### 4. Title and Subtitle

**Homeostatic and Circadian Modulation of Cognition:**
Integrating Mathematical and Computational Modeling Approaches

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Approved for public release; distribution is unlimited.

### 14. Abstract

Generic predictions of fatigue do not translate to correct predictions of performance impairment on a given task because a) fatigue affects different components of cognitive functioning differentially; b) the effects of fatigue on cognition are inherently stochastic; and c) there are systematic individual differences. In this project, these issues were addressed by 1) refining a state-of-the-art mathematical model of sleep/wake homeostasis; 2) disentangling distinct aspects of the effects of fatigue on cognition; 3) developing new computational models of performance, using the ACT-R cognitive architecture; 4) embedding the refined mathematical model in the ACT-R computational model platform; 5) developing a statistical framework for the estimation of model parameters; and 6) examining possible mechanisms whereby individual differences observed in previously collected experimental data may be incorporated. This project helps to address the need of the Air Force to understand the effects of fatigue on cognitive capability and thereby on mission safety and success.

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The main findings of this project have been published in the peer-reviewed open literature. This report summarizes those findings; full details of the research can be found in the corresponding publications as indicated.

Introduction

Air Force missions and other military operations require minimization of human error and maximization of mission success in the face of fatigue due to sleep loss and circadian misalignment. Fatigue can be mitigated through optimized operational planning and appropriate targeting of countermeasures. Detailed predictions of cognitive impairment due to fatigue are essential in this context, but available models of fatigue and performance are limited in their usefulness because they do not differentiate between the various distinct components of cognition. This project advanced the state of the art by developing a mathematical/computational platform for detailed predictions of the effects of fatigue on specific cognitive performance tasks.

Joint Project

Building on a previously established collaboration focused on developing computational models of cognitive performance under conditions of fatigue, this project involved a joint, integrated effort by the Sleep and Performance Research Center at Washington State University Spokane (PI: Hans P.A. Van Dongen, PhD) and the Performance and Learning Models team of the Air Force Research Laboratory (AFRL; PI: Glenn Gunzelmann, PhD). Additional project deliverables will be presented in a forthcoming final report from our AFRL collaborators.


Sustained attention and psychomotor reactions are foundational components of performance in many laboratory and applied tasks. In sleep research studies, individual differences in baseline attentional vigilance are compounded by individual differences in vulnerability to the negative consequences of fatigue due to sleep loss, producing large differences in reaction time profiles. We presented a theory and model to explain individual differences in reaction time performance in a sustained attention task, both at baseline and as overall alertness declines across 88 hours without sleep. The model captured the performance of individual human participants, and illustrated how individual differences in processing speed and differences in susceptibility to fatigue from sleep loss may be combined to produce unique performance profiles.

Circadian rhythms cause alertness declines at night, producing performance decrements across cognitive domains and tasks. Building on the learning mechanisms for declarative knowledge instantiated in the ACT-R cognitive architecture, we sought to explain the effects of circadian rhythms on performance of an orientation task administered repeatedly across two weeks to participants working either day or night shifts. The differences in performance between the two groups were best explained by varying the decay rate in declarative knowledge as a function of the time of day the task was performed. The model accounted well for task learning reflected in decreases in response times across days, as well as differences in learning between the day and night shift conditions.


Sleep and cognition are temporally regulated by a homeostatic process generating pressure for sleep as a function of sleep/wake history and a circadian process generating pressure for wakefulness as a function of time of day. Under normal nocturnal sleep conditions, these two processes are aligned in a way that provides optimal daytime performance and consolidated nighttime sleep. Under conditions of sleep deprivation, shift work or transmeridian travel, the two processes are misaligned, resulting in fatigue and cognitive deficits. Mathematical models of fatigue and performance have been developed to predict these cognitive deficits. Recent studies demonstrating long-term effects of chronic sleep restriction on performance suggest that the homeostatic process undergoes gradual changes that are slow to recover. New developments in mathematical modeling of performance are focused on capturing these gradual changes and their effects on fatigue. Accident risk increases as a function of fatigue severity as well as the duration of exposure to fatigue. Work schedule and accident rate information from an operational setting can thus be used to calibrate a mathematical model of fatigue and performance to predict accident risk. This provides a fatigue risk management tool that helps to direct mitigation resources to where they would have the greatest effect.

Olofsen E, Van Dongen HPA, Mott CG, Balkin TJ, Terman D. Current approaches and challenges to development of an individualized sleep and performance prediction model. The Open Sleep Journal, 2010; 3: 24–43.

Operational safety and productivity may be enhanced considerably with the development and application of individualized sleep and performance prediction models. These models predict an individual’s operational performance based on his/her unique sleep schedule, individual sleep requirements, and individual pattern of responses to sleep loss across a variety of cognitive performance domains. Progress in the individualization of such models is the result of integrated efforts based on an expanding understanding of the relevant physiological processes underlying
the sleep/circadian/performance interactions, as well as novel empirical and statistical approaches. This paper presents an overview of the latest efforts in the individualization of sleep and performance models, with sections on current efforts in model integration, the application of Bayesian forecasting techniques to the problem of model individualization, construction of Bayesian confidence intervals for predicted performance, and the problem of generalizability of individualized model predictions – i.e., the problem of using models constructed with performance data from one cognitive domain to predict performance in another cognitive domain.


Individual differences in cognitive functioning during extended work hours and shift work are of considerable magnitude, and are observed both in the laboratory and in operational settings. These individual differences have a biological basis in trait-like, differential vulnerability to fatigue from sleep loss and circadian misalignment. Trait-like vulnerability is predicted in part by gene polymorphisms and other biological or psychological characteristics, but for the larger part it remains unexplained. A complicating factor is that whether individuals are vulnerable or resilient to sleep deprivation depends on the fatigue measure considered – subjective versus objective assessment, or one cognitive task versus another. Such dissociation has been observed in laboratory data and in data from a simulated operational setting. Discordance between subjective and objective measures of fatigue has been documented in various contexts, and may be one of the reasons why vulnerable individuals do not systematically opt out of professions involving high cognitive demands and exposure to fatigue. Discordance in vulnerability to fatigue among different measures of cognitive performance may be related to the “task impurity problem,” which implies that interrelated cognitive processes involved in task performance must be distinguished before overall performance outcomes can be fully understood. Experimental studies and cognitive and computational modeling approaches have been employed to address the task impurity problem and gain new insights into individual vulnerability to fatigue across a wide range of cognitive tasks. This research is driving progress in the management of risks to safety and productivity associated with vulnerability to cognitive impairment from fatigue in the operational environment.


Although the phenomenon of cognitive fatigue during sustained task performance is well documented, surprisingly little was known about its temporal dynamics. This chapter focused on the interaction of cognitive fatigue across time on task with the influence of sleep loss (time awake) and circadian rhythm (time of day). We presented new data analyses showing that the impact of sleep loss on the time-on-task effect generalizes from acute total sleep deprivation to
more commonly experienced conditions of chronic sleep restriction. We also presented new analyses of data from studies of repeated sleep deprivation, which revealed poor replicability of the rate of performance degradation across time on task. This finding pointed to considerable influence of an as yet unknown stochastic process. We introduced a theoretical account for this stochastic process, which we hypothesized involves the presence of a use-dependent sleep state in local neuronal assemblies involved in task performance. We also proposed a model of the underlying mechanisms (see Figure 1), suggesting that cognitive fatigue from sustained task performance and fatigue from sleep loss and circadian rhythm may have common neurobiological pathways.

**Figure 1:** Model of local, use-dependent sleep and other neurobiological mechanisms involved in time-awake and time-on-task effects on cognitive performance. On the smallest time scale (in the order of milliseconds), information processing in a neuronal assembly such as a cortical column triggers a biochemical cascade that promotes the local sleep state (light gray part of the schematic). When the neuronal assembly is in the wake state and stimulated by input stemming from the cognitive task at hand, it responds with synaptic transmission to process the input signal and generate corresponding output. This triggers release of adenosine triphosphate (ATP) into the extracellular space and increases local metabolic activity. Rapid breakdown of extracellular ATP results in accumulation of adenosine, in proportion to the amount of synaptic transmission in response to stimulation (use). Binding of adenosine at purine type 1 receptors promotes the neuronal assembly sleep state, during which there is hyperpolarization (changing the evoked potential triggered by the input stimulus) and synaptic transmission is fundamentally altered. This effectively removes the assembly from the coordinated response of the many assemblies involved in the task at hand, resulting in a lapse of information processing. Thus, the local sleep state causes output variability which, at the behavioral level, leads to cognitive performance instability. On a longer time scale (minutes and hours), ATP through binding at purine type 2 receptors (dark gray part of the schematic) induces release of sleep regulatory substances (SRSs) such as tumor necrosis factor (TNF) and interleukin-1 (IL1). Continued stimulation (use) of the neuronal assembly causes these SRSs to accumulate and effect an increase in the density of post-synaptic receptors binding adenosine. As a consequence, the probability of entering the sleep state increases in a use-dependent manner, at the behavioral level giving rise to the time-on-task effect. The SRSs also promote the neuronal assembly sleep state through activation of GABAergic inhibitory neurons. The GABAergic neurons inhibit the glutamatergic excitatory neurons, which prevents these glutamatergic neurons from promoting the local wake state. The SRSs together with metabolic...
products such as adenosine also influence regional blood flow and thereby oxygen and metabolic nutrient supply. A rest break allows SRS, ATP and adenosine levels to decay, resetting the time-on-task effect. On an even longer time scale (hours to days), basal metabolic activity present in all neuronal assemblies, and associated conversion of ATP to adenosine, leads to a steady build-up of SRSs over time awake. This is modulated by the circadian pacemaker in the suprachiasmatic nuclei of the hypothalamus which influence circadian rhythm in the cellular machinery across the whole brain. Accordingly, the magnitude of the time-on-task effect is affected by both time awake and time of day. Subcortical circuits involved in the coordination and consolidation of whole-brain sleep (black part of the schematic) are influenced by the collective neuronal assembly states, as integrated across the brain through neuronal mechanisms involving the SRSs. The sleep regulatory circuits include the ventrolateral preoptic area (VLPO), which can shut down the wake-promoting (e.g., glutamatergic) neurons of the reticular activating system and other systems such as the cholinergic networks of the basal forebrain (not shown). These subcortical systems orchestrate sleep/wake states across the whole brain, and induce global sleep to prevent interaction with the environment when too many neuronal assemblies are in the local sleep state. Cognitive performance could otherwise be dangerously impaired, as can be seen when externally imposed sleep deprivation overrides the effects of the subcortical regulatory nuclei. The global sleep state allows SRS concentrations and receptor densities to be (partially) restored in a coordinated manner across all neuronal assemblies, resetting both the time-on-task effect and the time-awake effect in the process. This model offers a putative mechanistic explanation for the effects of time on task (and rest) and time awake (and sleep) on task-specific cognitive fatigue.


Mitigation of cognitive impairment due to sleep deprivation in operational settings is critical for safety and productivity. Achievements in this area have been hampered by limited knowledge about the effects of sleep loss on actual operational tasks. Sleep deprivation has different effects on different cognitive performance tasks, but the mechanisms behind this task-specificity have remained poorly understood. It is important to recognize that cognitive performance is not a unitary process, but involves a number of component processes that are differentially affected by sleep loss. Experiments have previously been conducted to deconstruct sleep-deprived performance into underlying cognitive processes using cognitive-behavioral, neuroimaging and cognitive modeling techniques. Computational modeling in cognitive architectures has been employed by our group to simulate sleep-deprived cognitive performance on the basis of the constituent cognitive processes. These efforts are beginning to enable quantitative prediction of the effects of sleep deprivation across different task contexts.

This paper, which summarized project deliverables, outlined a theoretical framework in which the effects of sleep loss on cognition may be understood, from the deficits in the underlying neurobiology to the applied consequences in real-world operational tasks.
PERSONNEL, PUBLICATIONS, TRANSITIONS, AND INVENTIONS

Personnel Supported and/or Associated with the Project

Faculty
Hans P.A. Van Dongen, Ph.D. (PI, Washington State University, supported)
Gregory Belenky, M.D. (co-PI, Washington State University, supported)
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Pia M. Forsman, Ph.D. (postdoctoral fellow, Washington State University, supported)
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Devon A. Grant, M.S. (Ph.D. student, Washington State University, supported)
Clark J. Kogan (Ph.D. student, University of Montana, supported)
Marcella Oonk, M.S. (Ph.D. student, Washington State University, supported)

Associated investigators
Glenn Gunzelmann, Ph.D. (co-PI, Air Force Research Laboratory, not supported on grant)
David F. Dinges, Ph.D. (University of Pennsylvania, not supported on grant)
Leonid V. Kalachev, Ph.D. (University of Montana, not supported on grant)
Daniel J. Mollicone, Ph.D. (Pulsar Informatics, Inc., not supported on grant)
Erik Olofsen, Ph.D. (Leiden University Medical Center, the Netherlands, not supported on grant)

Publications

Peer-reviewed papers and chapters
Gander P, Signal L, Van Dongen HPA, Muller D, Van den Berg M. Stable inter-individual differences in slow-wave sleep during nocturnal sleep and naps. Sleep and Biological Rhythms, 2010; 8: 239–244.


Mollicone DJ, Van Dongen HPA, Rogers NL, Banks S, Dinges DF. Time of day effects on neurobehavioral performance during chronic sleep restriction. Aviation, Space, and Environmental Medicine, 2010; 81(8): 735–744.

Olofsen E, Van Dongen HPA, Mott CG, Balkin TJ, Terman D. Current approaches and challenges to development of an individualized sleep and performance prediction model. The Open Sleep Journal, 2010; 3: 24–43.


Miscellaneous publications


Van Dongen HPA. Connecting the dots: From trait vulnerability during total sleep deprivation to individual differences in cumulative impairment during sustained sleep restriction. Sleep, 2012; 35(8): 1031–1033.

Interactions and Transitions

Participation/presentations at meetings, conferences, seminars, etc.
May 2009 (Van Dongen): Lecture “Investigating the temporal dynamics and underlying mechanisms of cognitive fatigue,” Cognitive Fatigue Conference; Atlanta, Georgia.
November 2009 (Van Dongen): Lecture “Managing sleep, fatigue, and performance in flight operations,” Civil Aviation Administration of China; Beijing, China.
April 2010 (Van Dongen): Lecture “Fatigue, physiology, and neurobehavioral performance,” Université du Littoral Côte d’Opale; Dunkerque, France.
April 2010 (Van Dongen): Lecture “Mathematical modeling of fatigue,” Université du Littoral Côte d’Opale; Dunkerque, France.
August 2010 (Van Dongen): Lecture “Fatigue modeling in aviation maintenance,” MX Fatigue Workgroup; Houston, Texas.
September 2010 (Van Dongen): Lecture “Sleep homeostatic regulation of cognitive performance: Dynamic modulation over days and weeks,” European Sleep Research Society; Lisbon, Portugal.
September 2010 (Van Dongen): Lecture “Sleep deprivation sheds light on brain and cognition,” University of Amsterdam; Amsterdam, The Netherlands.
January 2011 (Van Dongen): Lecture “Performance prediction modeling and its role in fatigue risk management,” Transportation Research Board 90th Annual Meeting; Washington, D.C.
February 2011 (Van Dongen): Lecture “Vigilance and performance: Variability over tasks, individuals, and time,” VU University Amsterdam; Amsterdam, The Netherlands.
March 2011 (Van Dongen): Lecture “Fatigue risk management: Applying sleep science in operational settings,” University of Amsterdam; Amsterdam, The Netherlands.
April 2011 (Van Dongen): Lecture “Predicting cognitive impairment: On the dynamics of sleep homeostasis,” Centre for Integrated Research and Understanding of Sleep; Sydney, Australia.
April 2011 (Van Dongen): Lecture “New concepts and developments in model-based fatigue risk management,” Woolcock Institute of Medical Research; Sydney, Australia.

May 2011 (Van Dongen): Lecture “Applying models to the real world,” Harvard University; Cambridge, Massachusetts.

May 2011 (Van Dongen): Lecture “Developing multi-scale models: From local brain states to overt cognitive functioning,” Harvard University; Cambridge, Massachusetts.


August 2011 (Van Dongen): Lecture “Predicting cognitive impairment due to sleep loss,” Drexel University; Philadelphia, Pennsylvania.


November 2011 (Van Dongen): Lecture “Sleep deprivation and cognition: Breaking new ground,” Wright-Patterson Air Force Base; Dayton, Ohio.


April 2012 (Van Dongen): Lecture “Sleep loss and cognition,” Medical Center Haaglanden – Westeinde; The Hague, The Netherlands.

Consultative and advisory functions to other laboratories and agencies


March 2009–present (Van Dongen): Member of Maintenance Fatigue Work Group, Civil Aerospace Medical Institute.

May 2009–present (Van Dongen): Program Committee member for the Annual Meetings of the Associated Professional Sleep Societies.


April 2010 (Van Dongen): Member of MITRE special initiative on aviation fatigue research roadmap expert panel.

October 2010–November 2010 (Van Dongen): Member of Goal-Specific Working Group #1 advising the Sleep Disorders Research Advisory Board of the National Center for Sleep Disorders Research at the NIH.

January 2011–present (Belenky): Chair of Modeling Working Group, MITRE Aviation Fatigue Research Roadmap Team.
January 2011–present (Van Dongen): Chair of Tools & Mitigation Working Group, MITRE Aviation Fatigue Research Roadmap Team.

February 2011–present (Van Dongen): Visiting Professor at University of Amsterdam’s research priority program “Brain and Cognition.”

April 2011–October 2011 (Van Dongen): Chair of graduation jury for Rémy Hurdiel, Université du Littoral Côte d’Opale, France.


March 2012–present (Van Dongen): Member of dissertation committee for Clark J. Kogan, University of Montana.

Transitions

- We transitioned the mathematical model developed as part of this project to the Air Force Research Laboratory for implementation in the cognitive architecture ACT-R (key individuals involved: Glenn Gunzelmann, Ph.D. and Rick Moore, Ph.D. of the Air Force Research Laboratory).

- We transitioned the mathematical model developed as part of this project to Pulsar Informatics, Inc., who are providing an implementation suitable for integration with crew rostering to the U.S. Navy (key individuals involved: Daniel Mollicone, Ph.D. and Mike Stubna, Ph.D. of Pulsar Informatics, Inc.).

- We transitioned a numerical library for the mathematical model developed as part of this project to the Université du Littoral Côte d’Opale, France, who are developing a fatigue risk management toolkit for air traffic controllers (key individuals involved: Denis Theunynck, Ph.D. and Rémy Hurdiel, Ph.D. of the Université du Littoral Côte d’Opale).

- We transitioned fatigue predictions for standard schedules in rapid renewal road construction projects to Battelle Center for Human Performance & Safety, who are developing a fatigue management toolkit for the Transportation Research Board (key individuals involved: Thomas Sanquist, Ph.D. and Elizabeth Jackson, Ph.D. of Battelle Center for Human Performance & Safety).

New Discoveries, Inventions, or Patent Disclosures

A provisional patent application “Alertness Monitoring Systems and Associated Methods” for cognitive performance monitoring and prediction in automobile drivers, based on the concept of dissociable components of cognition as investigated in this project, has been submitted (November 2011).