each participant and model. Simulations were conducted using large-scale computational resources (Harris, 2008).¹⁰ The supplementary material contains additional information about model fitting procedures.

We used two criteria to assess model fit: the G^2 statistic and the Bayesian Information Criterion (BIC). The BIC is calculated from the G^2 statistic according to

$$BIC = G^2 + m \cdot \log(n), \quad (16)$$

where m is the number of free parameters and n is the total number of observations per participant aggregated across all PVT sessions.

Experiment 1: Acute total sleep deprivation

The first experiment involved a 62-h total sleep deprivation condition and a well-rested control condition in a laboratory (Whitney et al., 2015). Participants in the sleep deprivation condition ($n = 13$) remained awake for 62 h, starting at 08:00 after two baseline days, whereas participants in the control condition ($n = 13$) received 10 h time in bed (TIB; 22:00–08:00) each night (Fig. 3, top left). Participants performed the PVT approximately once every 2 h during scheduled wakefulness. Because each session contained relatively few response time observations (mean $\pm$ SD: 94 ± 8), we collapsed data across sessions that occurred within each 24-h period of the experiment (22:00–22:00) for each participant. This yielded aggregate data sets for day 0 (0–15 h awake, baseline), day 1 (16–39 h awake in the sleep deprivation condition), and day 2 (40–62 h awake in the sleep deprivation condition).

Figure 6 shows the average proportions of responses that occurred before or within 150 ms of stimulus presentation (i.e.,

false starts), from 150–500 ms after stimulus presentation (i.e., alert responses), and more than 500 ms after stimulus presentation (i.e., lapses) during each day of the experiment. As time awake increased, participants in the sleep deprivation condition responded more slowly, committed more false starts, and experienced more lapses (see Supplementary Fig. 2 for individuals' data). None of these effects appeared for participants in the control condition (see Supplementary Fig. 3 for individuals' data).

Figure 6 also shows the fits of the diffusion and ACT-R models to the observations. Fits for individual participants are shown in Supplementary Figs. 2 and 3, and cumulative distributions based on quantile response times are shown in Supplementary Figs. 44 and 5. Table 3 contains measures of model fit to the quantile response times of the individuals in the sleep deprivation and control conditions, and Tables 4 and 5 contain the parameter estimates. The G^2 statistic was lower for the diffusion model in both conditions; however, this measure does not take model complexity into account. The BIC, which does take model complexity into account, favored the ACT-R model in the control condition and the diffusion model in the sleep deprivation condition, but the absolute differences between the model fits were small. Comparison of the models' outputs to one another reinforces this conclusion (Supplementary Table 3).

The diffusion model closely matched the observed response time distributions (Fig. 6). The sum of squared errors for each participant ranged from .007 to .017 with a mean ($\pm$ SE) of .010 ($\pm$.001). Correlations between the predicted and observed proportions of responses in 10-ms bins for each participant ranged from $r = .90$ to .97 (Supplementary Fig. 2). As time awake increased, the diffusion model responded more slowly and produced more lapses. This occurred because of changes in the rate of evidence accumulation. The drift rate scaling slope (a_V) was significantly less than zero, $t(12) = 16.86$, $p < .001$ (Table 4, Experiment 1). Consequently, the response time distribution shifted to the right and the distribution became more skewed with increasing time awake.

¹⁰ See <http://www.mindmodeling.org>

Table 3 Average model fits to individuals in Experiments 1 and 2 (± 1 standard error across individuals)

	Model	Model df	Experiment df	G^2	Observations	BIC
Experiment 1:	Diffusion	8	29 $\pm$.1	120 $\pm$ 11	2623 $\pm$ 15	182 $\pm$ 11
Sleep deprivation	ACT-R	6		137 $\pm$ 9		184 $\pm$ 9
Experiment 1:	Diffusion	8	28 $\pm$.3	89 $\pm$ 8	1698 $\pm$ 3	148 $\pm$ 8
Control	ACT-R	6		94 $\pm$ 11		138 $\pm$ 11
Experiment 2:	Diffusion	8	78 $\pm$ 1	431 $\pm$ 33	7700 $\pm$ 21	502 $\pm$ 33
Night shift	ACT-R	6		451 $\pm$ 52		505 $\pm$ 52
Experiment 2:	Diffusion	8	79 $\pm$.6	366 $\pm$ 25	7692 $\pm$ 31	437 $\pm$ 25
Control	ACT-R	6		394 $\pm$ 27		447 $\pm$ 26

The diffusion model also committed more false starts across days. This occurred because of changes in stability during the pre-stimulus interval. The decay rate scaling slope (a_λ) was significantly less than zero, $t(12) = 3.80$, $p < .01$. Reduced decay rate partially compensated for the effect of fatigue on drift rate once the stimulus appeared. However, reduced decay rate also inadvertently allowed noise to drive the diffusion process beyond the decision criterion during the pre-stimulus interval, causing more false starts. The average value of the decay rate scaling slope ($-.0010$; Table 4) is small because the term is multiplied by relatively large values from the biomathematical model (up to 24; Fig. 3), and because small changes in decay have a large impact on performance. With an average value of $-.0010$ for reduced decay, the integration time constant changes from 264 ms at baseline to 192 ms after 3 days of total sleep deprivation.

The ACT-R model closely matched the observed response time distributions as well (Fig. 6). The sum of squared errors for each participant ranged from .008 to .014 with a mean ($\pm$ SE) of .011 ($\pm .001$). Correlations between the observed and predicted response time distributions in 10-ms bins for each participant ranged from $r = .91$ to .96 (Supplementary Fig. 2). The ACT-R model responded more slowly and generated more lapses with increasing time awake. This was because of the rising frequency of microlapses. The utility intercept

was greater than the threshold intercept, $t(12) = 6.98$, $p < .001$ (Table 5; Experiment 1). Consequently, production utilities predominantly exceeded the utility threshold during early sessions, minimizing microlapses. However, the utility scaling slope (a_P) was more negative than the threshold scaling slope (a_T), $t(12) = 11.93$, $p < .001$. Consequently, production utilities fell below the threshold during later sessions with increasing probability, resulting in more microlapses. Microlapses slowed alert responses, and sometimes delayed responses beyond 500 ms, causing lapses.

The ACT-R model also committed more false starts across days. This occurred because of changes in the threshold. The threshold scaling slope (a_T) was significantly less than zero, $t(12) = 7.02$, $p < .001$. Reducing the utility threshold partially compensated for the effect of fatigue on production utilities. However, lowering the threshold also reduced the influence of the mismatch penalty on the *respond* production, leading to more false starts.

Analyzing the response time distributions by day emphasizes the homeostatic process of sleep regulation; performance declines across days of sleep deprivation. Performance also varies within days in accordance with the circadian process. To examine the dynamics across time of day, we calculated the proportions of false starts and lapses and the median times of alert responses for each session during the 3 days (Fig. 7). Due to the interaction between the homeostatic and circadian processes, participants committed more false starts and lapses and

Table 4 Diffusion model parameters estimates for individual participants (± 1 standard error across individuals) for Experiments 1 and 2

Parameter	Experiment 1: Sleep deprivation	Experiment 2: Shift work
a_V	$-.024 \pm .001$	$-.027 \pm .003$
b_V	$1.35 \pm .03$	$1.34 \pm .02$
a_λ	$-.0010 \pm .0001$	$-.0016 \pm .0001$
b_λ	$.040 \pm .002$	$.043 \pm .002$
η	$.23 \pm .01$	$.21 \pm .01$
A	$.101 \pm .002$	$.107 \pm .003$
T_{ND}	$.146 \pm .006$	$.136 \pm .005$
SD	$.101 \pm .007$	$.077 \pm .006$

Table 5 ACT-R parameter estimates for individual participants (± 1 standard error across individuals) for Experiments 1 and 2

Parameter	Experiment 1: Sleep deprivation	Experiment 2: Shift work
U	$5.07 \pm .05$	$4.98 \pm .11$
a_P	$-.014 \pm .001$	$-.022 \pm .001$
T	$4.59 \pm .06$	$4.51 \pm .07$
a_T	$-.010 \pm .001$	$-.015 \pm .001$
FP_{dec}	$.984 \pm .003$	$.983 \pm .006$
$Cycle$	$.041 \pm .003$	$.034 \pm .002$

