Sleep Deprivation, Stimulant Medications, and Cognition
Sleep Deprivation, Stimulant Medications, and Cognition

Edited by

Nancy J. Wesensten, Ph.D.
Center for Military Psychiatry and Neuroscience, Department of Behavioral Biology,
Walter Reed Army Institute of Research, Silver Spring, MD, USA
**Contents**

List of contributors  page vii  
Foreword: Sustaining cognitive performance: a modern imperative  ix  
David Dinges  
Preface  xi  

**Section 1: Basic Mechanisms: Cognitive Performance and Sleep**

1 The true nature of sleep loss-induced “neurocognitive performance deficits”: a critical appraisal  1  
  Thomas J. Balkin  
2 Using fMRI to study cognitive function and its modulation in sleep-deprived persons: a selective overview  7  
  Michael W. L. Chee and Su Mei Lee  
3 Neurochemistry of wakefulness and sleep  23  
  Robert E. Strecker and James T. McKenna  
4 Genetic basis of individual vulnerability to sleep loss and responsivity to stimulants  43  
  Phillip J. Quartana and Tracy L. Rupp  

**Section 2: Stimulant Reversal of Cognitive Deficits**

5 Modafinil reversal of cognitive deficits during sleep loss  58  
  Nancy J. Wesensten  
6 Utility of caffeine: evidence from the laboratory  82  
  Michael H. Bonnet and Donna L. Arand  

7 Caffeine: mechanism of action, genetics, and behavioral studies conducted in task simulators and the field  93  
  Christina E. Carvey, Lauren A. Thompson, Caroline R. Mahoney, and Harris R. Lieberman  
8 Stimulants in models of shift work and shift work disorder  108  
  Jonathan R. L. Schwartz and Aaron M. Henley  
9 The potential for abuse of stimulants in chronically sleep-restricted populations  122  
  Emma Childs and Harriet de Wit  
10 Cognitive enhancers versus stimulants  136  
  Megan St. Peters and Martin Sarter  
11 Novel pathways for stimulant development I: targeting the histaminergic system  152  
  John J. Renger  
12 Novel pathways for stimulant development II: the hypocretin/orexin system  165  
  Ravi K. Pasumarthi and Thomas S. Kilduff  

**Section 3: Alternatives for Sustaining Cognitive Performance During Sleep Loss**

13 Light exposure for improving cognition during sleep loss and circadian misalignment  184  
  Kenneth P. Wright, Jr., Tina M. Burke, and Mark R. Smith
Contents

14 Nutritional countermeasures for cognitive performance decrements following sleep deprivation 199
   Caroline R. Mahoney and Harris R. Lieberman

15 The role of alertness monitoring in sustaining cognition during sleep loss 209
   Melissa M. Mallis and Francine O. James

16 Sustaining neurobehavioral performance on less sleep: is SWS enhancement the key? 223
   Janine M. Hall-Porter and James K. Walsh

Section 4: Summary and Conclusions

17 Use of stimulants in operational settings: issues and considerations 237
   Nicholas Davenport, Cheryl Lowry, and Brian Pinkston

18 Fatigue management: the art of the state 257
   Tracy L. Rupp, Nancy J. Wesensten, and Thomas J. Balkin

Index 268
Contributors

Donna L. Arand, Ph.D.
Clinical Director of the Kettering Medical Center
Sleep Disorders Center, Wallace Kettering
Neuroscience Institute, Kettering, OH, USA

Thomas J. Balkin, Ph.D.
Chief, Behavioral Biology Branch,
Center for Military Psychiatry and Neuroscience,
Walter Reed Army Institute of Research,
Silver Spring, MD, USA

Michael H. Bonnet, Ph.D.
Professor of Neurology, Wright State University
School of Medicine and Director of the Sleep Center
at the Department of Veterans Affairs Medical Center,
Dayton, OH, USA

Tina M. Burke, M.S., Ph.D.
Department of Integrative Physiology,
Sleep and Chronobiology Laboratory, University of
Colorado at Boulder, CO, USA

