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Effects of chronic and acute sleep deprivation on sleep-wake regulation and cognition

vorgelegt von M.Sc. Eva Hennecke

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Erstgutachter: Prof. Dr. Joachim Vogt
Zweitgutachter: PD Dr. Eva-Maria Elmenhorst

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Dissertation prepared by M.Sc. Eva Hennecke

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Erklärung

Erklärung gemäß § 9, Abs. 1 der Allgemeinen Bestimmungen der Promotionsordnung der Technischen Universität Darmstadt vom 08.02.2018.

Hiermit erkläre ich, Eva Hennecke, dass ich die Arbeit - abgesehen von den in ihr ausdrücklich genannten Hilfen - selbstständig verfasst habe. Alle Stellen, die aus anderen Quellen entnommen wurden, sind eindeutig als solche kenntlich gemacht worden. Ich habe die Arbeit mit einem Verzeichnis aller benutzter Quellen versehen.

Diese Arbeit wurde keiner anderen Prüfungsbehörde vorgelegt.

Datum, Unterschrift

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Summary

Recuperative sleep contributes substantially to cognitive performance. Sleep deficits are associated with impaired cognitive functions and consequently augment the probability for errors and accidents. Shift workers are especially at risk for sleep deficits because they rather sleep at adverse circadian times and thus are exposed to light or noise during sleep opportunities. However, great inter-individual differences exist in the vulnerability to sleep deprivation effects. Moreover, cognitive functions are differentially affected by sleep deficits. Progress in the understanding of the before mentioned parameters has the potential to improve work safety by establishing personnel selection and assistance systems accordingly.

The following thesis was written in the scope of the scientific junior group “Chronic sleep loss: from molecular neuroimaging to safety and health in space” (SomnoSafe) at the Institute of Aerospace Medicine of the German Aerospace Center (DLR). The three publications of this cumulative dissertation are based on two elaborative cooperation projects with the Institute of Neuroscience and Medicine (INM-2) of the Forschungszentrum Jülich. Given that sleep during space missions is shortened and disturbed (Whitmire et al., 2010), the present work aims at contributing to the understanding of the effects of chronic and acute sleep deficits on sleep-wake regulation, cognition and their inter-individual differences. Concerning sleep-wake regulation and cognition, the first publication focuses especially on adenosinergic mechanisms, the second publication on sleep structure and the third publication on possible interaction effects of chronic and acute sleep deprivation.

A promising approach in elucidating inter-individual differences in sleep-wake behavior is the investigation of the adenosinergic system. Adenosine dampens cerebral nervous activity. It accumulates during wakefulness and is depleted during sleep in rodents and cats (Porkka-Heiskanen et al., 2000). Thus, adenosine is thought to be the neuromolecular correlate of the need for deep sleep that increases during wakefulness and decreases during

sleep as measured with polysomnography. The first publication focuses on human cerebral A1 adenosine receptor (A1AR) availability during and after recovery from extended wakefulness. A1AR was quantified by [^{18}F]CPFPX positron emission tomography scans after 52 hours of wakefulness and after a 14-h recovery sleep opportunity and compared to reference data from a well-rested sample. The results show increased human cerebral A1AR availability during extended sleep deprivation and a reduction of A1AR to baseline levels after recovery sleep. On the individual level, high A1AR availability during sleep deprivation was associated with higher cognitive performance and lower sleep pressure. Thus, differences in endogenous adenosine and receptor availability might account for the individual sleep loss responses.

The second publication explores the physiology of extended recovery sleep and recovery processes after prolonged wakefulness. After an adaptation and a baseline night, participants were sleep deprived for 58 hours and had a 14-h sleep opportunity thereafter. Sleep was recorded with polysomnography. We analyzed and compared the proportion of sleep stages between baseline and recovery sleep on an hourly basis. Our results revealed, that the sleep stage proportions of the two nights approximate as a function of sleep duration. In accordance with predictions of the two process model (Borbély, 1982), slow-wave activity was already recovered after approximately 10 hours of recovery sleep. Interestingly, intraclass correlation coefficients for the sleep parameters further increased thereafter, suggesting ongoing recovery processes. For most sleep parameters, the individual sleep structure could be reestablished after 14 hours of recovery sleep. The results emphasize the robustness of the individual sleep structure and give insights in recovery from prolonged wakefulness.

Cognitive performance during chronic and acute sleep deprivation and recovery from sleep loss effects is addressed in the third publication. A question that has not previously been answered is whether chronic sleep loss followed by one recovery night, predisposes individuals to impaired neurocognitive functioning during a subsequent period of additional acute sleep deprivation. Therefore, we investigated single and combined effects of sleep

restriction, acute sleep deprivation and recovery sleep on performance (verbal and spatial working memory, declarative memory). Chronic and acute sleep deprivation were separated by one recovery night. Our study design mimicked possible sleep-wake scenarios of shift-workers on earth as well as of astronauts on the International Space Station, where chronic sleep restriction effects might be paired with acute sleep deficits in case of special operations. After an adaptation night and two baseline nights, participants underwent 5 nights of chronically restricted sleep to 5 hours time in bed (TIB; chronic sleep restriction group) or 5 nights of normal sleep with 8 hours TIB (control group). After one night of normal sleep (8 hours TIB), there was a night of acute sleep deprivation (38 hours) for both groups and a final 10-h recovery night. During wakefulness, participants performed a cognitive test battery at 3-hourly intervals. Declarative memory was tested with paired-associate lists, verbal and spatial working memory was measured with N-back tasks. The results show that declarative memory recall and verbal working memory were unaffected by chronic sleep restriction. Spatial working memory performance, however, was impaired during chronic sleep restriction. Individuals with prior sleep restriction showed also stronger impairments of spatial working memory during acute sleep deprivation than individuals of the control group. Thus, we found interaction effects of chronic and acute sleep loss for this cognitive domain despite one intervening recovery night. Furthermore, chronic sleep restriction effects were partly initially covert and revealed during acute sleep deprivation. This finding is of special importance as recovery sleep might provide individuals with a false sense of complete recuperation.

The results of our investigations give new insights into the adenosinergic contribution to homeostatic sleep-wake regulation. For the first time in humans, we provide evidence for increasing and decreasing adenosine receptor availabilities in accordance with wakefulness and sleep. With the second publication we further show recovery processes in addition to those predicted by the homeostatic sleep-wake regulation. The third publication provides

evidence for longer lasting effects of chronic sleep deprivation on performance. Our findings underline the importance of adequate sleep and recovery periods. Especially, the complex interplay between inter-individual differences in sleep-wake regulation and cognition as well as the danger of insufficient recovery of cognitive functions after recovery sleep need further investigation. The factors should further be considered with regard to employee selection and the development of assistance systems.

The cumulative dissertation consists of two parts. Part 1 constitutes the synopsis. The first chapter details the theoretical background of the publications. An introduction to sleep, cognition and sleep deprivation effects on cognition is given. Chapter 2 explains the methods applied in the two laboratory sleep studies, on which the three publications are based. Chapter 3 gives an overview on each of the three publications. Chapter 4 provides a comprehensive general discussion. Part 2 of the dissertation consists of the references to the original publications.