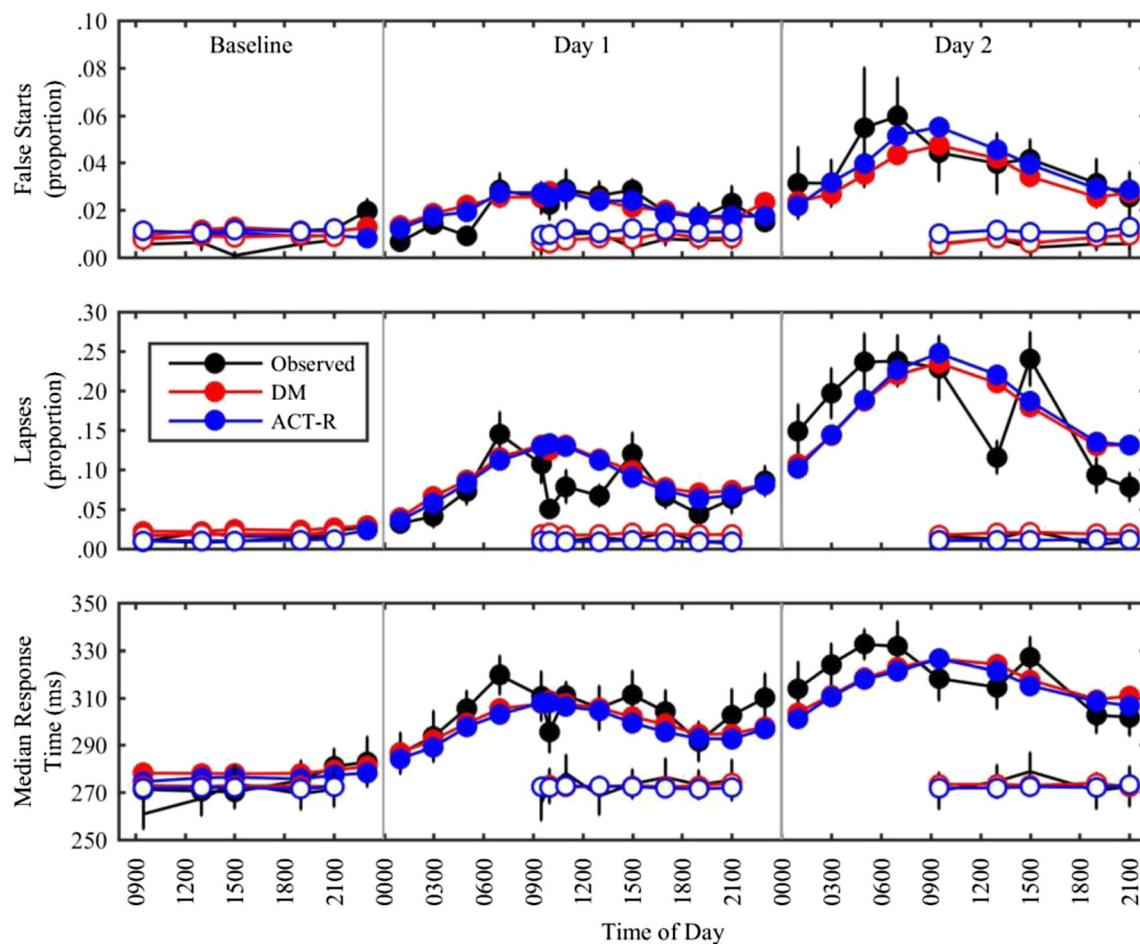


Fig. 7 Proportion of false starts (**top panel**), proportion of lapses (**middle panel**), and median times of alert responses (**bottom panel**) for each session in Experiment 1. Filled shapes correspond to the 62-h

total sleep deprivation condition; open shapes correspond to the control condition (for which there was no testing during the nights). Error bars indicate ± 1 standard error

they responded more slowly during the early morning hours. As instantiated in the biomathematical model of McCauley et al. (2013), the circadian process interacted nonlinearly with the homeostatic process, such that time-of-day effects were greater in the sleep deprivation condition than in the control condition.

The diffusion and ACT-R models reproduced the effects of the circadian process and its interaction with the homeostatic process. Fits to the proportion of false starts (diffusion model: $r = .92$ ACT-R: $r = .92$), lapses (diffusion model: $r = .91$; ACT-R: $r = .91$) and median response times (diffusion model: $r = .95$; ACT-R: $r = .95$) were close to the observations for both models.

Experiment 2: Simulated night shift work

Night shift work is associated with increased fatigue and deficits in cognitive performance due to circadian misalignment (Åkerstedt, 1988; Van Dongen, 2006). The second experiment we modeled involved a simulated night shift condition and a control condition in a laboratory (Van Dongen et al., 2011c).

Participants in the night shift condition ($n = 13$) completed two 5-day night-time duty cycles with duty time spanning from 20:00 until 10:00 (Fig. 3, top right). The two duty cycles were separated by a 34-h break from the primary task of driving a high-fidelity driving simulator.¹¹ The 34-h break included a 5-h nap opportunity from 10:00 until 15:00, a night of sleep from 22:00 until 08:00, and another 5-h nap opportunity from 15:00 until 20:00. Participants in the control condition ($n = 14$) completed two 5-day daytime duty cycles with duty time spanning from 08:00 until 22:00. The two duty cycles were separated by a 34-h break from the primary task of driving as well, but the sleep schedule was unaltered.

Participants performed the PVT eight times per duty day. Because each session contained relatively few observations (mean $\pm$ SD: 96 ± 1), we combined data from sessions that occurred at the same time of day across duty days and duty cycles. In the control condition, sessions occurred at 09:05,

¹¹ Figure 3 only shows the output of the biomathematical model through the first duty cycle and break. The output for the second duty cycle is nearly identical.

09:55, 12:05, 12:55, 15:05, 15:55, 18:05, and 18:55. In the night shift condition, session times were offset from these times by 12 h. The fitting procedure and evaluation metrics were identical to those used in Experiment 1.

In Experiment 2, performance varied primarily by time of day (Van Dongen et al., 2011c). Performance remained relatively constant across time of day in the control condition, but degraded across duty hours in the night shift condition (Fig. 8). The number of false starts increased significantly, albeit slightly, from the initial to the final testing session in the night shift condition, but not in the control condition. The number of lapses and the median response times also increased across time of day in the night shift condition, but not in the control condition.

Table 3 contains measures of model fit to the quantile response times from the daytime and night-time conditions. The G^2 statistic was slightly lower for the diffusion model in both conditions, as was the BIC. However, model fits were skewed by the poor correspondence between their outputs and the data of one participant (Participant 13, Supplementary Fig. 6). Neither model was fully able to account for the peakedness of the participant's RT distributions. Excluding this participant reduced the average G^2 values (DM = 439; ACT-R = 422), and the resulting BIC scores (DM = 491; ACT-R = 451).

Model parameter estimates for Experiment 2 were similar to those for Experiment 1 (Tables 4 and 5), indicating generality of the models across different experimental manipulations inducing fatigue. We used the best fitting parameter estimates to generate response time distributions for the diffusion and ACT-R models for each participant (Supplementary Figs. 6 and 7). We calculated the expected proportions of false starts and lapses, and the median times of alert responses during each of the scheduled testing sessions. Both models predicted an effect of duty hour in the nighttime condition only (Fig. 8), characterized by progressively worse performance throughout the night shift. Fits to the proportions of false starts (diffusion model: $r = .85$; ACT-R: $r = .82$), lapses (diffusion model: $r = .89$; ACT-R: $r = .66$) and median response times (diffusion model: $r = .92$; ACT-R: $r = .93$) were comparable between the models.

Experiment 3: Sustained sleep restriction

Sleep restriction, when sustained across multiple nights, results in cumulative deficits in cognitive performance (Belenky et al., 2003; Van Dongen et al., 2003). The homeostatic process in the McCauley et al. (2013) biomathematical model tracks cumulative fatigue due to sustained sleep restriction,

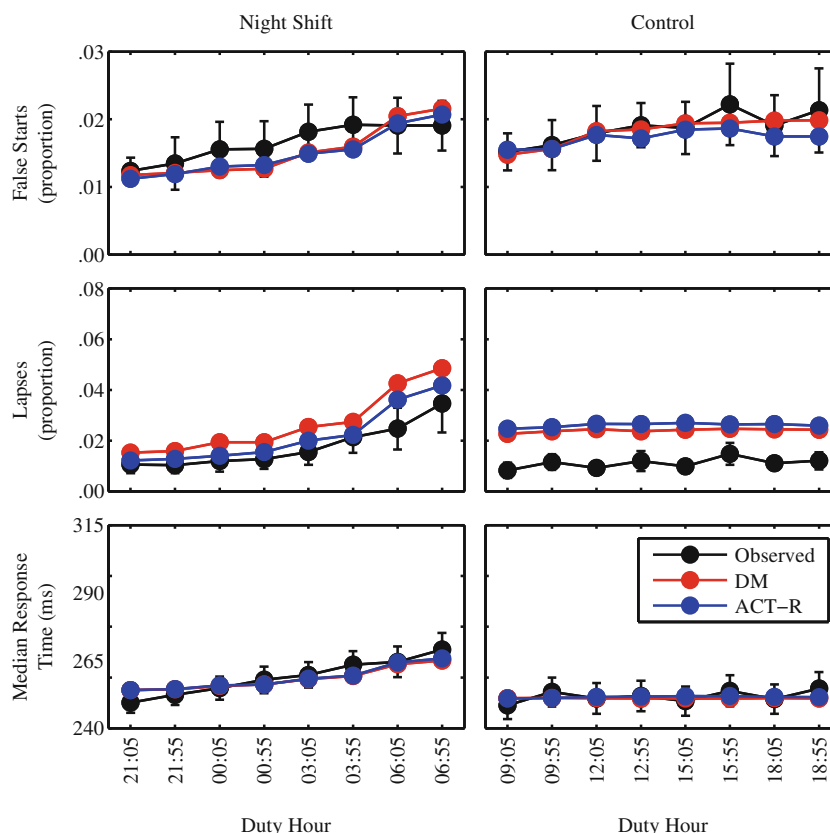


Fig. 8 Proportion of false starts (**top panel**), proportion of lapses (**middle panel**), and median times of alert responses (**bottom panel**) for each session in Experiment 2. Black circles show observations, red

circles show diffusion model predictions, and blue circles show Adaptive Control of Thought – Rational (ACT-R) predictions. Error bars indicate ± 1 standard error

and can thus capture the resulting deficits. The third experiment we modeled involved restricting sleep to 4, 6, or 8 h TIB each night over 14 days (Van Dongen et al., 2003). The experiment began after 3 days of baseline adaptation, and continued for 14 consecutive days (Fig. 3, bottom).

To examine whether the integrated diffusion and ACT-R models extend to sustained sleep restriction, we generated predictions using the parameter sets recovered from the total sleep deprivation condition of Experiment 1. We followed this approach because the published data on sustained sleep restriction only included the number of lapses, which was not adequate to fit the model. We collapsed predictions across PVT sessions that occurred within each 24-h period of Experiment 3, and computed the expected proportions of false starts and lapses, and the median response times, for the three experiment conditions (Fig. 9). In agreement with the results from Van Dongen et al. (2003), both models predicted dose-dependent, mounting impairment across days for participants in the 4- and 6-h conditions, but not for participants in the 8-h condition (see also Belenky et al., 2003).

Alternate parameterizations

In the preceding sections, we considered theoretically-constrained parameterizations of each model. The model fits provided evidence that allowing two parameters (v and λ in

the diffusion model and *Utility* and *Threshold* in the ACT-R model) to vary with fatigue was sufficient to capture the effects of fatigue on PVT performance. We next examined whether these parameterizations were adequate by fitting variants of the diffusion and ACT-R models where each parameter was allowed to vary alone with fatigue, or all combinations of two parameters were allowed to vary with fatigue.

For this purpose we used the data from the sleep deprivation condition of Experiment 1, where the effects of fatigue were most substantial. We fitted 21 versions of the diffusion model (six where one parameter varied and 15 where all combinations of two parameters varied) and 11 versions of the ACT-R model (four where one parameter varied and seven where all combinations of two parameters varied). We compared fits among diffusion model variants and ACT-R model variants using BIC scores calculated from the G^2 values (Supplementary Tables 4 and 5).

Of the diffusion models, the best fitting variant was the one used in the previous sections, in which drift rate and decay varied with fatigue (BIC = 182). Other variants that performed well included ones where fatigue affected drift rate alone (BIC = 190), drift rate and drift rate variability (BIC = 191), and drift rate and decision criterion (BIC = 193). Of the ACT-R models, the best fitting variant was the one used in the previous sections as well, in which utility and threshold varied with fatigue (BIC = 184). All

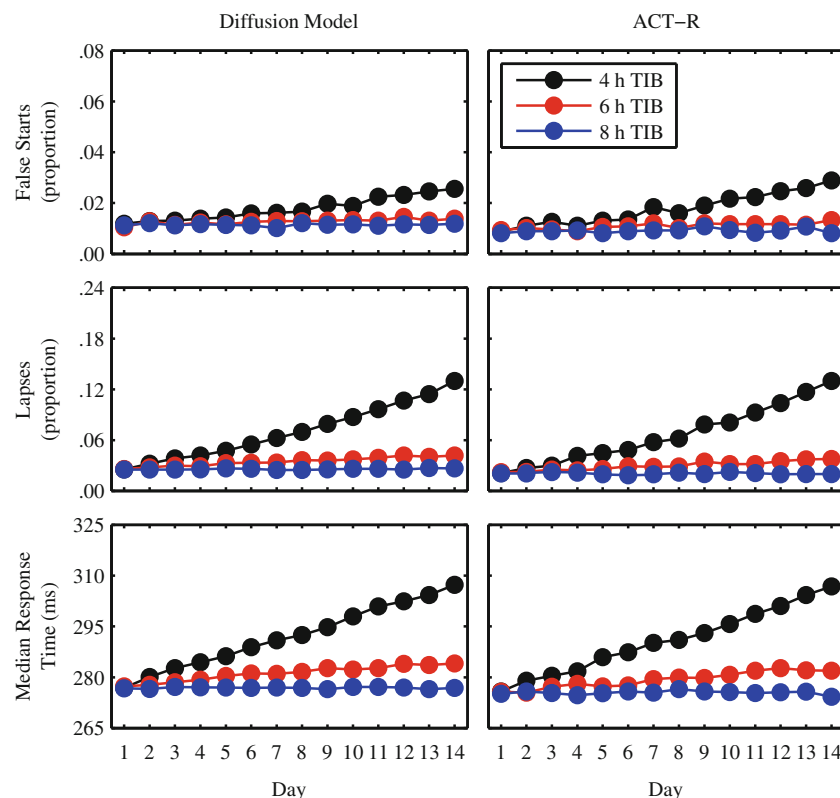


Fig. 9 Proportion of false starts (**top panel**), proportion of lapses (**middle panel**), and median time of alert responses (**bottom panel**) for each day in Experiment 3

other variants fitted substantially more poorly. In the next best-fitting variants, fatigue affected utility and FP_{DEC} ($BIC = 226$), or utility and cycle time ($BIC = 226$). In sum, the *a priori* model variants explored in the previous sections, which were based on existing computational theories of fatigue (Gunzelmann et al., 2009a; Ratcliff & Van Dongen, 2011), also provided the best fits to the experimental data.

One might also wonder whether a different implementation of the diffusion model in which RTs arise from the convolution of a distribution from the diffusion process and a separate contaminant distribution based on random guesses better fits the data (Ratcliff & Van Dongen, 2009; Ratcliff & Tuerlinckx, 2002). According to this account, *false starts* could be a consequence of fatigue increasing the probability of random guesses rather than decreasing inhibition. This possibility implies two ancillary assumptions: (1) Guesses are distributed over some interval both preceding and following stimulus onset, and (2) the probability of random guesses increases with fatigue, producing more false starts. We explored this possibility by replacing the LCA process with a random guesses process (see Ratcliff & Van Dongen, 2009). To capture false starts, which occur before the stimulus is presented, we treated the interval of assumption 1 as elapsed time from the offset of feedback from the previous trial to the length of the slowest response after the stimulus – that is, the ITI plus the duration of the slowest response. We fitted the model to data from participants in the total sleep deprivation condition of Experiment 1, and found that the estimated proportion of random guesses increased with fatigue, contributing to the rise in false starts. Still, the goodness-of-fit was lower in the diffusion model with random guesses than in the model with the LCA process on average ($BIC = 204$ vs. $BIC = 182$), and for nine of 12 participants. As such, we favored the diffusion model with the LCA process.

Sources of individual differences

Inter-individual differences in PVT performance may be due to baseline performance differences and/or differences in the dynamic changes across time awake and time of day (Van Dongen et al., 2004; Van Dongen, Bender, & Dinges, 2012). We investigated which parameters in the integrated diffusion and ACT-R models accounted for these sources of inter-individual variability.

We first identified parameters that produced inter-individual differences in baseline performance, measured as the proportion of lapses during Day 0 of Experiment 1. Across the total sleep deprivation and control conditions, non-decision time (T_{ND}) from the diffusion model significantly correlated with the proportion of lapses ($r = .61$, $p < .01$), as did cycle time ($Cycle$) from the ACT-R model ($r = .51$, $p < .01$). The estimates of individuals' non-decision and cycle times were correlated ($r = .79$, $p < .001$) (Fig. 10), indicating that these parameters produced similar effects.

We then identified parameters that produced inter-individual differences in vulnerability to fatigue, measured as the increase in lapses and false starts from Day 0 to Day 3 in Experiment 1. Drift rate scaling slope (a_v) from the diffusion model significantly correlated with the increase in lapses ($r = .80$, $p < .001$), as did the utility scaling slope (a_p) from the ACT-R model ($r = .70$, $p < .01$). Across individuals, drift rate and utility slopes were correlated ($r = .63$, $p < .05$) (Fig. 10), indicating that these parameters produced similar effects. Further, the decay rate scaling slope (a_λ) in the diffusion model and the threshold scaling slope (a_T) in the ACT-R model were correlated with the increase in false starts from Day 0 to Day 3 (decay slope: $r = .66$, $p < .05$; threshold slope: $r = .70$, $p < .01$), but not with the increase in lapses. Across individuals, decay and threshold slopes were correlated ($r = .59$, $p < .05$), again indicating that these parameters produced similar effects.

The inter-individual differences in non-decision time (T_{ND}), drift rate scaling slope (a_v) and decay rate scaling slope

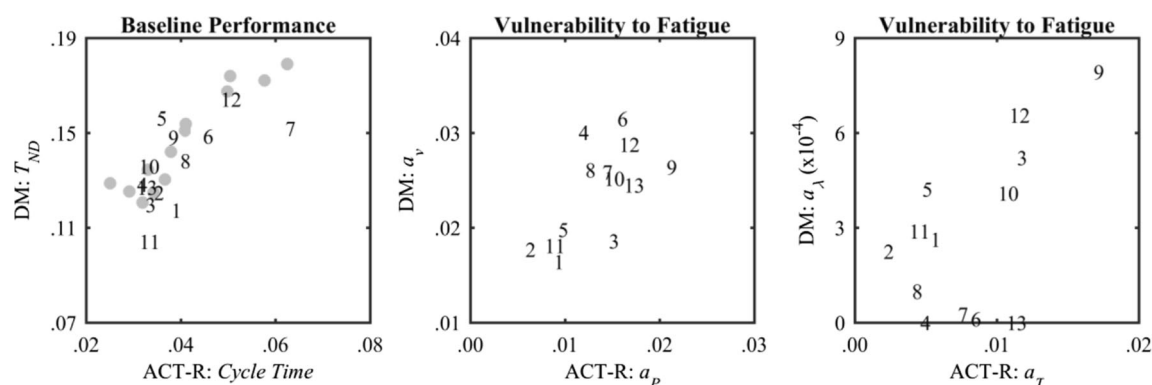


Fig. 10 Model parameters in the diffusion model (DM) and the Adaptive Control of Thought – Rational (ACT-R) model capturing inter-individual differences in baseline performance (left) and vulnerability to fatigue (middle and right). Each gray point in the left scatter plots represents

an individual participant from the control condition of Experiment 1, and each number in plots represents an individual from the total sleep deprivation condition, whose data are plotted in Supplementary Fig. 2

(a_λ) of the diffusion model were all moderately interrelated (T_{ND} vs. a_V : $r = .45$; T_{ND} vs. a_λ : $r = .05$; a_V vs. a_λ : $r = .17$). The individual differences in cycle time (*Cycle*), utility scaling slope (a_P) and threshold scaling slope (a_T) of the ACT-R model were also moderately interrelated, with the exception of a_P and a_T , which were strongly interrelated (*Cycle* vs. a_P : $r = .52$; *Cycle* vs. a_T : $r = .42$; a_P vs. a_T : $r = .92$).

Taken together, these observations suggest that individual differences in baseline performance are fundamentally distinct from individual differences in vulnerability to performance impairment from sleep loss (Van Dongen et al., 2004).¹² The relatively weak interrelationships among the individual subjects' diffusion model parameters also suggest that individual differences in degradation of the decision process (after stimulus presentation) and degradation of inhibition (before stimulus presentation) during sleep deprivation are distinct, which may be indicative of different mechanistic pathways. This would not seem to be confirmed by the ACT-R model, in which individual differences in degradation of the decision process and degradation of inhibition are highly correlated. However, strong interrelationships between individual differences in parameter estimates may also be caused by intrinsic correlation among the parameter estimates in the model fitting. An experimental manipulation of the PVT that deliberately dissociates the decision process from the inhibition process will be needed to resolve this issue.

Discussion

Fatigue from sleep loss degrades cognitive performance. The effects of fatigue are especially pronounced for tasks that involve sustained attention, such as the PVT (for others, see e.g., Killgore, 2010). The PVT is commonly used in sleep research because of its high sensitivity to fatigue from sleep loss and circadian rhythms. This sensitivity suggests that understanding the mechanisms associated with performance degradation on the PVT may provide insight regarding the impact of sleep loss and circadian rhythms on cognition more generally.

We used two computational cognitive models to study how fatigue affects cognitive performance: the first is based on the diffusion model (Ratcliff & Van Dongen, 2011), and the second on ACT-R (Gunzelmann et al., 2009a). We integrated each cognitive model with a biomathematical model of fatigue (McCauley et al., 2013). We then investigated the performance of the integrated models across three PVT experiments that measured the effects of fatigue arising from total sleep deprivation, simulated shift work, and sustained sleep restriction. The integrated diffusion and ACT-R models reproduced

three key phenomena in the PVT under conditions of fatigue: increased lapses, increased false starts, and slower alert responses. The two models were also able to account for the complete response time distribution in detail.

We did not reject either model; that was neither the aim nor were we prompted by our findings to do so. Both models provided excellent fits to a wide range of empirical data. They involve fundamentally different levels of abstraction, but we found that they account for the effects of fatigue in surprisingly equivalent ways. This result may have broader implications than would rejecting either model. Juxtaposing the two models and examining why they produce such similar outcomes despite their substantive differences is informative both theoretically and from an applied computational point of view.

Mechanistic effects of fatigue

That the same biomathematical model was used to induce fatigue in the diffusion and ACT-R models did not mean, *prima facie*, that the two integrated accounts would yield converging results. Each account's predictions emerged from interactions among (1) the biomathematical model, (2) the cognitive processing mechanisms instantiated in the accounts, and (3) the manner in which fatigue impacted these mechanisms. Thus, although using different biomathematical models would produce varying results, using the same model does not guarantee convergence. This further depends on how fatigue impacted processing mechanisms in each account, as we discuss next.

With regard to their theoretical basis, the diffusion and ACT-R models are quite distinct. The diffusion model is devoid of specifics about the performance task at hand. The onset of a stimulus drives the continuous accumulation of evidence toward a decision criterion. The ACT-R model, in contrast, contains a set of cognitive processes thought to be involved in performing a given task. The onset of a stimulus alters which processes occur and in what order.

The diffusion and ACT-R models are also quite distinct in terms of their computational implementations. The models differ in whether they treat the decision to respond as a unitary or repeated event. Decision time in the diffusion model is determined by the duration of the diffusion process, which is implemented as one ongoing process. Slow responses arise from low values of the drift rate, which prolong decision time. In contrast, decision time in the ACT-R model corresponds to aggregate time across multiple, short-duration production cycles preceding selection of the *attend* and *respond* productions. The duration of one production cycle is relatively brief (between 30 and 50 ms, Table 5). But because a production can be enacted only when its value exceeds the utility threshold, many production cycles may occur before the model responds. Slow responses arise from reduced utility values,

¹² Even so, it has been reported that baseline diffusion model drift rate can be used to predict PVT performance during total sleep deprivation (Patanaiik et al., 2015).

which tend to cause microlapses and thereby increase the number of production cycles.

Related to this, the diffusion and ACT-R models differ in whether they treat evidence accumulation as continuous or discrete. In the diffusion model, a response is initiated when accumulated evidence exceeds the decision criterion. If a response has not yet occurred and drift rate is positive, the probability of responding increases over time. In the ACT-R model, a response is initiated when the utility value of the *respond* production exceeds that of all other productions and the utility threshold. If a response has not yet occurred and the state has not changed, the probability of responding during the next production cycle essentially remains the same (Eq. 10).

Against the backdrop of these differences, the accounts capture the detrimental effects of fatigue through two essentially identical component interactions (Table 6). First, in both models, fatigue reduces the signal-to-noise ratio in the decision process, albeit in computationally different ways. In the diffusion model, the signal-to-noise ratio in the decision process is reduced because of the decreasing mean drift ratio, which nominally corresponds to the signal-to-noise ratio in the evidence accumulation process (Ratcliff & Van Dongen, 2011). In ACT-R, the signal-to-noise ratio in the decision process is reduced because of the decreasing production utilities relative to the utility threshold. In both models, dynamic decreases in the signal-to-noise ratio produce increasingly skewed response time distributions with longer right tails.

Second, in both models, fatigue reduces response inhibition – the ability to suppress actions that are inappropriate in the current context and that interfere with goal-driven behavior (Mostofsky & Simmonds, 2008) – but again in computationally different ways. In the diffusion model, the reduction in response inhibition arises from the decreasing decay rate in the LCA component. As decay decreases, so too does the suppression of responses prior to stimulus onset. In ACT-R, the reduction in response inhibition arises from the decreasing utility threshold. This allows actions that were previously suppressed on the basis of their low utility to be enacted. In both models, dynamic changes to response inhibition partially compensate for the primary effect of fatigue and increase the probability that a response will eventually be made after the stimulus appears. These changes also cause more responses to occur before the stimulus appears.

The sufficiency of these two mechanisms in accounting for the effects of fatigue on cognitive performance is shown by our simulations of experiments involving total sleep deprivation, circadian misalignment, and sleep restriction (see above, Experiments 1, 2, and 3). The necessity of the two mechanisms is corroborated by our exploration of alternate model variants (see above, *Alternate parameterizations*). Allowing only a single parameter or any other combination of two parameters in each model to vary with fatigue reduced the goodness of fit. It is also noteworthy that the relationship between

how the models implemented fatigue, evident at the group level, held at the level of individual participants. The positive correlations between parameter values in the two models across individuals (drift rate slope and utility slope; decay slope and threshold slope) provide further evidence for equivalent effects in the two modeling frameworks.

The ACT-R model can be thought of as approximating a discrete diffusion process with 38-ms time steps τ (i.e., the mean duration of a production cycle), a decision criterion of $0.1\sqrt{\tau}$, and a decay of 1.0.¹³ For all combinations of *utility* and *threshold* in the ACT-R model, there is a corresponding drift rate in the diffusion model that yields an identical probability of the process terminating after one step (Fig. 11). As seen in the figure, decreasing *utility* with fatigue in the ACT-R model has the same effect as decreasing drift rate in the diffusion model, a point confirmed in an earlier model mimicry simulation study (Fisher, Walsh, Blaha, & Gunzelmann, 2015). This is not to say that ACT-R is merely a special case of the diffusion model (or vice versa). The two approaches are motivated by entirely different considerations, and they are implemented in completely different ways. Yet despite these differences, the conceptual relationship between *utility* and *threshold* in the ACT-R model, and *drift rate* in the diffusion model underlies their similar behavior with respect to the PVT.

There is also a relationship between *threshold* in the ACT-R model and *decay* in the diffusion model. Decay dampens accumulated evidence, which arises from both signal and noise. When decay is low, the probability of noise driving the decision process beyond the decision criterion increases. Likewise, utilities in ACT-R reflect a production's underlying value in addition to noise (Eq. 7). When threshold is low, the probability of noise causing a non-matching production to exceed the threshold increases.

Although the diffusion and ACT-R models describe the mechanisms underlying PVT performance at different levels of abstraction and in distinct ways, they capture the detrimental effects of fatigue through essentially equivalent component interactions. The insight gained here from comparing the two modeling frameworks – that fatigue reduces the signal-to-noise ratio in the decision process (after stimulus presentation) *as well as* response inhibition (both before and after stimulus presentation) during performance of the PVT – is a new finding.

Relationship to neuronal theories of fatigue

The substantial convergence between models helps to constrain possibilities for the neuronal mechanisms underlying the effects of fatigue on PVT performance. The wide

¹³ Setting decay to 1.0 renders the process memoryless, and setting the decision criterion to $0.1\sqrt{\tau}$ causes the process to terminate immediately once positive evidence is accumulated.

Table 6 Primary and secondary effects of fatigue in diffusion model and ACT-R model

	Diffusion model	ACT-R	Behavioral outcome
Primary effect	Decreased drift rate	Decreased utility	Slower alert responses Increased lapses
Secondary effect	Decreased decay	Decreased threshold	Increased false starts

applicability of the diffusion model across different performance tasks as documented in the literature (see Ratcliff & McKoon, 2008) implies that a single generic underlying mechanism may be able to account for the impact of fatigue on performance. However, ACT-R simulations of fatigue effects across different task platforms underline the importance of differentiating the cognitive processes involved (Gunzelmann et al., 2005, 2009b, 2012; Halverson, Gunzelmann, Moore, & Van Dongen, 2010; see also Jackson et al., 2013). At the neuronal level, these considerations point to mechanisms in which fatigue degrades cognitive processing in a generic fashion (i.e., common to many neuronal pathways) that is nonetheless process-specific (i.e., in neuronal pathways involved in select cognitive processes). Current paradigms positing that subcortical brain mechanisms induce global cortical changes responsible for the effects of fatigue on cognitive performance (Aston-Jones, Chen, Zhu, & Oshinsky, 2001; Doran et al., 2001; Saper et al., 2005; Thomas et al., 2000) fail to explain this process-specificity of fatigue effects (Jackson et al., 2013).

An emerging theoretical view of how sleep deprivation may affect cognitive task performance posits that while the brain as a whole is awake, individual cortical columns involved in task performance may independently “fall asleep” (Jackson et al., 2013; Van Dongen, Belenky, & Krueger, 2011a). Based on the concept of local, use-dependent sleep (Krueger et al., 2008), this paradigm postulates that as a consequence of prior use, cortical columns may temporarily fail to

process information, effectively reducing functional connectivity and thereby degrading the quality of cognitive processing (Krueger, Huang, Rector, & Buysse, 2013; Van Dongen, Belenky, & Krueger, 2011a). Prior use is a function of time awake and is further modulated by task load (Van Dongen, Belenky, & Krueger, 2011b), which is determined by stimulus density and time on task (i.e., cumulative cognitive processing requirement) and is particularly high in repetitive, attention-demanding tasks such as the PVT. The effects of local sleep on performance depend on the number of functional neuronal circuits available to process information for a given task – that is, level of redundancy, or cognitive capacity – which may vary across tasks and among individuals (Chee & Van Dongen, 2013).

The concept of local, use-dependent sleep is consistent with the results of the computational cognitive models considered here, and fits well with the notion of reduced signal-to-noise ratio in the decision process. The transient loss of a subset of neural columns involved in task performance would be expected to reduce the quality of stimulus processing and evidence accumulation (as in the diffusion model), or to produce microlapses (as in the ACT-R model). The idea of local, use-dependent sleep also fits with the notion of reduced response inhibition, provided that inhibition is viewed as an *active* process that is also susceptible to local sleep. The implication that PVT performance relies not only on the ability to sustain attention but also on the ability to maintain inhibition, and that these are distinct aspects of cognition that may each separately instill vulnerability to PVT performance impairment due to fatigue, is a novel insight derived from our computational model comparison.

Predictive generalizability

By examining how fatigue impacts specific underlying mechanisms in each model, the accounts allow exploration of how fatigue may impact cognitive processing in other task contexts. The integrated diffusion model we developed explains the effects of fatigue from sleep loss on performance in terms of temporal changes in degradation of information processing in central cognition. Dynamic changes in drift ratio during sleep deprivation or night work are associated with reduced signal-to-noise ratio and, consequently, degraded quality of cognitive processing. This perspective is supported by neuroimaging data, which indicate that sleep deprivation is

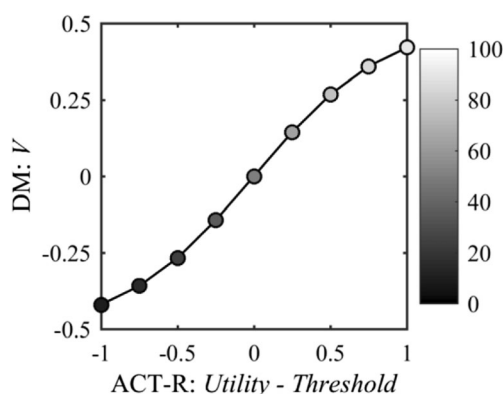


Fig. 11 Difference between utility and threshold in the Adaptive Control of Thought – Rational (ACT-R) model (x-axis) and value of drift rate that produces identical probability of reaching the decision criterion after one 38-ms time step (y-axis). Grayscale shows probability of reaching the criterion after one step

associated with a reduction in neuronal connectivity (Verweij et al., 2014) or available functional neuronal circuits, especially those that are most intensively used for the task at hand (Chee & Asplund, 2013).

However, the integrated diffusion model does not elucidate which circuits are most intensively used during performance of a given task. Thus, it is *a priori* unclear to what extent the model's predictions may generalize from one task to another. The integrated ACT-R model, on the other hand, is explicit regarding which aspects of cognition (i.e., ACT-R modules) are assumed to be involved in task performance, and how intensively. Furthermore, ACT-R modules have been linked to specific brain regions (Borst & Anderson, 2013), suggesting which neuronal circuits may be involved in performance of a given task. Most relevant for the PVT, production rules are thought to be instantiated by networks involving basal ganglia structures including the striatum, the pallidum, and the thalamus (Anderson, 2007). The utility threshold and the compensatory response to fatigue have been posited to be associated with the thalamus (Gunzelmann et al., 2009a), as supported by findings of decreased thalamic activation during sleep deprivation (Chee et al., 2008; Thomas et al., 2000).

As such, it is reasonable to assume that, while the *a priori* predictive generalizability of the integrated diffusion model is limited to generic changes in scaled performance outcomes over time, the integrated ACT-R model could generalize to novel tasks and contexts in terms of absolute performance predictions (see Gunzelmann et al., 2015). Additionally, unlike the diffusion model, the scope of ACT-R extends beyond one- and two-alternative forced-choice tasks. As a first step toward demonstrating these capabilities, we recently combined an ACT-R account of fatigue with validated ACT-R models of multi-tasking and driving behavior to make *a priori* predictions about the effects of extended wakefulness on task performance (Gunzelmann et al., 2009b; Gunzelmann et al., 2011; Khosroshahi, Salvucci, Veksler, & Gunzelmann, 2016). This is not to say the diffusion model cannot play an important role in simulations of complex tasks as well. For example, in the driving domain, brake light detection can be modeled as a signal detection process. In this way, the diffusion model can be used to simulate braking, one component of driving performance (Ratcliff & Strayer, 2014).

Integrated theories of cognition

Computational models have been applied to myriad topics in cognitive science. Integrative and comparative approaches such as those used here provide a pathway towards unification and the development of a coherent whole (Newell, 1990). In this paper, we integrated between cognitive capacities and a cognitive moderator, fatigue. To achieve this integration, we leveraged existing cognitive computational models (Gunzelmann et al., 2009a; Ratcliff & Van Dongen, 2011) and a

biomathematical model of fatigue (McCauley et al., 2013). Such model reuse has been recommended as a practice to accelerate cognitive architecture research (see Gluck, 2010).

The constituent models had previously been validated in isolation, and many of the constraints that shaped their development, though typically unrelated to the PVT, limited the number of assumptions we needed to make in order to create an account of the effects of fatigue on PVT performance. Integrating existing models thus allowed us to reduce the danger of the irrelevant-specification problem (Newell, 1990) – that is, needing to make a large number of under-constrained design decisions to allow the simulation to run.

Rather than adding new knowledge to the cognitive computational models (i.e., constructing new agents) to capture performance under conditions of fatigue, we used the same computational cognitive models and adjusted the settings of architectural parameters. Others have used this approach. For example, Ritter et al. (2007) adjusted the values of declarative memory and motor parameters to simulate the effects of caffeine and anxiety on serial subtraction performance. Likewise, published accounts of arousal capture the effects of fatigue by manipulating aspects of ACT-R's utility calculation (Belavkin, 2001; Jongman, 1998; Gonzalez, Best, Healy, Kole, & Bourne, 2011). Our approach goes a step further by linking parameter values with an underlying physiological account – the effects of fatigue on architectural parameters vary continuously over time and in the manner specified by a validated biomathematical model (McCauley et al., 2013). In doing so, the cumulative models get “further down the list” (Newell, 1990, p. 16) of areas to be covered by a unified theory of cognition.

The practice of implementing moderators by directly adjusting parameter values, though suitable for studying fatigue in isolation, may prove to be impractical for studying the combined effects of multiple moderators. One promising direction for future work is to integrate physiological models of the body – models that represent the combined effects of multiple moderators – with cognitive architectures (Dancy, Ritter, Berry, & Klein, 2015). A similar approach has been used to model the combined and often conflicting effects of emotions such as fear, anger, sadness, and happiness on architectural parameters (Hudlicka, 2007).

Integration is a potentially fruitful approach for leveraging multiple non-overlapping models. This was the case for the diffusion and ACT-R models, and the biomathematical model. However, the diffusion model and the ACT-R model account for the same decision process. When such a “zone of contention” exists, the typical approach is to try to falsify one of the models (McClelland, 2009). In this regard, our results do not point to a clear victor. At the same time, the models share an underlying theoretical interpretation, emphasizing the complementary rather than contradictory nature of their mechanisms (see also, Lebiere, Gonzalez, & Warwick,

2009). Because both theories have utility in advancing our understanding of the mechanisms of fatigue, we chose to focus on their shared perspective rather than their individual limitations. Only by determining how to best account for the effects of fatigue on PVT performance using both modeling formalisms did we recognize their theoretical correspondence.

Conclusion

The adverse effects of fatigue from sleep loss on cognitive performance are substantial, yet most computational models of performance do not include fatigue as a cognitive moderator. We leveraged existing models to explore how fatigue from sleep loss affects cognitive processes. Integrating a biomathematical model of fatigue with computational cognitive models produced a more comprehensive account than either approach alone: the integrated diffusion and ACT-R models captured in detail how fatigue impairs psychomotor vigilance performance. Juxtaposition of the integrated models, which provide accounts of cognitive performance at fundamentally different levels of abstraction, revealed a surprisingly consistent picture of how fatigue affects central cognition during PVT performance: (1) by reducing the signal-to-noise ratio in decision processes, and (2) by reducing response inhibition. Further, by considering response inhibition as an active process, both of these effects can be seen as arising from the loss of processing resources due to local sleep. These findings advance our theoretical understanding of fatigue and illustrate the synergy that can be achieved by comparing computational cognitive modeling at different levels of abstraction, focusing not only on how they differ, but also on how and why they converge.

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A dynamic attentional control framework for understanding sleep deprivation effects on cognition

Paul Whitney^{a,b,*}, John M. Hinson^{a,b}, Amy T. Nusbaum^a

^a*Department of Psychology, Washington State University, Pullman, WA, United States*

^b*Sleep and Performance Research Center, Washington State University, Spokane, WA, United States*

**Corresponding author: Tel.: +1 509-335-3860, e-mail address: pwhitney@wsu.edu*

Abstract

The cognitive effects of sleep loss are often attributed to compromised functioning of the prefrontal cortex (PFC). However, compromised PFC functioning does not account for well-known effects of sleep deprivation on vigilance. Furthermore, the executive attentional control functions associated with the PFC show considerable variability in the effects of sleep deprivation. Evidence from neuroimaging suggests that sleep deprived people are sometimes able to maintain performance on cognitive tasks by increasing PFC activation of task-relevant circuits and by recruiting new circuits not typically involved in a particular cognitive operation. Still, little is known about how such compensatory processes work on a functional level, or what tradeoffs in processing they may entail. We propose a dynamic attentional control framework to bridge the gap between the evidence on sleep deprived neural circuits and cognitive task performance. We review evidence that shows that the pattern of preserved and compromised task performance can be understood in terms of sleep deprivation's influence on frontostriatal circuitry such that the ability to maintain task-relevant information in the focus of attention is relatively spared but the ability to update task-relevant information in response to changing circumstances is more negatively affected. This framework helps account for why some tasks are more affected by SD than others, and why individual differences in the effects of sleep deprivation are task-specific.

Keywords

Cognitive control, Cognitive flexibility, Individual differences, Dopamine, Gene polymorphisms, Cognitive impairment, Sleep loss

1 Introduction

The impact of sleep deprivation (SD) on cognition is noteworthy not only because of its ability to compromise performance, but also because of the variability of these effects. Variability is manifest at two levels. First, some cognitive tasks are greatly impaired by SD while others remain relatively unaffected (e.g., Killgore, 2010; Lim and Dinges, 2010). Second, there are large individual differences in the extent to which tasks are susceptible to impairment by sleep loss (Van Dongen et al., 2004). Understanding both dimensions of the variability of SD effects is a challenging research problem, but one that is critical to efforts to mitigate the effects of sleep loss, which can result in catastrophic errors particularly in round-the-clock, high-pressure operational environments (e.g., Honn et al., 2018).

An apparent paradox has emerged from research on the task selectivity of SD effects. Numerous investigators have argued that the prefrontal cortex (PFC) is particularly vulnerable to sleep loss, and the executive attentional control functions often considered to be the province of the PFC provide a potential way to account for a wide range of operational errors (e.g., Harrison and Horne, 2000; Drummond et al., 2000, 2004). However, while the PFC is highly engaged in our most complex and sophisticated cognitive processes, several meta-analyses comparing the magnitude of the effects of SD on cognitive tasks have found that more complex cognitive tasks typically show *less* of an effect of SD than seemingly simple tasks that assess arousal and vigilant attention (e.g., Lim and Dinges, 2010; Wickens et al., 2015).

Several general approaches suggest ways to resolve inconsistencies between the PFC vulnerability hypothesis and the greater impact of SD on less complex tasks. One suggestion is that SD has a large effect on simple, sustained attention and the effects observed in more complex tasks are consequences of the downstream disruption of sustained attention (cf., Lim and Dinges, 2010; Ma et al., 2015). A second suggestion is that the PFC vulnerability hypothesis is largely correct, but smaller SD effects are observed on many complex tasks because these tasks are more arousing and people engage in compensatory strategies to make their performance under SD as resilient as possible (e.g., Drummond et al., 2004; Harrison and Horne, 2000). From the compensatory processing perspective, the greater influence of SD on many simple cognitive tasks stems from lower levels of arousal and higher level of boredom engendered by such tasks. Of course, a third possibility is that SD has direct and separate effects on both vigilance and PFC-related cognitive processing.

Our goal here is to review current evidence on PFC vulnerability to SD and its effects on task performance and to offer a theoretical framework that holds promise for organizing the relevant literature. Our framework suggests new approaches to understanding both task variability and individual differences in susceptibility to the effects of SD. We focus mainly on the effects of short-term, total SD because the majority of relevant laboratory research uses a total SD manipulation. However, concepts in this approach should be useful for synthesizing research on changes in cognitive functions resulting from sleep restriction and circadian phase. Our theoretical approach, a dynamic attentional control framework, draws on insights from both

the PFC vulnerability hypothesis and the view that complex task performance can break down as a function of the downstream effects of early attentional processes. In addition, we integrate recent data on cognitive control and flexibility to provide a better means of characterizing why some tasks are more affected by SD than others and some reasons why this task variability is manifest differentially at the individual level.

2 PFC functions and SD

In a review examining a broad range of complex tasks, [Wickens et al. \(2015\)](#) found that total SD, sleep restriction, and performance during the circadian night all impaired complex task performance, but these tasks were generally less degraded than simple task performance. However, a major difficulty with interpreting the finding that complex tasks generally have smaller SD effects than tests of simple attention is that describing tasks as complex, or even as PFC-related tasks, is a very coarse level of analysis. By their nature, tasks high in complexity depend on the integration of multiple brain circuits and the coordination of multiple potentially dissociable cognitive processes. Thus, it is unsurprising that data on the vulnerability of complex tasks to SD present many inconsistencies. In this regard, while [Lim and Dinges \(2010\)](#) showed that SD effects on complex tasks are generally smaller than the effects on tests of vigilance and simple attention, their review also demonstrated that the effect sizes in tasks of complex cognition varied substantially across studies depending on the specific task used.

Can inconsistencies in the results on complex task performance be explained by downstream effects of lapses of attention? It is likely that some declines in higher level cognition during SD occur as a result of attentional lapses on the information available for reasoning or complex judgments (cf., [Lim and Dinges, 2010](#); [Sturm and Willmes, 2001](#)). In addition, SD reduces activation in the salience network (medial frontal cortex and insula), which is critical to attentional engagement of task critical stimuli ([Chen et al., 2016](#); [Ma et al., 2015](#)). However, there is convincing evidence that disruption of early attentional processing is not the whole story. For example, studies using tasks that require complex attentional control have shown large behavioral effects of SD that are independent of sustained attention, as measured by the PVT ([Venkatraman et al., 2011](#); [Whitney et al., 2015, 2017](#)). In addition, neuroimaging data across a variety of cognitive tasks have shown that sleep loss alters patterns of activation of the PFC and its connections to the parietal cortex (e.g., [Chee et al., 2010](#); [Drummond et al., 2000](#); [Krause et al., 2017](#); [Ma et al., 2015](#)).

Processing in circuits that connect the frontal lobe regions to the basal ganglia, i.e., the frontostriatal pathways, is of particular interest in attempts to understand how SD affects cognition because several lines of neuroimaging evidence suggest that these circuits are involved in compensatory efforts to maintain performance under SD (e.g., [Chuah et al., 2006](#); [Drummond et al., 2004](#); [Krause et al., 2017](#); [Nakashima et al., 2018](#); [Schmidt, 2014](#)). Similar claims have been made for

relatively preserved cognitive performance by people with chronic insomnia (e.g., [Ballesio et al., 2018](#)). For example, using a go/no go task as a measure of response inhibition, [Chuah et al. \(2006\)](#) found that SD produced tonic decreases in activation of the medial ventrolateral PFC and insula, but individuals who showed phasic increases in the right ventrolateral PFC were resilient to the effects of SD on the task. Another relevant example of evidence for compensatory activation was demonstrated by [Drummond et al. \(2004\)](#) using Baddeley's grammatical reasoning test. This test of logical reasoning is highly dependent on PFC-related working memory processes, but is frequently cited as an example of a complex cognitive task that is relatively unaffected by SD ([Harrison and Horne, 2000](#); [Lim and Dinges, 2010](#)). Drummond and colleagues parametrically manipulated the difficulty of the grammatical transformations used and found several brain areas unique to the SD group in which activation increased with task difficulty. These areas included portions of the PFC already recruited to perform the test as well as frontal and midbrain language centers, which would suggest use of a verbal strategy to assist in task performance.

Given the evidence for compensatory processing while performing cognitive tasks under SD, explaining the variability in SD effects requires an understanding of how people make dynamic adjustments to their information processing in order to preserve complex task performance to the extent possible. While the existing physiological data make a good case that compensatory processing is taking place under SD, the data offer few clues as to how such compensatory mechanisms operate and affect task performance (cf., [Giacobbo et al., 2016](#)). As a foundation for bridging between the physiological evidence for compensatory processing and a functional understanding of how compensatory processing operates, we next provide a brief overview of key concepts from the current literature on how attention is managed during cognitive tasks and how adjustments in processing are made dynamically as conditions change.

3 A dynamic attentional control framework

Findings from both animal models and humans, spanning studies of dopaminergic genetic polymorphisms, functional neuroimaging, and brain disorders, support the idea that the frontostriatal circuitry is fundamental to attentional control, decision making, and sleep-wake regulation ([Cools and D'Esposito, 2011](#); [Eisenberg and Berman, 2010](#); [Ernst and Steinhauser, 2017](#); [Holst et al., 2017](#); [Qiu et al., 2016](#)). Although we do not fully understand the processes of cognitive control that are implemented in the frontostriatal circuitry, it is clear that a fundamental issue in managing our cognitive system is the tradeoff between cognitive *stability* and cognitive *flexibility*. That is, we need stable maintenance of current goals and task relevant information in working memory to preserve information from distraction, but we must also be able to destabilize information in working memory to flexibly shift

goals and strategies as conditions in the environment change (e.g., [Armbruster et al., 2012](#); [Braver et al., 2009](#); [Whitney et al., 2017](#))

An illustration of the fundamental balancing act of cognitive control appears in the context of real-world operational tasks that are especially prone to errors due to sleep loss. Consider an operator in a power system control room when a major weather event or cyberattack begins. In this situation the operator is flooded with information from different monitoring systems, and the operator is under severe time pressure to make correct decisions about how and where to intervene ([Mijović et al., 2019](#)). Initial goals and plans for corrective action must be maintained in working memory in the face of distracting, lower priority information from sensors that are relevant to other, conflicting goals. When prior goals and other information become irrelevant as conditions change, cognitive flexibility is needed. If the operator cannot adapt to the new conditions errors will result from perseveration on previously relevant strategies. Such high-demand contexts are challenging to performance under the best of circumstances, but people who have had inadequate sleep are especially prone to errors when there is high information throughput, time pressure, and the need to process feedback to determine if conditions are changing dynamically over time ([Wesensten and Balkin, 2013](#); [Whitney et al., 2015](#)).

The cognitive control processes and neural circuitry fundamental to the stability-flexibility tradeoff are summarized in [Fig. 1](#). These processes have been

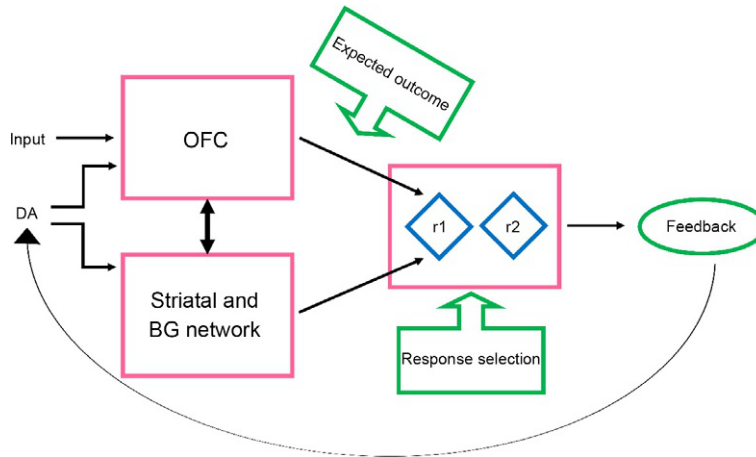


FIG. 1

The orbitofrontal cortex (OFC) and striatal network play complementary roles in making a series of choices between two response alternatives ($r1$ and $r2$). After sufficient feedback, expected outcomes are generated in working memory. Current goals, strategies, and expectations are maintained by dopamine (DA) dependent processing in the OFC. Feedback contrary to expectations serves as a trigger to destabilize working memory and shift responding on future choices. This flexibility is dependent on DA circuits in the striatal network.

studied in the laboratory using a variety of working memory, inhibitory control, and cognitive flexibility tasks that are sensitive to information maintenance, attentional distraction, and flexible updating. The maintenance and updating neural circuits are dissociable, and performance depends on the correct circuit taking precedence in the correct context (see [Barkley, 2012](#); [Braver, 2012](#); [Nigg, 2017](#) for reviews).

The dorsolateral PFC is especially important in the working memory processes of maintaining goal relevant information in the focus of attention and preserving the information from interference by distracting information. Decision making based on choices maintained in working memory is guided by representations of the value of choices for which the ventromedial PFC and related connections are critical. These processes are often studied in the laboratory using simulated gambling tasks (e.g., [Hartstra et al., 2010](#); [Lawrence et al., 2009](#)). For example, subjects might be presented with two options on each trial, one of which delivers positive outcomes at a higher probability than the other. Feedback over trials allows subjects to aggregate outcomes from each choice and anticipate the likely outcome of a choice (e.g., [Frank and Claus, 2006](#)). This guidance of choice processing and decision making based on expectations is known as top-down attentional control.

Next, consider what happens if the outcome probabilities associated with each choice are reversed, so the formerly superior choice becomes the inferior choice and vice versa. To switch response patterns after this change in contingencies requires updating of information in working memory to avoid perseveration on previously superior choices. A key to quickly adapting to the change in contingencies, i.e., to displaying cognitive flexibility, is that the top-down expectations about choice outcomes allow the subject to quickly recognize the reversal because of the conflict between expected outcomes and actual outcomes (e.g., [Klanker et al., 2013](#)). Whereas the original aggregation of outcomes to form an expectation is heavily dependent on working memory and orbitofrontal cortex circuits, the ability to show cognitive flexibility in response to the change in outcome probabilities is dependent on the striatum and basal ganglia circuits (e.g., [Izquierdo et al., 2017](#); [Klanker et al., 2013, 2015](#)). Dopamine plays a key role in both orbitofrontal cortex maintenance processes and the flexible response to changing outcome probabilities, with D1 receptors of primary importance in the OFC circuits and D2 receptors in the striatum and associated pathways of primary importance to flexibility (e.g., [Klanker et al., 2013, 2015](#)).

Not only are the neurological underpinnings of these cognitive functions distinct, but they appear to depend on a delicate neurotransmitter balancing act. High tonic dopamine (DA) levels are beneficial for stable cognitive functions, such as basic working memory maintenance and applying a repetitive rule. However, higher tonic levels can restrict phasic DA alterations, and phasic DA signaling is beneficial for flexible cognitive functions ([Grace, 2000](#)). Thus, high amounts of consistent DA activity can lower transient DA activity. This tradeoff extends to DA relationships in the PFC and striatum, where increases in striatal DA lead to restrictions in prefrontal DA, and vice-versa ([Cools, 2015](#)).

Studies of single nucleotide polymorphisms (SNPs) related to dopaminergic activity in the OFC and striatum provide important evidence for dopamine's role in attentional stability and flexibility. For example, COMT Val158Met codes for the amount of the catechol-*O*-methyltransferase enzyme in the PFC. This enzyme alters the levels of DA breakdown, with the Val allele resulting in higher amounts of enzymatic activity, translating into lower levels of baseline DA, and the Met allele resulting in lower amounts of enzymatic activity, translating into higher levels of baseline DA (Chen et al., 2004). Studies routinely find that the allele that offers an advantage for working memory and other tasks requiring stable maintenance of information the Met allele, is related to poorer performance on tasks that require cognitive flexibility. Bruder et al. (2005) found a Met advantage on a letter-number sequencing task, while Goldberg et al. (2003) found a Met advantage on an *n*-back task in the 1-and-2-back conditions, both suggesting that Met alleles are related to enhanced working memory abilities. However, Colzato et al. (2010) found that Met carriers had increased switch costs on a task switching task and Krugel et al. (2009) showed that Val homozygotes have enhanced performance on a reversal learning task, in addition to increased striatal fMRI responses to both positive and negative prediction errors. Thus, the benefits of Met alleles for working memory performance may serve to limit cognitive flexibility.

With regard to the effects of SD on these cognitive control processes, the emerging pattern of evidence supports the hypothesis that *SD has a greater effect on cognitive flexibility than on the maintenance of goal relevant information*. The more pronounced effect of SD on cognitive flexibility has important implications for understanding both task variability and individual differences in the study of SD. Evidence is beginning to emerge that variations in dopaminergic genes expressed in the frontostriatal circuitry may help explain individual differences in the cognitive effects of SD (e.g., Holst et al., 2017; see chapter “Unraveling the genetic underpinnings of sleep deprivation-induced impairments in human cognition” by Van Dongen, this volume). Studies of several SNPs related to dopamine expression, including BDNF, COMT, and DRD2 C957T, have found evidence of alleles that show resilience to the effects of SD specific to tasks that involve cognitive flexibility (Grant et al., 2018; Satterfield et al., 2018; Whitney et al., 2017).

Wide ranging evidence supports the notion that maintenance of task relevant information in the focus of attention is largely unimpaired by SD, at least within the number of hours of wakefulness typically employed in studies of total SD (e.g., Giacobbo et al., 2016; Tucker et al., 2010; Whitney et al., 2015). Note that while many tasks of working memory show a modest effect of SD on overall performance (Wickens et al., 2015), performance on tests of working memory include both executive and non-executive components. For example, SD produces slower mean reaction times on tests of working memory scanning in which people hold a memory set in the focus of attention and respond whether a probe item is in the memory set (Casement et al., 2006; Cui et al., 2015; Mu et al., 2005; Tucker et al., 2010). However, if working memory scanning is isolated from encoding and response speed by computing the slope of reaction time over memory set size, we see that the process

of scanning working memory is not affected by SD (Tucker et al., 2010). It is the non-working memory components of performance that are affected by SD. Converging evidence for the preservation of working memory capacity under SD was obtained by Giacobbo et al. (2016) who found that SD did not impair performance on the backward digit span test. Similar results have been obtained across other measures of the ability to maintain stable representations in the focus of attention (Casement et al., 2006; Cui et al., 2015; Tucker et al., 2011).

When interpreting the evidence for preserved working memory under SD it is important to bear in mind the evidence for compensatory processing noted above. In some cases, working memory and related executive processes may be preserved though greater activation of relevant circuitry or recruiting additional areas (e.g., Chuah et al., 2006; Drummond et al., 2004). If cognitive stability is preserved, in part through compensatory processing, does the compensatory activation produce tradeoffs that limit other cognitive processing? We do not know the answer to this question, but some interesting possibilities are raised by recent research on the neuroeconomics of cognitive effort (e.g., Westbrook and Braver, 2015). Attentional effort appears to be allocated based on a cost-benefit analysis of resources needed to complete current goals versus the potential benefit of having resources available for flexible use of resources as the context changes. If so, under SD the preservation of cognitive stability could come at the cost of cognitive flexibility.

What is clear from existing evidence is that cognitive flexibility declines substantially when people are sleep deprived. Two types of measures are commonly used to study cognitive flexibility: reversal learning and task switching (e.g., Dajani and Uddin, 2015). The power system control room example provided above to illustrate the distinction between cognitive stability and cognitive flexibility is representative of reversal learning in a natural context. Reversal learning tasks used in the laboratory typically involve learning novel stimulus-response pairings that must be updated based on choice feedback. For example, subjects might learn that choice A in a gambling game often leads to winning money, while choice B more often leads to losing money. These contingencies then change so that choice B is now the better option and subjects must update their choice patterns in order to be successful (e.g., Waltz and Gold, 2007).

When cognitive flexibility is studied with task switching, an individual is required to alternate between multiple stimulus-response sets based on cues that are associated with “rules.” One example of such a task switching procedure is a digit classification task in which subjects are told that one trial cue (e.g., a blue star) means they should report whether a number is odd/even and a different trial cue (e.g., a red circle) means they should report whether a number is greater or less than five (e.g., Wang et al., 2017). Subjects must switch their response patterns based on which cue is present on a given trial. The typical finding is that there is a switch cost manifest as slower or less accurate task performance on trials after a switch in task compared to trials in which the preceding trial involved the same task (e.g., Braver et al., 2003; Logan, 2003).

Whitney et al. (2015) investigated cognitive flexibility during SD using a reversal learning task in which subjects learned from feedback which four digits, out of eight,

they should respond to (go set) and which four digits that they should avoid responding to (no go set) under strict deadlines. The go and no sets were reversed without warning after subjects had mastered the original stimulus-response patterns. Rested subjects were able to detect and adapt to the reversal after 8–12 trials, but SD subjects had not adapted to the reversal after 40 trials of the reversal phase. Using the digit classification task switching procedure described above, [Couyoumdjian et al. \(2010\)](#) found evidence for substantial impairment of cognitive flexibility in sleep deprived subjects. Under SD, subjects had significantly larger switch costs than rested subjects. Similarly, [Slama et al. \(2018\)](#) found detrimental effects of SD on task switching but no effect on working memory.

4 “Complex cognition” and SD reconsidered

Although neurophysiological evidence has provided support for the general idea that higher-level decision making may be preserved under SD in part through compensatory processing, the mechanisms, benefits, and costs of such processing have been left largely unspecified. The dynamic attentional control framework described here may shed light on how and why some aspects of higher level cognition are more affected by SD than others. For example, individual economic decision making, i.e., decisions involving risk, uncertainty, and relative and absolute value of monetary outcomes, relies on the neurocognitive processes that are dependent on the PFC (e.g., [Lowe et al., 2017](#)). Because of the presumed vulnerability of the PFC to sleep loss ([Killgore, 2010](#); [Womack et al., 2013](#)), it therefore follows that economic decision making should be impaired by SD. Nevertheless, laboratory studies have shown that some decision making tasks that rely heavily on the PFC do not show consistent SD effects, while other PFC dependent decision making tasks do show SD effects ([Womack et al., 2013](#)).

One illustration of a decision making task that shows a surprising lack of compromise by SD is delay discounting ([Green and Myerson, 2004, 2010](#)). Delay discounting requires individuals to evaluate choices based on differences in delay and magnitude of options. For example, choice alternatives that are offered typically provide an immediate payoff with a small amount of money versus a delayed payoff with a large amount of money. A shift in preference for immediate options over more valuable delayed options is a hallmark of impulsivity in decision making, where people fail to adequately weigh future consequences of a choice, and it is predictive of risk taking behavior in real life settings ([Dalley and Robbins, 2017](#); [Evenden, 1999](#); [Madden and Bickel, 2010](#)). Yet, despite the fact that delay discounting tasks engage PFC processes that are often presumed to be compromised by sleep loss, studies of SD report no consistent alteration of delay discounting ([Acheson et al., 2007](#); [Demos et al., 2016](#); [Libedinsky et al., 2013](#)). By this well-established laboratory measure, SD individuals are not more impulsive or risk prone than they are when rested.

In contrast, studies employing the Iowa Gambling Task (IGT; [Bechara et al., 1997](#); [Dunn et al., 2006](#)), which also engages PFC processes, have consistently

reported impaired decision making during SD (Killgore et al., 2006, 2007). The IGT involves gambling with hypothetical gains and losses from four simulated decks of cards. Choices from two of the decks, designated as bad decks, produce frequent large gains, but these gains are offset by occasional larger losses. Choices from the other two decks, designated as good decks, produce frequent small gains, along with infrequent smaller losses. To maximize gains over the course of the task, individuals must learn to choose the smaller, but more reliable, gains provided by the good decks. The IGT shares the probabilistic uncertainty of many behavioral economic tasks, i.e., a good choice does not always result in a good outcome, but it also requires that individuals learn through outcome feedback which choices are advantageous and which choices are disadvantageous. When performing the IGT, SD subjects continue to make choices from bad decks rather than learning to make choices that are advantageous in the long run (Killgore et al., 2006, 2007). This pattern of choices is similar to that found when functions in some PFC regions, such as the ventromedial PFC, are compromised (Bechara et al., 1997).

Why should two different decision making tasks that engage the PFC produce such different patterns of performance impairment during SD? An initial suggestion was that the IGT might activate affective processes that are also compromised by SD and those affective processes are responsible for impaired decision making (Killgore, 2010). This suggestion gained support from research using economic decision making tasks manipulating the risk or uncertainty of choice options. One study examining choices of hypothetical monetary lotteries that contrasted different levels of risk found that SD subjects showed increased preference for risks involving gains, while also showing decreased preference for risks involving losses (McKenna et al., 2007). The change in risk preference was consistent with another study using risky economic decision making and fMRI which reported higher neural activation for gains and lower neural activation for losses (Venkatraman et al., 2007). However, subsequent research has cast doubt on the notion that affective biasing of value is responsible for the compromise of decision making during SD. These recent studies have found that risk preference, including the loss aversion bias that is characteristic of most well-rested people, is not affected by SD (Maric et al., 2017; Mullette-Gillman et al., 2015). Furthermore, it is not clear why delay discounting, which is unaffected by sleep loss, would not engage affective processes that are operative in other economic decision making tasks, as delay discounting is often used as assessment of impulsivity (Madden and Bickel, 2010).

If biasing of the neural valuation signals does not explain when decision making is compromised by SD, perhaps the influence of attentional control processes does. Delay discounting may be less susceptible to SD because it places lower demands on attentional control. Delay discounting tasks fully describe choice options, and do not require updating of information based on past choices. Thus, there is no need for a tradeoff between the stable maintenance of choice information and flexible updating. On the other hand, the IGT requires continual updating of choice information based on choice outcomes. In addition, the IGT has an implicit reversal learning element that requires flexibility in attentional control for good performance. On early IGT

trials subjects are given a long series of good outcomes from what is ultimately a bad deck (Dunn et al., 2006). Almost all subjects develop an immediate preference for this bad deck option based on these early trials. But subjects must overcome this newly developed preference to maximize overall outcomes. The early reversal in contingencies for the bad deck may be essential to group performance differences obtained from the IGT (Fellows and Farah, 2003). Thus, the attentional control requirements of the IGT, requiring a balance of stability and flexibility, may explain why its performance is more readily compromised by sleep loss than is performance on delay discounting, and a variety of other decision making tasks that do place great demands on attentional control. This is not to say, that affective processes and valuation of outcomes do not play in role in SD effects on decisions about risk. Clearly, affective processes are a part of risky decisions, and an important goal for future research is to further understand how affective processes and cognitive control processes mutually influence SD effects on decision making.

The dynamic attentional control explanation is also supported by more recent research on risk and uncertainty in economic decision making. For example, although risk preference may not be changed by SD, the means by which risk are evaluated may change (Mullette-Gillman et al., 2015). More specifically, SD may contribute to use of a satisficing strategy, which reduces demands on attentional resources, instead of relying on a more resource intensive maximizing strategy that is likely to be used when people are well rested (Mullette-Gillman et al., 2015). For example, the attentional control framework predicts that delay discounting during SD could be impaired by imposing a restriction on the throughput of information used to make decisions, such as by a decision deadline, or by otherwise challenging the allocation of attentional resources by dual task or divided attention requirements. The effect of sleep loss could be one of the multiple factors that influence the malleability of risk preference in judgment (Hinson et al., 2003; Lempert and Phelps, 2016).

5 Conclusions

The pattern of variability in SD effects across multiple cognitive tasks is consistent with an asymmetry in the fundamental cognitive control balance between stability and flexibility of information in the focus of attention. People who have experienced significant sleep loss have particular difficulty with flexible updating of task sets and processing strategies especially under fast-paced and dynamically changing conditions. This conclusion is consistent with behavioral evidence, neuroimaging, and dopaminergic genetic data related to the functioning of the frontostriatal circuitry.

In addition to accounting for the pattern of evidence on variability in SD effects, the attentional control framework proposed here suggests that a task whose performance does not appear to be compromised by sleep loss may be made more susceptible to the effects of sleep loss by adding or increasing the attentional control demands of the task. Taking the view that sleep loss is one of multiple situational challenges that can trigger compensatory processes situates SD research firmly

within a long tradition of research in cognitive neuroscience. We contend that research on the selectivity of SD effects on cognition can help us understand how the cognitive system is functionally organized and implemented in neural circuits, just as the selectivity of the effects of brain lesions or other challenges have helped us understand functional and neurophysiological aspects cognition in general (e.g., [Miller and Cohen, 2001](#)). The dynamic attentional control framework presented here makes use of recent research on the cognitive neuroscience of attentional control to better understand sleep deprivation effects on cognition. As we learn more about the implications of sleep deprivation's effect on the attentional stability-flexibility trade-off, we believe that sleep research can become a major contributor to development and testing of general theories of cognitive control.

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