Christina E. Carvey, M.S.
Research Dietitian, Military Nutrition Division,
US Army Research Institute of Environmental
Medicine, Natick, MA, USA

Michael W. L. Chee, M.B.B.S.
Cognitive Neuroscience Lab, Neuroscience and
Behavioral Disorders Program, Duke-NUS Graduate
Medical School, Singapore

Emma Childs, Ph.D.
The University of Chicago, Department of Psychiatry
and Behavioral Neuroscience, Chicago, IL, USA

Nicholas Davenport, M.D., M.P.H.
Naval Safety Center, Norfolk, VA, USA

Janine M. Hall-Porter, Ph.D.
Sleep Medicine and Research Center, St. Luke’s
Hospital, Chesterfield, MD, USA

Aaron M. Henley, B.A., R.P.S.G.T.
INTEGRIS Sleep Disorders Center and University of
Oklahoma Health Sciences Center, Department of
Medicine, Oklahoma City, OK, USA

Francine O. James, Ph.D.
Institutes for Behavior Resources, Inc., Baltimore,
MD, USA

Thomas S. Kilduff, Ph.D.
Center for Neuroscience, Biosciences Division, SRI
International, Menlo Park, CA, USA

Su Mei Lee, B.S.
Cognitive Neuroscience Lab, Neuroscience and
Behavioral Disorders Program, Duke-NUS Graduate
Medical School, Singapore

Harris R. Lieberman, Ph.D.
United States Army Research Institute of
Environmental Medicine, Natick, MA, USA

Cheryl Lowry, M.D., M.P.H.
MPH, United States Air Force Medical Support
Agency, Arlington, VA, USA

Caroline R. Mahoney, Ph.D.
Natick Soldier Research Development and
Engineering Center, Cognitive Sciences, Kansas Street,
Natick, MA, USA

Melissa M. Mallis, Ph.D.
Institutes for Behavior Resources, Inc., Baltimore,
MD, USA

James T. McKenna, Ph.D.
VA Boston Healthcare System and Harvard Medical
School, Research Service and Department of
Psychiatry, Brockton, MA, USA

Ravi K. Pasumarthi, Ph.D.
Center for Neuroscience, Biosciences Division, SRI
International, Menlo Park, CA, USA
List of contributors

Brian Pinkston, M.D., M.P.H.
MPH, United States Air Force, Medical Support
Agency, Arlington, VA, USA

Phillip J. Quartana, Ph.D.
Center for Military Psychiatry and Neuroscience,
Walter Reed Army Institute of Research, Silver Spring,
MD, USA

John J. Renger, Ph.D.
Senior Director, Site Lead, Neuroscience
Department, Merck Research Laboratories,
West Point, PA, USA

Tracy L. Rupp, Ph.D.
Behavioral Biology Branch, Center for Military
Psychiatry and Neuroscience, Walter Reed Army
Institute of Research, Silver Spring, MD, USA

Martin Sarter, Ph.D.
Department of Psychology, University of Michigan,
Ann Arbor, MI, USA

Jonathan R. L. Schwartz, M.D.
INTEGRIS Sleep Disorders Center and University of
Oklahoma Health Sciences Center, Department of
Medicine, Oklahoma City, OK, USA

Mark R. Smith, Ph.D., R.P.S.G.T.
Department of Integrative Physiology,
Sleep and Chronobiology Laboratory, University
of Colorado at Boulder, CO, USA

Megan St. Peters, Ph.D.
Department of Psychology, University of Michigan,
Ann Arbor, MI, USA

Robert E. Strecker, Ph.D.
VA Boston Healthcare System and Harvard Medical
School, Research Service and Department of
Psychiatry, Brockton, MA, USA

Lauren A. Thompson, B.S.
Research Technician, Military Nutrition Division, US
Army Research Institute of Environmental Medicine,
Natick, MA, USA

James K. Walsh, Ph.D.
Sleep Medicine and Research Center, St. Luke’s
Hospital, Chesterfield, MD, USA

Nancy J. Wesensten, Ph.D.
Behavioral Biology Branch, Center for
Military Psychiatry and Neuroscience, Walter
Reed Army Institute of Research, Silver Spring,
MD, USA

Harriet de Wit, Ph.D.
The University of Chicago, Department of Psychiatry
and Behavioral Neuroscience, Chicago, IL, USA

Kenneth P. Wright, Jr., Ph.D.
Department of Integrative Physiology, Sleep and
Chronobiology Laboratory, University of Colorado at
Boulder, CO, USA
It would be difficult to find a more relevant topic to describe the interaction of biology and behavior underlying the hyperactivity of modern human societies than this scholarly book on Sleep Deprivation, Stimulants, and Cognition, edited by Wesensten, which nicely integrates the burgeoning data on the use of stimulants to cope with the loss of sleep in modern societies. As the 24/7 pace of industrialized societies continues to spread globally, and electronic technologies permit billions of humans to compress time by multi-tasking and communicating across vast distances, time itself has been elevated to among the most precious of commodities. Every facet of modern life, from industrial production, health care, public safety, and military activity, to the distribution of money, goods, food, and people, depends upon using the night and stretching the day with artificial light. Electronically available entertainment, shopping, religious services, and social networks never sleep. There is no evidence that this pattern will abate, and every indication is that it will accelerate with the advent of ever more sophisticated technologies that create greater around-the-clock throughout of people, information, and goods.

In this simultaneously real and virtual world of time compression, the time required for essential behaviors that we share with members of the animal kingdom seems increasingly quaint and unnecessary. Foremost among these archaic requirements is the biological imperative to sleep approximately a third of every 24-hour period, and to do so at a time when we are physiologically programmed to sleep as a result of evolutionary pressures that shaped our adaptation and that of nearly all other animals to Earth’s light–dark cycle. There is accumulating evidence that, through economic incentives and logistical necessities, people in industrialized societies adapt to time compression by sleeping less. In most parts of the world, night work, which almost always results in sleep loss, is incented with additional compensation. However, even among day workers, compensated work time is the primary determinant of nocturnal sleep duration. For example, Americans tend to curtail their daily sleep primarily for economic (i.e., income) and logistical (i.e., commuting and other travel) reasons. Morning alarm clocks and evening prime time television have replaced sunrise and sunset as the daily regulators of sleep timing and duration.

Throughout the past century, scientific studies have established that reduced time for sleep results in deficits in both neurobehavioral (e.g., alertness) and neurocognitive (e.g., mental speed) functions. In recent years it has been discovered that these cognitive and behavioral deficits become progressively more severe when sleep duration is repeatedly reduced across days. At the same time, epidemiological studies have found that self-reported shorter sleep durations and disrupted sleep timing are associated with elevated risks of obesity, disease, and mortality. In the light of mounting evidence that reductions in sleep time adversely affect both behavior and health, one might reasonably ask how people attempt to cope with frequent sleep restriction. The answer appears to be by seeking stimulation when the cognitive or behavioral effects of sleep loss are experienced, while remaining awake for personal or professional reasons. Among the most popular forms of stimulation are caffeinated beverages and foods. Caffeine is an incredibly popular stimulant, and perhaps the most widely studied – there are thousands of published scientific articles on it. As the most commonly consumed stimulant in the
world, caffeine is among the most frequently detected compounds in organic wastewater. It is often consumed first thing in the morning, immediately after sleep, in large measure to block the sleep inertia (i.e., grogginess and lethargy) that results from premature awakening when homeostatic sleep pressure is still high. Hence it is used to rapidly transition from sleep to waking.3

Because it is classified as a safe food, caffeine is not subject to the restrictions that exist for stimulant medications. The US Anti-Doping Agency used to prohibit high levels of caffeine because it could provide athletes with an advantage (i.e., faster reaction times). They removed the ban in the past decade because so many athletes had high levels of caffeine that they could no longer enforce its prohibition. The 2012 Prohibited List – International Standard of the World Anti-Doping Agency includes caffeine in the monitoring program, but does not consider it a prohibited substance.

Caffeine was removed from the US Anti-Doping Agency list of prohibited substances around the same time that the stimulant modafinil was added to the list. Unlike caffeine, modafinil is a federally regulated medication used to treat excessive sleepiness and other conditions in the USA. Modafinil has triggered great scientific and social focus as a novel alertness-promoting agent. In the past 20 years, there have been approximately 1000 scientific reports on the effects of modafinil in animals and in both patients and sleep-deprived healthy adults, compared with only a third of that number of reports on the effects of dextroamphetamine, a safer form of amphetamine than methamphetamine. As evident in Chapters 3, 11 and 12 in this marvelously comprehensive book on Sleep Deprivation, Stimulant Medications, and Cognition, the neurobiological mechanisms of wakefulness and arousal are becoming increasingly understood, resulting in the development of novel stimulants that may be capable of safely promoting cognitive and behavioral capability in the face of elevated sleep pressure. As novel stimulants get developed, it is perhaps prudent to remember important realities. No stimulant has yet been found that is a biological substitute for sleep (i.e., that makes sleep altogether unnecessary and/or its frequent elimination devoid of adverse consequences). All current stimulants appear to activate wakefulness through mechanisms that either upregulate wake neurobiology and/or inhibit sleep neurobiology. The search for compounds that substitute for sleep, or that might maximize the recovery potential of shorter sleep periods (as discussed in Chapter 16 by Hall-Porter and Walsh) is a holy grail quest with an as yet unknown probability of success.

Extending human wakefulness and enhancing human cognitive and behavioral capability (even if only by preventing the effects of chronically inadequate sleep) is likely to remain a priority for all the reasons identified in the first openings paragraphs. As noted by St. Peters and Sarter in Chapter 10, it is uncertain whether pure cognitive enhancement pharmacologically is possible without affecting the neurobiology subserving other cognitive and non-cognitive domains. The development of stimulants makes it clear that there is a terrific synergy/overlap between the arousal/wake-promoting systems and the cognitive systems. Moreover, as noted in Chapters 13, 14, 15, and 18, there are other nonpharmacological avenues being developed for promoting human alertness and behavioral capability during periods of sleep loss.

Finally, and perhaps most importantly, we should be mindful of the extensive scientific evidence that consolidated normal sleep of adequate duration is in all respects the ultimate cognitive enhancer, stabilizing alertness and attention, consolidating memories, increasing cognitive and psychomotor speed, promoting emotional integration, and generally recovering neurobehavioral capability. As this text on Sleep Deprivation, Stimulants, and Cognition makes clear, even more effective and safe stimulants have an important place in the ethical and medical management of sleepiness and fatigue that pose risks to health and safety. However, we should not lose sight of the need to balance our waking desires with the pleasure and cognitive nourishment of sleep that “knits up the ravel’d sleave of care” (The Tragedy of Macbeth by William Shakespeare).

Preface

Publication of literally hundreds of peer-reviewed journal articles devoted to stimulant effects in humans attest to the ongoing interest in pharmacologic tools to sustain alertness and cognitive performance during sleep loss. Indeed, the significance of this topic appears to be growing – which is perhaps not surprising as an ever-expanding number of commercial, military, and private sector operations transition to global, round-the-clock endeavors.

This book provides a review, synthesis, and analysis of the literature pertaining to stimulant compounds (most notably caffeine and modafinil) and cognitive performance. The focus was limited to the utility of these agents for restoring and maintaining cognitive performance and alertness in sleep-deprived (but otherwise normal, healthy) individuals – an application which currently constitutes “off-label” (i.e., non-approved) use of medications such as modafinil. Also covered in this volume are related topics: the neurophysiologic underpinnings of sleep-loss-induced cognitive deficits, non-pharmacologic alternatives to stimulants, a review of stimulant abuse liability, and use of stimulants under actual operational settings (e.g., military use) – topics that provide the reader with a more comprehensive overview of issues relevant to application of stimulants for facilitating cognition in normals. My goal in editing this book was to gather such information into a single, comprehensive source that would serve as a reference guide for scientists, students, industrial and military leaders, and policy makers. There is necessarily some amount of content overlap among chapters. However, each chapter was written to serve as a stand-alone and cross-referencing was included to direct the reader to other chapters for additional information.

The book is divided into four sections. The first provides an overview of the nature of the problem, i.e., the effects of sleep loss on cognitive (or “neurobehavioral”) performance. In Chapter 1, Balkin leads with the notion that the ever-increasing number of studies devoted to cataloguing the effects of sleep loss on specific cognitive abilities (and, by implication, the effects of stimulants on reversing these abilities) have done little to reveal the true nature or function of sleep. By focusing on fMRI experiments conducted on sleep-deprived subjects, Chee and Lee propose in Chapter 2 that a common neurophysiologic (“top down”) attention-based mechanism underlies the neurobehavioral performance deficits seen during sleep loss. In Chapter 3, Strecker and McKenna set the stage for the second section by reviewing the major neurotransmitter systems involved in wake (and sleep) promotion. In the final chapter of this introductory section, Quartana and Rupp (Chapter 4) describe genetic variations in several of these neurotransmitter systems that impact neurobehavioral performance and response to stimulants during sleep loss.

The second section is devoted to an in-depth review of modafinil and caffeine effects on neurobehavioral performance during sleep loss. (Note: this section contains no review of dextroamphetamine effects during sleep loss – an intentional omission based on the fact that because dextroamphetamine is a Schedule II compound (see Chapter 9 for schedule definitions) with a well-known abuse liability, it is no longer considered an viable option for sustaining performance in operational environments). Chapter 5 is devoted to modafinil’s effects on neurobehavioral performance during sleep loss. Laboratory-based studies of caffeine are reviewed in Chapter 6, and field-based studies of caffeine are reviewed in Chapter 7. Schwartz and Henley review effects of modafinil on performance and alertness in individuals with shift work disorder, which is characterized by complaints of excessive on-shift sleepiness associated with rotating or night shift work. Two related topics also are included in this section: first, in Chapter 9, Childs and De Wit discuss methods for evaluating stimulant abuse liability and review the pertinent literature on caffeine, dextroamphetamine, and modafinil.
In Chapter 10, the extent to which stimulants act as “cognitive enhancers” in non-sleep deprived individuals is reviewed by St. Peters and Sarter, who conclude that there is little evidence that stimulants can enhance true cognitive performance in otherwise well-rested individuals. The second section finishes with chapters devoted to two neurotransmitter systems (the previously described histaminergic system and the more recently discovered orexin system). At present, these two systems hold the most promise for development of novel wake-(histamine) and sleep-(orexin) promoting therapeutics.

No volume devoted to stimulant effects on cognition during sleep loss would be complete without a section devoted to alternative approaches. In Section 3, these alternatives are discussed and include bright light (Wright and colleagues – Chapter 13), nutritional countermeasures (Mahoney and Lieberman – Chapter 14), alertness monitoring (Mallis and James – Chapter 15), and enhancement of slow wave sleep (Hall-Porter and Walsh – Chapter 16).

In the final section, Davenport and colleagues (Chapter 17) describe the mechanisms by which stimulants are prescribed and used to sustain operational performance in the military. They discuss the strict limitations placed on use of modafinil and dextroamphetamine and issues that may arise when using these compounds to support military operations. They also briefly discuss the extent to which use of stimulants poses an ethical dilemma (a topic not covered in detail in this book). Rupp and colleagues (Chapter 18) conclude by presenting an alternative to current prescriptive hours-of-service based scheduling (which leads to inadequate sleep and circadian misalignment) – i.e., prospective cognitive effectiveness prediction based on sleep, wake, and time of day. Such prospective effectiveness prediction allows for quantitatively based, informed application of stimulants to support operational effectiveness.

Numerous individuals have, in one way or another, supported my research efforts over the years that culminated in this book, and I am grateful to them. I would like to specifically acknowledge the following individuals: Dr. Thomas Balkin, Dr. Greg Belenky, COL Karl Friedl, and COL Carl Castro.