Zusammenfassung (German Summary)

Erholsamer Schlaf trägt substantiell zur kognitiven Leistungsfähigkeit bei. Schlafdefizite beeinträchtigen die kognitive Leistungsfähigkeit und erhöhen in der Folge die Wahrscheinlichkeit für das Auftreten von Fehlern und Unfällen. Schichtarbeiter sind besonders gefährdet, Schlafdefizite zu erleiden, da sie eher zu ungünstigen zirkadianen Zeiten schlafen und somit Licht oder Lärm während möglicher Schlafenszeiten ausgesetzt sind. Dabei gibt es große inter-individuelle Unterschiede hinsichtlich der Auswirkungen des Schlafentzugs. Ebenso zeigen sich Unterschiede in der Wirkung von Schlafentzug auf die verschiedenen kognitiven Leistungsbereiche. Ein besseres Verständnis dieser Zusammenhänge kann dazu beitragen, die Arbeitssicherheit durch eine entsprechende Personalauswahl sowie Assistenzsysteme zu verbessern.

Die vorliegende Arbeit wurde im Rahmen der Nachwuchswissenschaftlergruppe „Chronic sleep loss: from molecular neuroimaging to safety and health in space" (SomnoSafe) am Institut für Luft- und Raumfahrtmedizin am Deutschen Zentrum für Luft- und Raumfahrt (DLR) verfasst. Die drei Veröffentlichungen dieser kumulativen Dissertation basieren auf zwei aufwändigen Kooperationsprojekten mit dem Institut für Neurowissenschaften und Medizin (INM-2) des Forschungszentrums Jülich. Untersuchungen zum Schlaf während Weltraummissionen zeigen, dass dieser kurz und gestört ist (Whitmire et al., 2010). Die vorliegende Arbeit zielt daher darauf ab, zum Verstehen der Wirkungen von chronischem und akutem Schlafentzug auf die Schlaf-Wach-Regulation, Kognition und inter-individuellen Unterschieden beizutragen. Bezüglich der Schlaf-Wach-Regulation und Kognition beschäftigt sich die erste Veröffentlichung insbesondere mit adenosinergen Mechanismen, die zweite Veröffentlichung mit der Schlafstruktur und die dritte Veröffentlichung mit möglichen Interaktionen zwischen chronischem und akutem Schlafentzug.

Ein vielversprechender Ansatz um inter-individuelle Unterschiede im Schlaf-Wach–Verhalten aufzuklären, ist die Untersuchung des adenosinergen Systems. Adenosin dämpft die zerebrale Nervenaktivität. In Nagetieren und Katzen wurde nachgewiesen, dass es sich über die Wachphase hinweg anreichert und während des Schlafes abgebaut wird (Porkka-Heiskanen et al., 2000). Daher wird angenommen, dass Adenosin das neuromolekulare Korrelat des Tiefschlafbedarfs ist. Dieser steigt während der Wachheit ebenfalls an und fällt während des Schlafes, was durch die Polysomnographie erfasst wird. Die erste Veröffentlichung fokussiert sich auf die Verfügbarkeit menschlicher zerebraler A1 Adenosinrezeptoren (A1AR) während und nach der Erholung von verlängerter Wachheit. A1AR wurden durch [^{18}F]CPFPX Positron-Emissions-Tomographie Scans nach 52 Stunden Wachheit und nach einer 14-stündigen Erholungsschlaf-Möglichkeit quantifiziert und mit Referenzdaten einer erholten Stichprobe verglichen. Die Ergebnisse zeigen eine erhöhte zerebrale A1AR Verfügbarkeit während ausgedehntem Schlafentzug und eine Reduktion von A1AR auf ein ausgeruhtes Niveau nach dem Erholungsschlaf. Eine hohe A1AR Verfügbarkeit während des Schlafentzugs war mit einer höheren kognitiven Leistungsfähigkeit und einem geringeren Schlafdruck assoziiert. Unterschiede in der Konzentration des endogenen Adenosins und der A1AR Verfügbarkeit könnten so die individuelle Auswirkung von Schlafentzug begründen.

Die zweite Veröffentlichung untersucht die Physiologie von Erholungsprozessen nach verlängerter Wachheit. Nach einer Adaptationsnacht und einer Basisnacht wurden die Teilnehmer für 58 Stunden am Schlafen gehindert. Danach hatten sie die Möglichkeit eines 14-stündigen Erholungsschlafes, der mittels Polysomnographie aufgezeichnet wurde. Wir analysierten und verglichen die Anteile der Schlafstadien zwischen der Basis- und der Erholungsnacht auf einer stündlichen Basis. Es zeigte sich, dass die Proportionen der Schlafstadien der beiden Nächte sich mit zunehmender Schlafdauer angleichen. Im Einklang mit Vorhersagen des Zwei-Prozess Modells (Borbély, 1982) war der Bedarf an Tiefschlaf

schon nach ungefähr 10-stündigem Schlaf gedeckt. Interessanterweise stiegen die Werte der Intraklassen-Korrelations-Koeffizienten darüber hinaus im Verlauf der weiteren Schlafdauer an, was auf fortlaufende Erholungsprozesse hinweisen könnte. Für die meisten Schlafparameter wurde die individuelle Schlafstruktur erst nach 14 Stunden Erholungsschlaf wieder hergestellt. Die Ergebnisse heben die Robustheit der individuellen Schlafstruktur hervor und geben Einblicke in Erholungsprozesse nach verlängerter Wachheit.

Die kognitive Leistungsfähigkeit während chronischem und akutem Schlafentzug und die Erholung von Schlafmangel wird in der dritten Veröffentlichung adressiert. Eine bisher ungeklärte Frage ist, ob chronischer Schlafmangel, welcher von einer Erholungsnacht gefolgt ist, Individuen während einer darauf folgenden Phase der akuten verlängerten Wachdauer für eine beeinträchtige neurokognitive Leistung prädisponiert. Aus dem Grund untersuchten wir einzelne und kombinierte Effekte von Schlafrestriktion, akutem Schlafentzug und Erholungsschlaf auf die Leistungsfähigkeit (verbales und räumliches Arbeitsgedächtnis, deklaratives Gedächtnis). Chronischer und akuter Schlafentzug waren durch eine Erholungsnacht getrennt. Unser Studiendesign simulierte mögliche Schlaf-Wach-Szenarien von Schichtarbeitern auf der Erde sowie von Astronauten auf der Internationalen Raumstation, wobei im Fall von speziellen Einsätzen chronische Schlafrestriktion mit akuten Schlafdefiziten gepaart sein kann. Nach einer Adaptationsnacht und zwei Basisnächten unterzogen sich die Probanden 5 Nächten chronischer Schlafrestriktion mit 5 Stunden Zeit im Bett (TIB; chronische Schlafrestriktionsgruppe) oder 5 Nächten mit normalem Schlaf mit 8 Stunden TIB (Kontrollgruppe). Nach einer Nacht mit normalem Schlaf (8 Stunden TIB) gab es eine Nacht akuten Schlafentzug (38 Stunden) für beide Gruppen und eine letzte 10-stündige Erholungsnacht. Während der Wachphasen absolvierten die Probanden alle drei Stunden eine kognitive Testbatterie. Das deklarative Gedächtnis wurde mit gepaarten Assoziationslisten getestet, das verbale und räumliche Arbeitsgedächtnis wurde mit einer N-back Aufgabe gemessen. Die Ergebnisse zeigen, dass der deklarative Gedächtnisabruf und

das verbale Arbeitsgedächtnis von chronischer Schlafrestriktion unbeeinflusst waren. Jedoch war das räumliche Arbeitsgedächtnis während der chronischen Schlafrestriktion beeinträchtigt. Individuen mit vorangegangener Schlafrestriktion zeigten zudem während des akuten Schlafentzuges größere Beeinträchtigungen im räumlichen Arbeitsgedächtnis als die Individuen der Kontrollgruppe. So fanden wir Interaktionseffekte von chronischem und akutem Schlafverlust bezüglich dieser kognitiven Domäne trotz einer zwischenzeitlichen Erholungsnacht. Außerdem waren die Auswirkungen der chronischen Schlafrestriktion zunächst teilweise verdeckt und zeigten sich erst während des akuten Schlafentzugs. Diese Erkenntnis ist besonders wichtig, weil der Erholungsschlaf Individuen ein trügerisches Gefühl vermeintlich vollständiger Regeneration geben kann.

Die Ergebnisse unserer Untersuchungen geben Einblicke in die Beteiligung des zerebralen adenosinergen Systems an der homöostatischen Schlaf-Wach-Regulation. Wir liefern erste Hinweise auf eine steigende und fallende Adenosinrezeptor-Verfügbarkeit in Übereinstimmung mit Wachheit und Schlaf im Menschen. Mit der zweiten Publikation zeigen wir zudem Erholungsprozesse zusätzlich zu jenen, welche durch die homöostatische Schlaf-Wach-Regulation vorhergesagt werden. Die dritte Publikation liefert Beweise für länger anhaltende Auswirkungen von chronischem Schlafentzug auf die Leistungsfähigkeit. Unsere Ergebnisse heben die Wichtigkeit adäquater Schlaf- und Erholungsphasen hervor. Insbesondere das komplexe Zusammenspiel von inter-individuellen Unterschieden zwischen der Schlaf-Wach-Regulation und der Kognition sowie der Gefahr unzureichender Erholung kognitiver Funktionen nach Erholungsschlaf bedarf weiterer Untersuchungen. Ein weitergehendes Verständnis der Mechanismen inter-individueller Unterschiede wird besonders für die Bereiche Personalauswahl und Entwicklung von Assistenzsystemen bedeutsam sein.

Die vorliegende kumulative Dissertation besteht aus zwei Teilen. Teil 1 beinhaltet die Synopse. Im ersten Kapitel wird der theoretische Hintergrund der Veröffentlichungen

erläutert und eine Einführung zu Schlaf, Kognition und den Auswirkungen von Schlafentzug auf die Kognition gegeben. Im zweiten Kapitel werden die in den zwei Laborstudien angewandten Methoden erklärt, auf denen die drei Veröffentlichungen basieren. Kapitel 3 gibt einen Überblick zu jeder einzelnen Veröffentlichung. Kapitel 4 bildet eine übergreifende, allgemeine Diskussion. Teil 2 der Dissertation besteht aus Referenzen der Originalarbeiten.

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I Part 1: Synopsis

1. Introduction

The curtailment of sleeping hours and resulting sleep deficits are common in our society. Reasons for sleep deficits are manifold, ranging from environmental factors (e.g. shift work, noise, heat) and psychosocial aspects (e.g. psychological stressors, 'social jetlag' (Wittmann et al., 2006) as deviation between biological and social time) to diseases (e.g. depression, pain). Sleep deficits are associated with adverse health status and cognitive impairments (Banks & Dinges, 2007; Breslau et al., 1996; D. Elmenhorst et al., 2009; Ford & Kamerow, 1989; Gregory et al., 2009; Hibi et al., 2017; Lo et al., 2012; Phillips et al., 2017; Spiegel et al., 2005).

In Germany, a survey among the working population in the year 2019 revealed that during the last month before the survey, 18.1 % of the respondents worked in evening hours and 4.9 % worked night shifts on a regular basis (Statistisches Bundesamt, 2019). Shift workers are especially prone to sleep deficits due to irregular sleep-wake schedules and circadian misalignment which imply shorter, lighter and more disturbed sleep. Performance impairments due to sleepiness increase the risk of errors and accidents with possible fatal consequences given the high responsibilities of professions involved in shift work as for example medical professionals, truck drivers or pilots.

Investigations of sleep on the International Space Station (ISS) showed that sleep in space is shortened and disturbed. The average sleep duration in space during circadian alignment was reported to be 6.4 hours and during circadian misalignment 5.4 hours (Flynn-Evans et al., 2016). Sleep disturbances were reported to be a major reason for medication use in space (Barger et al., 2014). Taking sleep medication poses a great risk in case of emergency situations, as this medication is sleep inducing and therewith performance impairing and cannot be counteracted quickly.

Obviously, several factors can be influenced to ameliorate sleep quality and quantity. Especially, shift work has the potential to benefit from research guided suggestions for

improvement. Next to changes in sleep hygiene, health and safety could be advanced by improved knowledge about the neuromolecular basis of sleep-wake regulation, inter-individual differences in the sleep loss response and different vulnerabilities of cognitive domains. The dissertation project aimed at contributing to the understanding of the before mentioned factors.

The following sections of the introduction give an overview on the theoretical framework of the two research projects which provide the basis for the three publications.

1.1 Sleep

Humans still today sleep approximately one third of their lives despite the endeavor of enhancing efficacy in our society. This emphasizes the important function of sleep even though the question why we sleep is not completely understood. Sleep has been for example suggested to be involved in nervous system recuperation (Brown et al., 2012), especially in the elimination of potentially toxic waste through the glymphatic system function (Jessen et al., 2015). Moreover, sleep has been associated with memory consolidation and emotional regulation (Brown et al., 2012). Associations between disturbed sleep and psychiatric (Krystal, 2012) or medical conditions (Watson et al., 2015) further support the important role of sleep. In addition, early studies in rodents showed that a lack of sleep can lead to death (Everson et al., 1989).

1.1.1 Sleep architecture

Sleep can be measured by actigraphy or polysomnography, whereby the latter is the gold standard due to a higher degree of accuracy. For detailed information on polysomnography please see section 2.2.

Wakefulness is reflected in high-frequency, low-voltage electroencephalography (EEG)-waves and high muscle tone. Sleep in general is characterized by higher amplitude and lower frequencies of EEG-waves and decreased muscle tone (Brown et al., 2012). Human sleep consists of non-rapid eye movement (NREM) and rapid eye movement sleep (REM). Different functional roles of these two sleep states have been suggested and supported by differential brain area involvement (Brown et al., 2012). NREM sleep is, inter alia, generated by the forebrain and has been suggested to be involved in brain energy conservation and memory consolidation. REM sleep is initiated by the brainstem and has been associated with the regulation of emotions (Brown et al., 2012). According to the American Academy of Sleep Medicine (AASM), sleep is divided into four stages (Iber et al., 2007). NREM sleep is subdivided into sleep stages N1, N2, and N3. REM sleep constitutes a sleep stage itself.

As described by Carskadon and Dement (2000), human sleep consists of several sleep cycles with a duration of each around 90 to 110 minutes. During a sleep cycle, sleep progresses from light sleep to deep sleep (N1, N2, N3) and at the end of a sleep cycle REM sleep. During the beginning of a night, N3 sleep prevails, whereas during the end of a night, REM sleep is predominant.

For adults, a regular sleep duration of at least seven hours has been advised to maintain health (Hirshkowitz et al., 2015; Watson et al., 2015). However, the habitual and optimal sleep duration varies between individuals (Kitamura et al., 2016). Within individuals, sleep characteristics are highly stable and genetically determined as shown by twin studies (De Gennaro et al., 2008; Linkowski et al., 1989).

1.1.2 Sleep-wake regulation

The two process model of sleep regulation (Borbély, 1982) is the most influential model in sleep research to explain the regulation of sleep and wakefulness. As depicted in Figure 1, it suggests the existence of a circadian process (process C) and a sleep-dependent, homeostatic process (process S). The interplay of both processes accounts for the timing of wakefulness and sleep as well as the depth and duration of the latter.

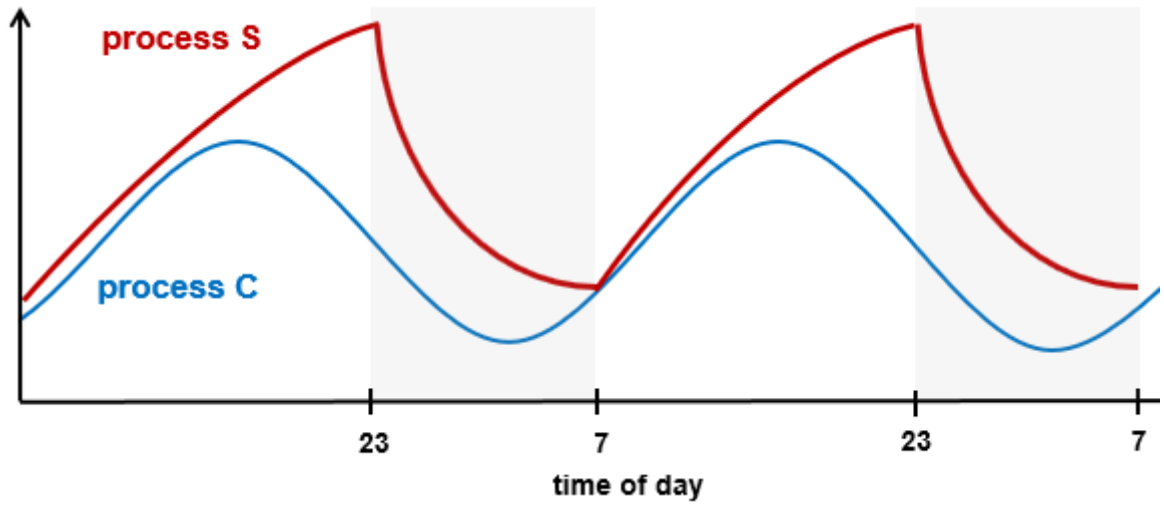

Figure 1: Two process model of sleep regulation according to Borbély (1982). The timing of sleep and wakefulness is determined by the interplay of 1) a homeostatic process (process S), here depicted in red, and 2) a circadian process (process C), here depicted in blue. Please note that the figure is only schematic for an explanatory purpose. It is not based on calculations.

The circadian process is an internal rhythm of approximately 24 hours ("circadian" means approximately a day, as deduced from the words "circa" and "diem"). It alternates periods of high (night) and low (day) sleep propensity. The circadian regulation is based on the biological clock in the suprachiasmatic nucleus of the hypothalamus (Dijk & von Schantz, 2005; Edgar et al., 1993). The power of the circadian system is impressive. Experiments showed that without time cues, participants sleep phase and duration occurred in line with their circadian phase (Czeisler et al., 1980).

The homeostatic process increases deep sleep propensity as a function of time spent awake. Slow wave activity (SWA; power density in the 0.75 – 4.5 Hz range), has been

suggested as a marker for homeostatic sleep drive. During undisturbed sleep, there is an exponential discharge of SWA (Borbély, 1982; Daan et al., 1984; Dijk et al., 1990). Homeostatic regulation is furthermore associated with the accumulation and depletion of adenosine (Basheer et al., 2004; D. Elmenhorst et al., 2007; Landolt, 2008; Porkka-Heiskanen et al., 2000). The important function of deep sleep is supported by findings of a deep sleep rebound in response to previous deep sleep deprivation (Ferrara et al., 1999).

Despite this theoretical framework, the exact sleep-wake regulatory mechanisms are not yet completely understood. Several investigations presented results that are not in accordance with model predictions. As such, sleep deprivation experiments showed increased SWA levels even in a second recovery night (Carskadon & Dement, 1985) or longer lasting performance decrements after chronic sleep deprivation (Cohen et al., 2010). Interestingly, there also seems to be a chronic sleep regulatory response across several nights. E.-M. Elmenhorst et al. (2008) showed an increase in sleep intensity across nights of chronic sleep deprivation.

1.1.3 Sleep and adenosine

Adenosine is an important endogenous neuromodulator. It results as a break-down product of the energy supplying adenosine triphosphate. Therefore, adenosine accumulates in active cells. Extracellular adenosine binds to adenosine receptors. Four receptor subtypes (A1, A2A and A2B as well as A3 receptors) have been identified which are implicated in diverse bodily functions (van Calker et al., 1978, 2019). The receptors are found in the body, for example in the heart and kidneys, and in the brain. In the following, the focus is on the A1 subtype, the subtype with the highest distribution in the central nervous system. In the brain, adenosine inhibits via A1AR the release of several neurotransmitters as glutamate, dopamine or serotonin, and neuronal signaling (van Calker et al., 2019). Regarding sleep-wake regulation, adenosine is associated with the homeostatic process (Borbély, 1982; D.

Elmenhorst et al., 2007; Porkka-Heiskanen et al., 2000). Extracellular adenosine in several brain areas was reported to increase during wakefulness and decrease during sleep in cats and rats (Porkka-Heiskanen et al., 2000). These effects on sleep-wake regulation could further be experimentally supported by the administration of A1AR agonists and antagonists in cats and rodents (Benington et al., 1995; Schwierin et al., 1996). One prominent antagonist of adenosine is caffeine. Caffeine acts on adenosine receptors to promote wakefulness. Inter-individual differences in caffeine effects on sleep were linked to a genetic variation in the adenosine receptor gene (Byrne et al., 2012; Rétey et al., 2007). In humans, adenosine levels of healthy individuals cannot be measured directly. Via positron emission tomography (PET), A1AR availability can be quantified. Previously, A1AR was found to increase during wakefulness (D. Elmenhorst et al., 2007). It is suggested that during extended wakefulness A1AR availability is upregulated along with increasing endogenous adenosine levels. Adenosine and adenosine receptor density are promising targets to elucidate the relationship between sleep and performance as well as sleep and psychiatric disorders (van Calker et al., 2019; Wolf et al., 2016). Sleep deprivation is for example known as an effective but short-lasting therapy for major depression although the exact involvement of the adenosine system is still under investigation (Hemmeter et al., 2010).

1.2 Cognitive functions

Diverse attentional and memory processes as well as executive functions are essential for survival and good cognitive performance. This is reasonable not only from an evolutionary perspective but also today when considering the effect of a lapse of attention during car driving or the inability to manage independent living with progressing memory deterioration in neurodegenerative diseases.

The initially mentioned domains of cognitive functions entail further subdomains. The relevant ones for this thesis are briefly outlined in the following sections. Although the description of all cognitive subdomains goes beyond the scope of this work, it is worth noting that it is hardly possible to record a "pure" measure of only one cognitive process.

1.2.1 Sustained attention

Sustained attention describes the continuous focusing of attention over an extended period of time (Chun et al., 2011; Rosenberg et al., 2016). It is an important form of attention which requires top-down control because of the conscious, endogenous selection of the attentional focus. The terms "sustained attention" and "vigilance" are often used interchangeably, although "vigilance" has different definitions depending on the discipline (Oken et al., 2006).

Attentional capacity in general, and also the capacity of sustained attention, is limited. Declining sustained attention performance as a function of time was described as "vigilance decrement" or "time-on-task effect" (J. F. Mackworth, 1964; N. H. Mackworth, 1948). Recuperation from the time-on-task effect is possible through task switching or breaks (Bergum & Lehr, 1962; Komaki, 1967).

Frontal and parietal cortex activation mainly in the right hemisphere have been associated with sustained attention performance (Sarter et al., 2001).

1.2.2 Working memory

Working memory enables short-term storage of information to carry out an action or a plan e.g. keeping numbers in mind for a calculation (Cowan, 2008). An influential theory about working memory was proposed by Baddeley and Hitch (1974). They proposed a multi-component model of working memory. The "central executive" exhibits control over two subsystems, the phonological loop and the visuo-spatial sketchpad. These subsystems serve as short-term storage with limited capacity.

The phonological loop is proposed to store speech-based information. Experiments support the existence of such a storage system. In healthy adults, about 7 words can be stored in the phonological loop (Yu et al., 1985). However, the exact span depends on the duration to pronounce words, known as the word-length effect (Ellis & Hennelly, 1980). To hold information on the phonological loop, it has to be repeated, otherwise the information fades quickly. The visuospatial sketchpad is suggested to hold visual information for a limited amount of time. A further component of the working memory model was added by Baddeley in 2010 (Baddeley, 2010). The episodic buffer was proposed to link the subsystems as well as information from working and long-term memory. Research supported the existence of the separate subsystems for example by demonstrating the lateralization of brain activity in phonological and visuospatial working memory tasks (Smith et al., 1996). Verbal working memory was shown to depend mainly on the left hemisphere whereas spatial working memory was shown to depend mainly on the right hemisphere.

1.2.3. Declarative memory

Declarative memory, together with non-declarative memory (priming, conditioning, procedures), built long-term memory (Cowan, 2008; Squire & Zola, 1996). Long-term memory constitutes information that is stored and that can be retrieved over an extended period of time.

Declarative memories, also referred to as explicit memories, are memories of facts and episodes. Three important steps in memory formation have to be considered. Memory encoding describes the acquisition of new information (Baddeley et al., 2009). Memory consolidation is the strengthening of the acquired information and research supports an important function of sleep for memory consolidation (Gais et al., 2006; Plihal & Born, 1997). Retrieval describes the recovery of this encoded information. Declarative memories have been linked to hippocampus and to temporal and frontal lobes (Squire & Zola, 1996; Weis et al., 2004).

A prerequisite to encoding is the attention to the relevant information. In neuropsychological practice, for example many patients go to an examination reporting that they have memory problems. However, when they are examined, they in fact often have attention deficits, and not memory deficits.

1.3 Sleep deprivation and cognition

In research, sleep deprivation is applied as a method to investigate functions of sleep and the regulation of sleep and wakefulness. Two forms of sleep deprivation are distinguished. Acute sleep deprivation typically describes prolonged wakefulness for one to three nights. Chronic sleep deprivation (sometimes also called chronic sleep restriction or chronic partial sleep deprivation) describes chronically shortened sleep periods over several nights. Acute sleep deprivation experiments were merely the focus of early studies. In contrast, less research was initially conducted on the topic of chronic sleep deprivation possibly due to the costly and elaborative study conduct.

1.3.1. Acute sleep deprivation

Sleep loss induced performance impairments are well documented. Performance over time is influenced by circadian rhythmicity and a homeostatic process. At least regarding sustained attention performance, an additional process accounting for a performance

decrement over time on a task was found (Basner et al., 2008; Van Dongen et al., 2011b; Van Dongen & Dinges, 2005). Another important general remark is the finding of great inter-individual differences in the vulnerability to performance impairments due to sleep loss (E.-M. Elmenhorst et al., 2018; Leproult et al., 2003; Van Dongen et al., 2004, 2005; Wilkinson, 1961). A twin study suggests underlying genetic influences (Kuna et al., 2012). Variants of clock genes and genetics underlying adenosinergic mechanisms have been associated with differential vulnerabilities to sleep loss (Bachmann et al., 2012; Pellegrino et al., 2014; Viola et al., 2007).

Regarding sleep loss effects, the most thoroughly investigated cognitive function is sustained attention. Sustained attention is very sensitive to sleep deprivation. Experiments on the temporal dynamics of sustained attention performance showed its accordance with predicted sleep drive of the two process model. As such, performance is most affected during the early and late morning following sleep deprivation. Later during the day, as sleep drive by process C is reduced, performance is partially recovered despite even prolonged wakefulness by that time (Hudson et al., 2020). Sustained attention performance is not only analyzed in terms of mean or median reaction times, but also regarding the occurrence of lapses of attention. The “lapse hypothesis” poses that brief moments of reduced arousal occur during sleep deprivation, causing deficits in timely task response (Williams et al., 1959). To additionally account for progressively more variable performance during sleep deprivation, the framework of the “state-instability hypothesis” as instability between sleep and wakefulness (Doran et al., 2001; Phillips & Robinson 2007) was proposed. A further observation was that the time-on-task effect shows an amplification during sleep deprivation (Doran et al., 2001; Van Dongen et al., 2011a; Wesensten et al., 2004).

In contrast to agreement of sleep loss effects on sustained attention, there has been some debate about the sleep loss effects on other cognitive domains (Lim & Dinges, 2010; Lo et al., 2012; Tucker et al., 2010). Findings of impaired executive functioning exist although

decrements were reported to be smaller compared to those of sustained attention (Lo et al., 2012). Furthermore, discrepancies between self-rated sleepiness and objective performance measures have been found which point at a subjective underestimation of sleep loss effects (Van Dongen et al., 2003, 2004).

Several theories try to explain the mechanisms underlying neurobehavioral performance under sleep loss. The theories should not be regarded as mutually exclusive. The "vigilance hypothesis" states that attentional processes are impaired by sleep deprivation but that they are a basis to higher order cognitive functions (Lim & Dinges, 2010). The "controlled attention hypothesis" posits that top-down control is compromised by sleep deprivation and needed in monotonous tasks. Engaging aspects of executive tasks may counteract this effect (Lim & Dinges, 2010; Pilcher et al., 2007). The "neuropsychological hypothesis" proposes that especially cognitive domains with a high dependence on the prefrontal cortex are affected by sleep deprivation (Harrison et al., 2000; Lim & Dinges, 2010). The "local sleep theory" supposes the possibility of use-dependent, local sleep in cortical columns (Krueger et al., 2008), accounting for the inconsistent sleep loss effects across cognitive tasks. Local changes in cells prior to lapses were documented which support this hypothesis (Nir et al., 2017).

Imaging studies shed light on brain activation underlying attentional performance under acute sleep deprivation. Reduced activation in fronto-parietal attention networks and in the salience network (medial frontal cortex and insula) was shown during sleep deprivation (Ma et al., 2015).

1.3.2. Chronic sleep deprivation

In accordance with neurobehavioral effects of acute sleep deprivation, differences in cognitive domains and between individuals have also been shown concerning chronic sleep deprivation (E.-M. Elmenhorst et al., 2018; Goel et al., 2009; Lo et al., 2012; Van Dongen et al., 2003). However, despite the high relevance of chronic sleep deprivation in our society, its sleep-wake regulatory mechanisms are currently not completely understood. Although the neurobehavioral dynamics of acute sleep deprivation fit with the two process model of sleep-wake regulation, limits with regard to practical implications concerning the dynamics during sleep restriction have been found (McCauley et al., 2009; Van Dongen, 2004). Most of all, long lasting effects of sleep restriction on neurobehavioral variables have been detected (Banks et al., 2010; Cohen et al., 2010; Dinges et al., 1997; E.-M. Elmenhorst et al., 2018). In a seminal work by Van Dongen et al. (2003), participants were exposed to 4, 6 or 8 hours of nightly sleep opportunity for 14 consecutive nights or three nights of acute total sleep deprivation. Sustained attention (psychomotor vigilance task), working memory performance (digit-symbol substitution task), cognitive throughput (serial addition/subtraction task) and self-rated sleepiness were assessed. The authors report cumulative and dose-dependent cognitive performance deficits due to sleep restriction (4 hours or 6 hours). Self-rated sleepiness revealed that chronically sleep-restricted individuals were largely unaware of cognitive sleep deprivation effects. Furthermore, performance deficits between individuals exposed to chronic sleep restriction of 4 and 6 hours were comparable to those of individuals with two nights without sleep. Recovery from chronic sleep loss became another topic of interest (Banks et al., 2010). Rupp et al. (2009) showed an association between nightly sleep duration prior to sleep restriction nights and performance impairment during sleep restriction and rate of recovery. Another investigation revealed that neurobehavioral deficits due to sleep restriction to 4 hours for 5 consecutive nights cannot be completely recovered during a 10 hours TIB recovery sleep opportunity (Banks et al., 2010). An important contribution to this

topic was also made by Cohen et al. (2010). With a forced desynchrony protocol they exposed participants to chronic sleep deprivation. After recovery sleep, performance seemed restored within the first hours after awakening but performance decreased at a faster rate with ongoing time awake. The authors suggest that chronic sleep restriction induces long-term neuromolecular changes in brain physiology which might be an increase of adenosine receptor density. Thus, important evidence exists that chronic sleep deficits accumulate over time (Belenky et al., 2003; Dinges et al., 1997) causing neurocognitive impairments comparable to acute sleep deprivation (Van Dongen et al., 2003). Recovery sleep did not always reset the functions (Banks et al., 2010). More importantly, studies showed that cognitive performance was initially recovered but thereafter deteriorated at a faster rate (Cohen et al., 2010). Furthermore, individuals are largely unaware of those neurocognitive consequences, thus underestimating sleepiness (Van Dongen et al., 2003).

On the molecular level, mechanisms explaining those longer-term effects of sleep restriction are still largely unexplored. Evidence for A1AR density upregulation in the rat brain has been reported by Kim et al. (2015). Based on these observations, the existence of a second homeostatic process was proposed (Cohen et al., 2010). On the one hand, the well-documented homeostatic process S seems to react to acute sleep deprivation on short-term basis. On the other hand, another homeostatic process is proposed by Cohen et al. (2010) reacting on chronically restricted sleep on a long-term basis.

2. Methods

2.1 Preparation and methodological basis for the conduct of laboratory sleep research

Well-controlled laboratory sleep studies need diligent preparation. Our approach is detailed (see also Figure 2) in the following. First of all, for each study, a proposal for ethical approval was written and submitted to the appropriate ethical committee. Concerning the first project, ethical approval was received from the University of Düsseldorf, concerning the second project, ethical approval was received from the Medical Board of North Rhine. Approval for the conduct of PET-measurements was received from the German federal office for radiation protection. Laboratories, necessary equipment and instruments were provided by our institute.

For participant recruitment, study participation was advertised on the internet and via flyers. Additionally, individuals from an internal data base were requested to participate. Participant selection is a crucial process in identifying relevant participants and in ensuring participant safety. For participant selection, firstly, interested candidates were screened with a pre-selection questionnaire. Individuals who passed this first step were further screened with questionnaires and a medical examination to meet the study requirements.

Several criteria had to be fulfilled as a prerequisite for inclusion in the sample. Concerning PET measurement, participants were screened to meet the following criteria: 1) 1st PET study, 2) no work exposure to radiation, 3) no metal in the body, 4) no tattoos on the body part used in the measurement, 5) no extensive metal grinding work in the last month, 6) no pregnancy, 7) no claustrophobia. Additional requirements were requested to exclude confounding variables in the sleep measurement. Therefore, participants were screened to meet the following requirements: 1) healthy, 2) sleep timing and duration according to the study requirements, 3) no regular shift work, 4) meeting the study defined age-range, 5) non-

smokers, 6) no individuals without legal capacity or people in custody, 7) no other reasons for exclusion from the experiment detected by the medical doctors e.g. non-compliance.

Time slots were arranged for suited individuals and informed consent was signed prior to participation. Individuals received financial compensation for participation. Prior to the start of the experiment, the laboratories were prepared, shift working schedules were set up and staff were instructed and trained.

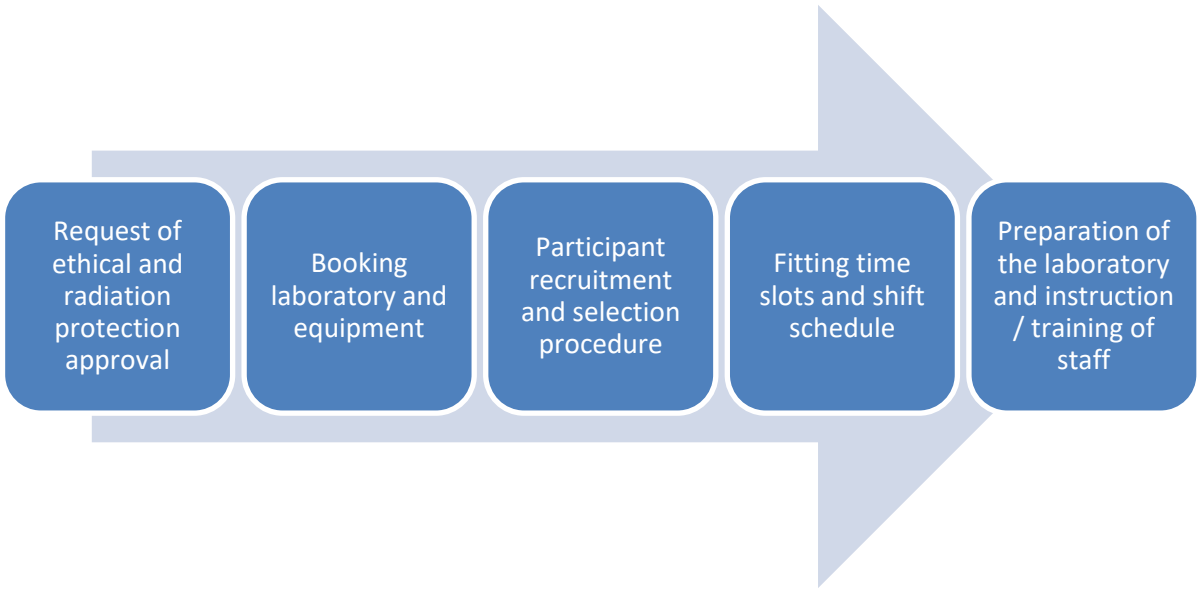

Figure 2: Steps of the study preparation.

Prior to the laboratory stay, participants adhered to a regular sleep-wake routine which was checked by using a sleep protocol and actimetry. Furthermore, individuals had to abstain from alcohol and caffeine prior to and during the laboratory stay.

During the study, participants were only allowed to do non-vigorous activities. They were under constant supervision to check adherence to the rules and help them to stay awake. During sleep and neuropsychological testing sessions, participants were in single, quiet rooms.

An important topic in general when conducting sleep research is the exclusion of the first night from analyses. Previous research showed that sleep during the first night in a new

environment is altered, consisting of reduced or disrupted REM sleep and arousals (Agnew et al., 1966). Because of this so called “first night effect”, the first night should not be considered for analysis in controlled experimental settings. For the exact study designs of the projects please see section 3 and original publications.

2.2 Polysomnography

Polysomnography is the gold standard for the measurement of sleep. Polysomnography consists of EEG (measurement of the electrical field activity of large groups of cortical cells), electromyography (EMG; assessing muscle activity), electrooculography (EOG; recording eye movements) and electrocardiography (ECG; measuring heart rate). Different electrical activation levels from the signals enable differentiating sleep and wake states (Iber et al., 2007).

Polysomnography is usually performed in a sleep laboratory. But equipment for sleep measurements in the field is also available.

In our studies, we prepared the skin for electrode attachment by cleaning it from fat with alcohol and roughened it with a special paste to ensure good signal conductance. We then attached EEG electrodes according to the international 10-20 system (Jasper, 1958). This system is applied to describe the standardized location of scalp electrode attachment. It accounts for individual head shape and size through calculation of distances between electrodes as percentages. Ear electrodes (A1/A2) were used as references for the contralateral scalp electrodes. In our experiments we attached electrodes frontally (F3/F4), centrally (C3/C4), and occipitally (O2/O1). In the first night we additionally screened for sleep disorders through the application of additional sensors.

The EEG signal was amplified (time constant: 2.3 sec) and low-pass filtered (70 Hz). Sampling rate was at 256 Hz. Sleep data were scored according to AASM criteria (Iber et al., 2007).

2.3 Positron Emission Tomography

PET is an imaging method that uses radioactive tracers to visualize metabolic functioning or neurochemical distributions in three-dimensional space. For imaging, a radioactive marker is injected, and emitted gamma rays in the body are subsequently detected. The results presented in publication 1 are based on PET-measurements. The radiotracer [^{18}F]CPFPX was used. It is a Fluor-18 radioactively marked version of the ligand 8-Cyclopentyl-1-propyl-3-(3-fluoropropyl)-Xanthin (Bauer, Holschbach, Cremer, et al., 2003; Holschbach et al., 1998). The neuroligand binds subtype-specifically to A1AR in the central nervous system. [^{18}F]CPFPX was produced in the institute for neuroscience and medicine (INM-5) of the Forschungszentrum Jülich. This institute is experienced with this ligand (Bauer et al., 2005; Bauer, Holschbach, Cremer, et al., 2003; Bauer, Holschbach, Meyer, et al., 2003; Boy et al., 2008; D. Elmenhorst et al., 2007, 2012, 2014; Hohoff et al., 2014; Meyer et al., 2004, 2007).

The neuroligand was injected via a bolus and thereafter constant infusion. The scan duration was 100 minutes.

2.4. Neuropsychological testing

Concerning the first project, a test battery was performed every 6 hours during wakefulness. In the second project, testing took place every 3 hours during wakefulness. In the beginning of the laboratory stay, participants were briefed on the conduct of the test battery by an experienced experimenter. During the tests, participants were monitored live (first project) or via a camera (second project). To exclude practice effects, participants performed a series of test sessions at the beginning of their stay, which were not included in the analysis.

2.4.1 Psychomotor vigilance task

The measurement of sustained attention with the psychomotor vigilance task (PVT; Dinges & Powell 1985) is the gold standard in sleep research. The PVT is a reaction time task with a high stimulus load, whereby the stimuli appear randomly according to varying inter-stimulus intervals. The PVT can be easily and frequently administered. It is free from practice effects (Basner et al., 2018). In the first project, a 3-minute version on a handheld computer, validated by E.-M. Elmenhorst et al. (2013), was applied (see Figure 3). In this version, the trigger to react is a lighting up of a battery lamp.

Figure 3: Psychomotor vigilance task. Participants had to respond to the lighting up of a battery lamp as fast as possible.

2.4.2 N-back task

We applied two versions of a N-back task (Gevins & Cutillo, 1993) for the assessment of working memory performance. The N-back task consisted of a spatial and a letter version (see Figure 4). In both versions, the stimuli (a dot in one out of nine positions in the spatial version; the letter B, C, D, F, G, H, J, K or M in the letter version) appeared consecutively and randomly.

Stimulus presentation was 500 ms, the inter-stimulus interval was 1500 ms. Both versions consisted of three separate trial blocks (1-back, 2-back and 3-back) which varied in task load. Per trial block, 60 stimuli were presented, of which one third were hit targets.

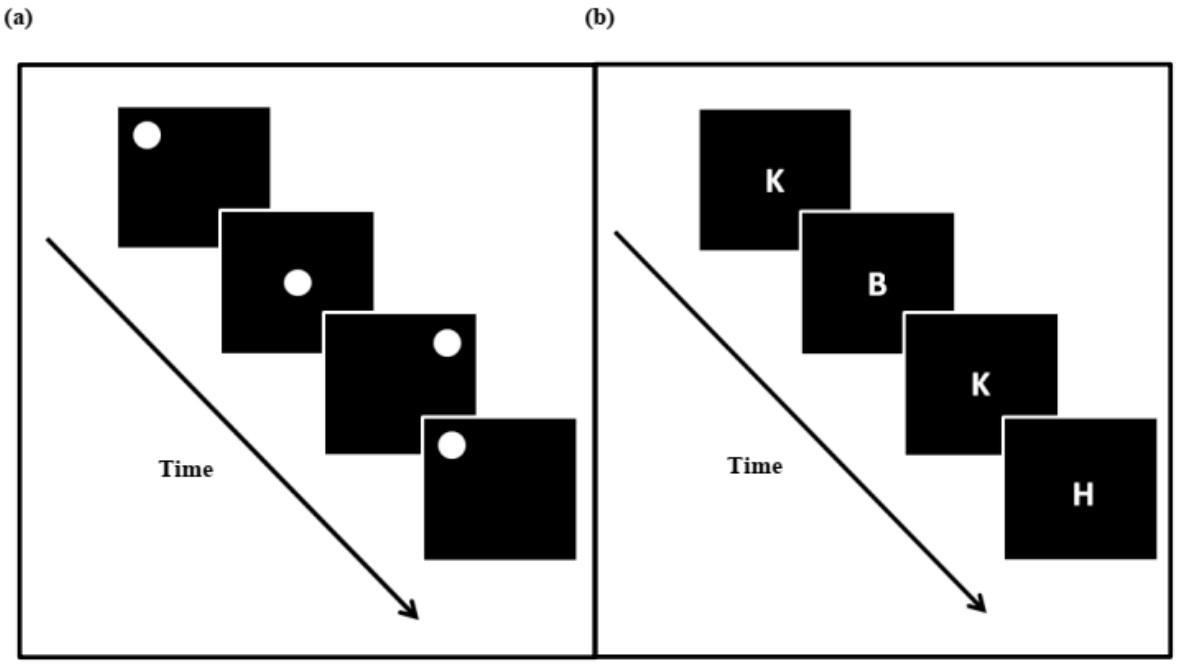

Figure 4: N-back task. During the spatial version (a), a dot appeared in one of nine positions. Participants were instructed to indicate whether the current stimulus matches the position of the dot n steps earlier. As an example, a 3-back match is shown (dot in the upper left corner matches with screen three steps back). The letter version (b) required the participants to indicate whether the current letter matches that of n steps earlier. A 2-back match is shown regarding the letter “K”.

The two versions of the N-back task account for the separate subsystems of working memory proposed by Baddeley and Hitch (1974). Accordingly, spatial N-back is thought to depend on the visuo-spatial sketchpad whereas verbal N-back is thought to depend on the phonological loop. Although letters in the verbal N-back are presented visually, it is most likely that participants remembered them by verbally repeating the letters rather than by visually representing them.

2.4.3 Word-pair test

To test overnight declarative memory recall, an adapted version of the paired-associate list task (Plihal & Born, 1997) was applied in the project Somnosafe, on which the third publication is based. Every evening, one hour prior to bedtime, in the case of acute sleep deprivation at baseline time, 32 new, semantically related German word pairs were presented successively. Each word pairs appeared for 5 seconds. Subsequently, participants had to recall words in a cued recall procedure without time pressure, i.e., one word was shown and the other had to be recalled and entered in the notebook computer. A success rate of at least 60 % had to be reached to ensure encoding. Otherwise, the learning phase was repeated (for an overview of the test procedure see Figure 5).

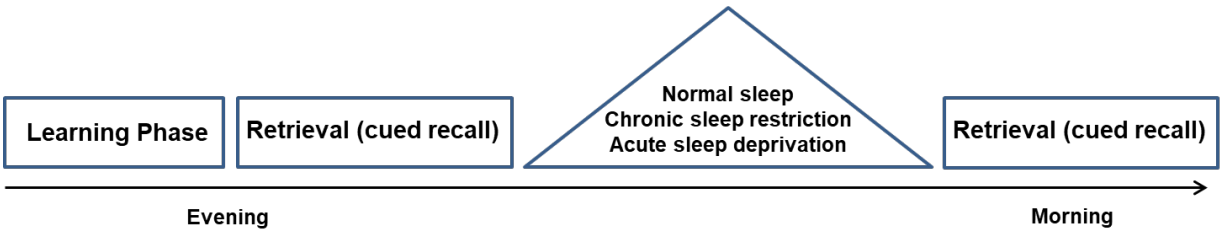

Figure 5: Overview of the test procedure of the word-pair test. The evening session consisted of a learning phase and a subsequent retrieval in a cued recall procedure. To ensure encoding, the session was repeated in cases of a retrieval of less than 60%. In the morning, word recall was assessed again in a cued recall retrieval phase. The test was performed throughout the experiment, thus under conditions of normal sleep, sleep restriction and acute sleep deprivation.

The sequence of stimuli was randomized for participants and repeated trials. To prevent primacy and recency effects, the first and last four words were excluded from analyses. In the mornings, recall performance was assessed in a cued recall procedure without time pressure.

2.5 Data preparation and analyses

Detailed descriptions of the data preparation and analyses can be found in the respective publications and the supporting information of the publications.

Concerning publication 3, some additional information is presented here. We tested for influences of age and gender on neurobehavioral results. However, the respective variables included in the mixed models for repeated measures were not significant. Furthermore, in parallel to publication 1, we were interested in possible inter-individual differences on neurobehavioral outcomes. Therefore, we correlated the individual chronic sleep loss response with the individual acute sleep loss response. However, we did not detect a significant association.

3. Overview of the publications

The effect of chronic and acute sleep deprivation on sleep-wake regulation and cognition was investigated in this thesis. The Institute of Aerospace Medicine of the German Aerospace Center focuses on health and performance in aviation, space, and on earth. The department of Sleep and Human Factors Research investigates research questions concerning the regulation of sleep and wakefulness and its relation to cognition and health. Other subjects of the department are noise effects research, baromedicine and digital health. The first two publications are based on the project “Schlafstudie 5” (SC-5). The third publication is based on the project “SomnoSafe”. Both were cooperation projects of the Forschungszentrum Jülich, Institute of Neuroscience and Medicine (INM-2) and the Department of Sleep and Human Factors Research of the German Aerospace Center. