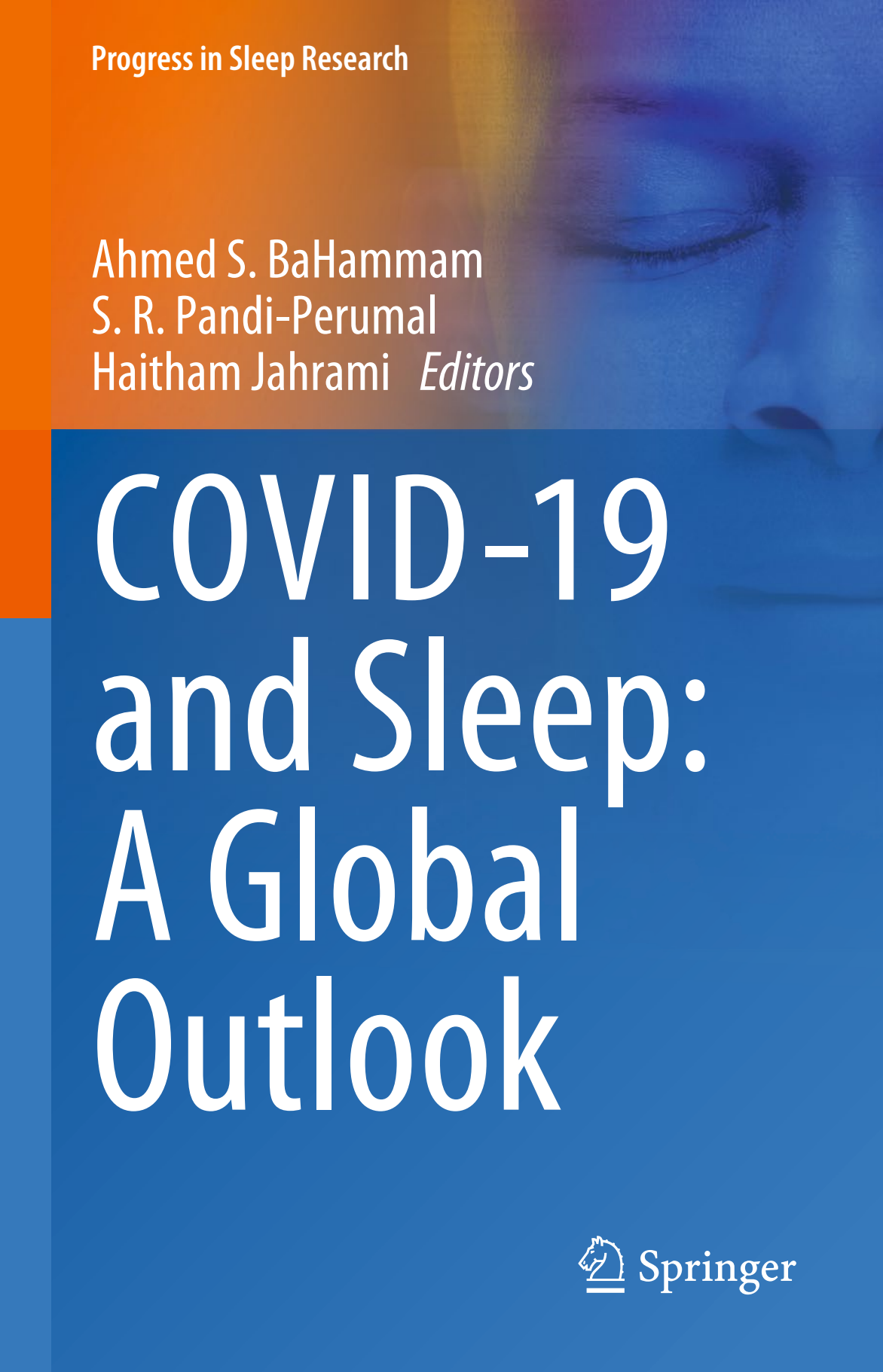
Progress in Sleep Research
Ahmed S. BaHammam
S. R. Pandi-Perumal
Haitham Jahrami Editors
COVID-19 and Sleep: A Global Outlook
Springer

Progress in Sleep Research

The book series provides an overview of the physiological processes involved in sleep regulation and the essential role of sleep in various vital physiological processes. It also summarizes the different stages of sleep and the clinical features of common sleep disorders. The individual books discuss the neurological and neuropsychological implications of sleep and highlight the relation between sleep and brain structure-functions. It explores the impact of sleep on circadian biology, neuroanatomy, neurophysiology, neuropharmacology, neuroendocrinology, neuroimmunology, neuropathology, basic neurology, biological psychiatry, and the behavioral sciences. It reviews the genetic factors associated with normal sleep and sleep disorders. It also describes the recent advances in research aiming to elucidate the neurochemical mechanisms regulating sleep and wakefulness.

Ahmed S. BaHammam • S. R. Pandi-Perumal • Haitham Jahrami
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COVID-19 and Sleep: A Global Outlook

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This volume is dedicated to our respective families.

Foreword

The COVID-19 pandemic had and continues to have profound effects on the world's health and economy. COVID-related morbidity and mortality, long COVID, COVID variants, and threat of new outbreaks mark the virus' impact on world health, while lockdowns, work stoppages, workdays lost, mobilization of healthcare systems, vaccine development efforts, and supply-chain breakdowns each add to COVID's burden to the world's economy.

The editors of COVID-19 and Sleep: A Global Outlook have chosen to examine the impact of the COVID-19 pandemic through its impact on and interactions with the essential physiological processes of sleep and circadian rhythms. They have assembled an international corps of experts in sleep and circadian rhythm research and medicine to explore sleep/COVID relationships. COVID impacts sleep directly in those who became infected and indirectly both in those who treat COVID patients and those who suffer the impact of the public health measures of lockdown and social distancing. Very often, these sleep disruptions were accompanied by cognitive and functional impairment as well as mental health disturbances such as increased depression or anxiety. Further, regular sufficient sleep promotes immune function and correspondingly disturbed sleep leads to immune function compromise.

COVID-19 and Sleep: A Global Outlook offers a comprehensive and authoritative exploration of the interactions of sleep and circadian rhythms and COVID-19. These explorations address a wide range of important topics, including, among others, sleep and circadian rhythm and immune system interactions, impact of COVID-19 and resultant lockdowns on sleep in various populations, interactions of COVID-19 with various sleep disorders, long-term impact of COVID-19 on sleep and circadian rhythms, interventions to improve sleep during COVID-19, and impact of the pandemic on the practice of sleep medicine.

The occurrence of another COVID pandemic is a potential threat to world health for which we must be prepared. Much has been learned from the world response to

COVID-19 that will allow for such a future pandemic to be better faced. COVID-19 and Sleep: A Global Outlook provides an outstanding compendium of the lessons learned, knowledge gained, and directions for future research concerning the role of sleep during such a world health crisis.

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Michael V. Vitiello

Preface

The editors are pleased to present the first edition of COVID-19 and Sleep: A Global Outlook, which has been included in the prestigious Progress in Sleep Research series. As editors, we are pleased about this decision as our volume fits perfectly in this landmark biomedicine and clinical sciences series from Springer.

All animal species require sleep, which shows that sleep is essential for maintaining essential functions. However, the time people spend sleeping at night is decreasing, and this trend is becoming more pronounced in modern 24-h societies. According to epidemiological and experimental studies, sleep deprivation has been linked to deleterious effects on physical and mental health, well-being, longevity, and general health-related quality of life.

Immune interactions related to sleep are a common occurrence in real life and conventional wisdom. Being sick makes us sleepy and want to sleep more, which is why getting a good night's sleep is sometimes referred to as "nature's best medicine" for infections. It is believed that improving sleep during an infection will act as a feedback loop for the immune system to support host defense. Therefore, sleep promotes host resistance against infection and inflammatory stimuli by acting as an immune-supportive mechanism. Indeed, sleep influences several immune parameters, is linked to a lower risk of illness, and can enhance the course of infection and the effectiveness of vaccinations.

Numerous research conducted over the past few decades have explicitly demonstrated that sleep and immunity have mutually beneficial interactions. Notably, sleep and the immune system seem to work in tandem, particularly when the body is fending off illness. Immune system operations are strongly regulated by sleep and the circadian (~24-h periodicity) rhythm, which affects how well our body defends itself innately and adaptively. Along these lines, chronic sleep deprivation is believed to impair our body's immune system, making us more susceptible to infections such as the common cold. The immune system is stimulated by microbial challenges, which results in an inflammatory response. This reaction can either increase sleep duration and intensity or interrupt sleep depending on its severity

and time course. A chronic inflammatory state and an increased risk for infectious/inflammatory pathologies, such as cardiometabolic, neoplastic, autoimmune, and neurodegenerative dysfunctions, have been linked to sleep deprivation and altered innate and adaptive immunological parameters.

To enhance physical and mental well-being across animal species, including humans, sleep quality and adaptation to individual and environmental conditions are crucial. The connection between sleep and the immune system and how sleep disruptions may upset the delicate balance with serious consequences for health outcomes have been the subject of growing evidence in recent years.

Sleep has drawn particular attention in recent years due to its possible impact on the immune system. Several studies have shown that lack of sleep alters several immune system components, including the percentages of cell subpopulations and cytokine levels, making people less resistant to infections, particularly viral infections [1]. Additionally, the immune response to infections affects sleep patterns, indicating a possible bidirectional relationship between sleep and immune responses [2].

In this specialized volume, the editors have come together to address the current coronavirus disease (COVID-19) pandemic crisis. COVID-19 transformed into a horrible global public health problem that impacted the general people's and healthcare professionals' sleep and mental health. This stressful situation significantly impacted everyone's everyday activities and sleep patterns, affecting hundreds of millions worldwide. Moreover, systematic reviews have reported a high prevalence of sleep problems globally, with the most affected groups being patients with COVID-19 and healthcare workers, in addition to the general public [3–5]. During the pandemic and lockdown, insomnia symptoms, circadian rhythm disruption, dream recall frequency, and nightmares were common. Additionally, subsequent studies suggested that some sleep disorders could be linked to COVID-19. For example, evidence suggests that OSA patients may be more likely to experience severe COVID-19 [6].

The term "long COVID" has recently appeared, reflecting the persistence of some symptoms, after recovery from the acute illness, for weeks to months following a relapsing and remitting course. It has been shown that sleep problems may persist months after COVID-19 infection [7]. A recent international survey of 14,000 participants from 16 nations reported that long-lasting sleep problems, such as insomnia and excessive daytime sleepiness in COVID-19 patients, were linked to the disease's severity [8].

Moreover, the quarantine, curfew, and infection control measures have changed the medical practice during the pandemic, affecting sleep medicine practice and the performance of diagnostic and therapeutic sleep medicine procedures. Therefore, to meet the pandemic's demands and unforeseen circumstances, COVID-19 required a significant adjustment in healthcare policies and practices, such as the complete shift to home sleep apnea testing and telemedicine [9, 10].

To address current pandemics and upcoming ones, it is therefore vital to compile all of this accumulating data for academics and practitioners in one volume. This

volume combines novel basic research and clinical aspects and is the first of its kind to take a critical look at the rapidly expanding areas linking COVID-19 with sleep science, sleep disorders, and sleep medicine practice. The practical importance and the availability of new data were taken into consideration while selecting the topics for this volume, though the majority of authors emphasize the need for more research. The volume brings together leading international scientists and clinical researchers to present research at the forefront of this field and explore the ramifications of advances in these cutting-edge areas, as well as their implications for an improved treatment paradigm. Additionally, each contributor represents a particular area of expertise in the study of sleep and COVID-19 and hails from a different world region. We expect this volume to provide an authoritative reference resource for researchers, practitioners, trainees, and students.

This specialty volume covers a wide range of important topics related to COVID-19 and sleep, including the link between sleep and circadian rhythm with the immune system, sleep disturbances and circadian rhythm disorders in various populations during the COVID-19 pandemic, impact of COVID-19 infection and pandemic on common sleep disorders, management of sleep disorders during the COVID-19 pandemic, role of telemedicine in the management of sleep disorders during pandemics, running of sleep medicine services during pandemics, and positive airway pressure management and the risk of aerosol during pandemics. This volume will be a great addition to the growing data on the impact of COVID-19 on sleep, sleep disorders, and sleep medicine.

We consider ourselves fortunate to have compiled this volume. We learned a lot while editing this important volume as part of our assignment. We sincerely hope that readers will find this volume extremely useful as a research and clinical resource. We sincerely hope that this volume will be useful to researchers and clinicians in the field. However, as the topic is evolving, this book aims as well to spark further discussion and stimulate more research ideas.

Riyadh, Saudi Arabia — Ahmed S. BaHammam
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COVID-19 and Sleep: A Global Outlook provides scientific and medical information to all healthcare workers interested in basic, translational, and clinical medicine. We are pleased to acknowledge the contributions of those who were instrumental in producing this book.

First and foremost, Prof. Michael Vitiello of Psychiatry and Behavioral Sciences at the University of Washington, who agreed to write the foreword for this volume, deserves our heartfelt gratitude. We would like to thank him for his contribution.

We want to express our deep appreciation to all the contributors for their scholarly contributions that facilitated the development of this volume. These authors have produced authoritative chapters that synthesize vast amounts of scientific and clinical data to create informative chapters. The expertise of contributors to COVID-19 reflects the broad diversity and knowledge concerning current research in this field, which has continued to grow over the last few years. These authors represent the cutting edge of basic and applied research and provide the most recent information regarding how such knowledge can be utilized in clinical settings. Their informed opinions and insights have significantly contributed to our scientific understanding of the interaction between COVID-19 and sleep and have provided essential interpretations regarding future research directions.

The highly talented people of Springer, USA, have made this project an incredibly pleasurable one. In addition, we were delighted to have the professional and highly enthusiastic support of Springer Nature's editorial and production team (specifically Dr. Bhavik Sawhney, Mahalakshmi Shankar and Ashok Kumar). Without their continuous and unstinting support, this volume would not have been possible.

It was a pleasure to work with the entire production team of Springer. Their guidance, technical expertise, and commitment to excellence were invaluable.

Finally, and most importantly, we want to thank our spouses and families for their support and understanding during the development of this book.

About This Volume

This volume combines novel basic research and clinical aspects and is the first of its kind to take a critical look at the rapidly expanding areas linking COVID-19 pandemic infection with sleep, circadian rhythm, and sleep disorders. The volume brings together leading international scientists and clinical researchers to present research at the forefront of this biomedical field and explore the ramifications of advances in these cutting-edge areas, as well as their implications for an improved treatment paradigm. Topics covered include, but are not limited to, the following themes:

- The link between sleep and circadian rhythm with the immune system
- Sleep disturbances in various populations during the COVID-19 pandemic
- Sleep during the COVID-19 pandemic: structural inequity and racial disparity
- The impact of COVID-19 infection and pandemic on common sleep disorders
- Management of sleep disorders during the COVID-19 pandemic
- Running of sleep medicine services during pandemics
- Positive airway pressure management and the risk of aerosol during pandemics
- The role of telemedicine in the management of sleep disorders during pandemics

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Chapter 1
The Effect of Sleep Disruption and Circadian Misalignment on the Immune System

Sergio Garbarino, Nicola Luigi Bragazzi, and Egeria Scoditti

Abstract Sleep disruption and circadian misalignment are associated with an increased risk for infectious and inflammatory pathologies, including cardiometabolic, neoplastic, autoimmune, and neurodegenerative diseases. Sleep and circadian rhythms are closely involved in the regulation of the immune system. Impairments of sleep quantity, quality, and timing, as well as circadian misalignment, result in derangements of innate and adaptive immune responses leading to a chronic inflammatory state and a decrease of the immune defense and reaction to threats (infection or injury). The immune system potentially plays an important mechanistic role in the relation between sleep disruption and circadian misalignment, and adverse health effects. By regulating the immune system, sleep- and circadian-centered intervention may beneficially impact overall health and on the prevention—and treatment—of infections and chronic diseases, especially in the modern lifestyles characterized by a multiplicity of social and environmental pressures on sleep and circadian rhythms, and in times of infectious disease outbreaks, such as COVID-19, where an effective immunity is of utmost importance.

Keywords Sleep · Circadian rhythm · Immune system · Infection · Chronic disease

1.1 Introduction

There is a time for many words, and there is also a time for sleep. Homer. The Odyssey.

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Since antiquity, sleep has been recognized as essential for overall health. Sleep is an active physiological process necessary for life, being involved in the regulation of physical, mental, and emotional health.

Key components in the regulation and maintenance of the sleep/wake cycle are the endogenous 24-h body clock/circadian system that drives wakefulness throughout the day and sleep during the night; and the wake-dependent homeostatic drive that generates a sleep pressure during the day, which is dissipated during sleep. However, an exogenous drive that is the product of our societal temporal structure (e.g., school and work times) forces an exogenous sleep/wake pattern influencing sleep opportunities and thereby sleep duration, quality, and efficiency, potentially resulting in sleep and circadian rhythm disruption (Zielinski et al. 2016).

On this background, patterns of sleep quantity, quality, and timing are influenced by health status, cultural, social, psychological, behavioral, and environmental factors (Grandner 2017). Expert consensus recommendations suggest that adults should sleep a minimum of 7 h per night on a regular night to promote optimal health (Consensus Conference et al. 2015a, b). Apart from sleep/circadian disorders however many factors, including jet lag syndrome, social jet lag, work schedule, growing frequency of technology use, higher rates of obesity and diabetes, inadequate nutrition, and other lifestyle factor changes occurring in the twenty-first century as well as the COVID-19 pandemic are increasingly and often negatively impacting on sleep quantity, quality, and timing, so that sleep problems have constantly arisen in the general population and special groups of vulnerable people, including children/adolescents or workers. Population-based studies reported that sleep duration among adults has changed over the past few decades and, in particular, the prevalence of adults sleeping less than 6 h per night has stably increased over a long period (Gilmour et al. 2013; Ford et al. 2015a, b; Zomers et al. 2017). This phenomenon is also occurring among children and adolescents (Matricciani et al. 2012), so 58% and 73% of middle and high school-aged adolescents, respectively, do not meet the American Academy of Sleep Medicine sleep duration recommendations (Wheaton et al. 2018). A parallel increasing prevalence of insomnia has been documented in several countries (Ford et al. 2015a, b).

In addition to excessive daytime sleepiness, fatigue, tiredness, depressed mood, poor daytime functioning, and impaired cognitive and safety-related performance, inadequate sleep is associated with an increased risk of adverse health outcomes, including weight gain, obesity, type 2 diabetes mellitus, hypertension, cardiovascular (CV) and neurodegenerative diseases, mental diseases, cancer as well as all-cause mortality (Vgontzas et al. 2009, 2013; Irwin 2015; Smagula et al. 2016; Cappuccio and Miller 2017).

Another integral part of human physiology and behavior tightly regulating sleep is the circadian rhythms, which are orchestrated by a central "master" clock, i.e., the suprachiasmatic nucleus (SCN) located in the anterior hypothalamus, that coordinates alignment between circadian clocks in other brain regions and peripheral tissues with external synchronizing agents (the environment and behaviors). Indeed, circadian rhythms are modulated by endogenous (genetic, physiological) as well as environmental (light) and behavioral (activity, feeding) factors. Various behaviors

and physiological functions of the body show circadian rhythms, such as the sleep–wake cycle and food intake, blood pressure, blood lipids, coagulation/fibrinolysis system, heart rate, body temperature, locomotor activity, hormone levels, cell metabolism and proliferation (Sulli et al. 2018). The advantages of internal clocks are to enable individuals to anticipate, rather than react to, daily recurring events and align their physiology and behavior to the changing environment.

The "molecular circadian clock" refers to genes that maintain autoregulatory feedback loops in which oscillating outputs regulate their expression (circadian locomotor output cycles kaput [CLOCK], brain and muscle ARNT-like [BMAL], period [PER], REV-ERB/nuclear receptor subfamily 1, group D [NR1D], and cryptochrome [CRY]). The formation, trafficking, and degradation of different clock protein complexes throughout this transcriptional cycle establish the intrinsic 24 h period of the cellular clock. Furthermore, at the cellular level, molecular clock components generate circadian fluctuation in basic cellular functions, e.g., gene expression, protein translation, and intracellular signaling, which are all involved in fundamental processes, including cell cycle regulation, nutrient sensing/utilization, metabolism, stress response, redox regulation, detoxification, and cell defense (immunity and inflammation) in a tissue-specific manner (Mure et al. 2018). Circadian disruption may occur as a result of a misalignment between external factors (such as the natural light/dark cycle, social and work requirements, and behaviors such as sleep and meal timing) with the master circadian clock as well as with endogenous circadian clocks in other tissues. Misalignments can occur among two (or more) rhythms which may be both internal (central vs. peripheral rhythms), or one may be internal and the other external (e.g., central vs. light/dark or peripheral vs. feeding/fasting). Social jet lag, jet lag syndrome, shift work, and inappropriately timed light exposure (evening or night) are common causes of circadian (external-internal) misalignments in modern society.

Circadian disruption has important public health implications due to its prevalence in modern society as well as its association with serious safety- and performance-related issues (Mitler et al. 1988) and adverse health outcomes (Boivin et al. 2022). Subjects with a nondaytime working schedule (shift work), exposure to light pollution, social jet lag, or evening chronotype are at increased risk for circadian disruption. Circadian disruption in humans is associated with broad and significant consequences for mental and physical health, increasing the risk for the development of cancer (Sulli et al. 2019), neurodegenerative, psychiatric (Abbott et al. 2020), cardiometabolic (Scheer et al. 2009), and immune disorders (Fishbein et al. 2021). Importantly, changes in circadian function are often accompanied by sleep–wake disturbances. Therefore, increasing scientific efforts have been devoted to understanding the health consequences of sleep disruption and circadian misalignment, and to translating this science to directly impact human health.

The immune system functions to preserve the integrity of the body by sensing physiological disturbances (microbes or tissue injury) and reinstating homeostasis via both inflammatory immune responses and processes of tissue repair and physical barrier regulation. In many chronic diseases, a deregulated and/or exacerbated immune response shifts from repair/regulation towards immune-driven unresolved

inflammatory responses (Hand et al. 2016). Several anatomic and molecular mechanisms, including neurons, glial cells, leukocytes, nerve fibers, soluble mediators, cellular receptors, the blood–brain barrier (BBB), the neuroendocrine hypothalamus-pituitary-adrenal (HPA) axis, and the autonomic nervous system, participate in orchestrating the bidirectional brain-immune crosstalk that fine tunes the immune response and its relationship with sleep and the circadian systems (Dantzer 2018). In this contest, the circadian system and sleep have emerged as important intertwined regulators of the immune system. It follows that sleep disruption and circadian misalignment may result in deregulated immune responses and pro-inflammatory responses, that contribute to an increase in the risk for the onset and/or worsening of infections as well as inflammation-related chronic diseases, including cancer, cardiometabolic and neurodegenerative diseases (Labrecque and Cermakian 2015; Scheiermann et al. 2018; Garbarino et al. 2021).

This Chapter focuses on the regulation of the immune system by sleep and the circadian rhythm, and the consequences for the immune function of sleep disruption and circadian misalignment.

1.2 Immune Regulation by Sleep

The sleep–immune interaction hypothesis was first suggested by pioneering studies attempting to identify substances involved in sleep regulation. The hypothesis of humoral regulation of sleep dates back to the early 1900s and posited that substances accumulated during waking could trigger subsequent sleep. Accordingly, experimental studies found that injection of cerebrospinal fluid from sleep-deprived dogs into rested recipient dogs caused the recipient dogs to fall into a narcosis-like sleep state (Ishimori 1909; Legendre and Piéron 1913). Subsequent animal studies replicated this result, pointing to the existence of hypnotoxins mediating sleep induction (endogenous factor(s) S, where S stands for sleep), and led to the identification of several sleep-promoting factors.

Among these hypnotoxins, muramyl peptide, a component of bacterial cell wall able of activating the immune system and inducing the release of immune regulators, such as cytokines, was recognized as the first molecular link between the immune system and sleep (Krueger et al. 1982). Other microbial-derived factors such as the endotoxin lipopolysaccharide (LPS), as well as mediators of inflammation, such as cytokines (interleukin [IL]-1, tumor necrosis factor [TNF]-α), prostaglandins (PG), uridine, growth factors, were found to regulate sleep (Zielinski and Krueger 2011). These factors, through the BBB or via afferent nerve fibers, establish a signaling network with other brain factors involved in sleep regulation, such as neurotransmitters (acetylcholine, dopamine, serotonin, norepinephrine, histamine), neuropeptides (orexin), nucleosides (adenosine), the hormone melatonin as well as the hypothalamus-pituitary (HPA) axis.

Animal studies have consistently reported a role for the cytokines IL-1 and TNF-α and the prostaglandin PGD2 in the physiologic, homeostatic nonrapid eye

movement (NREM) sleep regulation in a dose- and time-of-day-dependent manner, so that the inhibition of the biological action of these substances resulted in a decrease of spontaneous NREM sleep, whereas administration of these substances enhanced NREM sleep amount and intensity and suppressed REM sleep (Opp 2005; Urade and Hayaishi 2011). Anti-inflammatory cytokines, including IL-4, IL-10, and IL-13, have been found to inhibit NREM sleep in animal models (Kubota et al. 2000). In humans, the circulating levels of IL-1, IL-6, TNF-α, and PGD2 are highest during sleep and, the available evidence, though indirect, converge to suggest the involvement of these immune mediators in the physiologic regulation of sleep (Besedovsky et al. 2019).

Accordingly, infection or inflammatory diseases induce immune activation and associated altered cytokine concentrations and profiles, which are transmitted to the central nervous system inducing adaptive and energy-saving responses, including sleep (Besedovsky et al. 2019). Acute mild immune activation enhances NREM sleep and suppresses REM sleep, and the increase in NREM sleep was a favorable prognostic factor for rabbits during infectious diseases (Toth et al. 1993). Contrarily, severe immune response with an upsurge of cytokine levels causes sleep disturbance with suppression of both NREM and REM sleep (Toth et al. 1993; Mullington et al. 2000; Sharpley et al. 2016). Chronic infectious, such as HIV infection (Chaponda et al. 2018), and inflammatory diseases, such as inflammatory bowel disease or rheumatoid arthritis (Ranjbaran et al. 2007; Uemura et al. 2016), are associated with sleep disturbances.

Evidence of the immune-supportive effect of sleep that may favor host defense is provided by vaccination studies. In humans, compared with nocturnal wakefulness, sleep after vaccination boosted both the memory phase and the effector phase of the immune response, underscoring the adjuvant-like effect of sleep on the immunological function (Lange et al. 2011). Similarly, habitual (and hence chronic) short sleep duration (less than 6 h) compared with longer sleep duration decreased the long-term clinical protection after vaccination against hepatitis B (Prather et al. 2012).

In exerting these effects, sleep may benefit the immune response through different mechanisms. Sleep influences the T helper (Th) phenotype and the cytokine balance between Th1 and Th2 cells thus determining the types of the effector mechanisms of the immune response. Th1 polarization state is typical of immune response to intracellular viral and bacterial challenges and is characterized by increased release of IFN-γ, IL-2, and TNF-α. It supports various cell-mediated responses, including macrophage activation, phagocytosis, the killing of intracellular microbes, and antigen presentation (Zhu and Zhu 2020). Th2 immunity is characterized by the expression of IL-4, IL-5, IL-10, and IL-13, and mediates humoral defense by stimulating mast cells, eosinophils, and B cells (with the production of IgG2,4 and IgE) against extracellular pathogens (Zhu and Zhu 2020).

The balance of Th1/Th2 immunity is critically involved in antimicrobial and antitumor immune responses. Th2 overactivity is found in some forms of allergic responses, and increases the susceptibility to infection (Moser et al. 2018), as well as to tumor development and progression, by limiting cytotoxic T lymphocytes proliferation and modulating other inflammatory cell types (Disis 2010). In contrast,

Th1 immunity supports cytotoxic lymphocytes with the potential of elimination or control of tumor cell growth; indeed, a Th1 adaptive immune response may be associated with improved survival or prognosis (Disis 2010; Lee et al. 2019).

Furthermore, sleep is associated with a reduction in circulating immune cells that most likely accumulate into lymphatic tissues thus increasing the probability to encounter antigens (immunological synapse) and trigger the immune response. An effective adaptive immune response to an immunological challenge may be facilitated by specific immune-active hormones associated with slow wave sleep (SWS)-rich early sleep, which is characterized by minimum concentrations of immunosuppressive hormones, such as cortisol, and high levels of immune-stimulating hormones such as growth hormone (GH), prolactin, and aldosterone, which support pro-inflammatory cytokine production and Th1 cell-mediated immunity (Besedovsky et al. 2019). Therefore, through pro-inflammatory hormones and cytokines night-time sleep facilitates the onset of adaptive immune responses, while during daytime activity, anti-inflammatory signals, hormones, and cytokines support immediate reactions to biological and other environmental challenges.

1.3 Sleep Disruption and Immune Consequences

In agreement with the sleep–immunity relationship, several lines of evidence from experimental and epidemiological studies converge on the significant effects of sleep disruption on immune function and related clinical outcomes.

Early animal studies found that sleep loss, besides being lethal after several weeks, was associated with dysfunction of host defense (Everson and Toth 2000; Everson et al. 2008, 2014) thus suggesting the importance of sleep for the immune system. More pertinently, the effect of sleep on immune function has emerged in studies in which immune parameters, including circulating levels of cytokines and cell adhesion molecules, leukocyte counts, and activity, were measured under the manipulation of sleep duration compared with undisturbed sleep.

Collectively most human and animal findings report on the supportive effect of sleep—and the detrimental effect of disturbed sleep—on several immune regulators. Indeed, compared with regular nocturnal sleep, acute and mostly sustained sleep loss has been found: (a) to alter circulating leukocyte counts with studies reporting increased numbers of total leukocytes and specific cell subsets mainly neutrophils, monocytes, B cells, decreased circulating natural killer (NK) cells, and changes in circulating CD4+ T cells (Born et al. 1997; Dimitrov et al. 2007; van Leeuwen et al. 2009; Lasselin et al. 2015; Said et al. 2019); (b) to alter the diurnal rhythm of circulating leukocytes, resulting in higher levels during the night and at awakening and a flattening of the rhythm (Born et al. 1997; Lasselin et al. 2015); (c) to increase the plasma levels of pro-inflammatory cytokines such as IL-1, IL-6, CRP, and, less consistently, TNF-α, MCP-1, and a homeostatic increase in endogenous inhibitors such as IL-1 receptor antagonist (IL-1ra) and TNF receptor I and II in an attempt to limit the increased cytokine levels and activity (Shearer et al. 2001; Hu et al. 2003;

Vgontzas et al. 2004; van Leeuwen et al. 2009); (d) to transiently decrease the cytotoxic activity of NK cells, the proliferation capacity of lymphocytes (Irwin et al. 1994), and the phagocytic activity of neutrophils, important against infection (Said et al. 2019); (e) to enhance circulating levels of endothelial adhesion molecules such as intercellular adhesion molecule (ICAM)-1 and E-selectin, suggesting endothelial activation and enhanced risk for vascular dysfunction (Sauvet et al. 2010); (f) to reduce the stimulated production of IL-2 and IL-12, which normally support the adaptive immune response (Dimitrov et al. 2007; Axelsson et al. 2013); (g) to reduce the levels of Mac-1 positive lymphocytes suggesting reduced migratory capacity of immune cells (Redwine et al. 2004). Compared to undisturbed sleep which is predominantly characterized by a Th1 response (mainly during early sleep), experimental sleep deprivation leads to a shift from a Th1 pattern towards a Th2 pattern in humans (Dimitrov et al. 2004; Axelsson et al. 2013). Elderly people (Ginaldi et al. 1999), alcoholic subjects (Redwine et al. 2003) as well as insomnia patients (Sakami et al. 2002), all characterized by disturbed sleep, show a cytokine shift towards Th2.

At the molecular level, findings demonstrate that a single night of partial sleep deprivation (4 h of sleep) (Irwin et al. 2006, 2015) or chronic partial sleep deprivation (4 h of sleep for five nights) (van Leeuwen et al. 2009) in healthy adults led to increased protein production and mRNA levels of inflammatory cytokines (IL-6, IL-1β, TNF-α, IL-17). Accordingly, prominent genome-wide gene expression changes have been found in response to acute (Irwin et al. 2006) or chronic (Aho et al. 2013; Moller-Levet et al. 2013) partial sleep deprivation in human circulating monocytes, so most of the genes and associated biological pathways upregulated after sleep loss compared with unrestricted sleep were related to immune and inflammatory processes (leukocyte activation and differentiation, cytokine positive regulation, innate and adaptive immunity, TLRs signaling), as well as to oxidative stress, response to stress, apoptosis, collectively indicating activation of the immune system. Interestingly, genes associated with B cell activation and Th2 cell differentiation were upregulated, whereas those associated with Th1 cell differentiation were downregulated (Aho et al. 2013), suggesting that the Th2 immune response driven by sleep deprivation, as observed in many studies, is regulated at the level of gene expression. In contrast, biological processes associated with genes downregulated following sleep deprivation compared with unrestricted sleep included chromatic organization and modification, gene expression, cellular macromolecule metabolism (Moller-Levet et al. 2013), cholesterol/lipid metabolism and transport, as well as NK cell function thus contributing to the reduced immune response against pathogens (Aho et al. 2013). The same expression profile of several genes identified in the experimental sleep deprivation was observed in a cohort of subjects with self-report of insufficient sleep (Aho et al. 2013), highlighting the physiological relevance of the experimental results at the population level in real-life conditions.

The pro-inflammatory transcriptomic response observed after sleep deprivation mainly involves the activation of the pro-inflammatory NF-κB family of transcription factors (Irwin et al. 2006, 2008; Aho et al. 2013). NF-κB mediates the expression of genes (e.g., cytokines, chemokines, growth factors, receptors/transporters, enzymes, adhesion molecules) involved in the activation of inflammation, adaptive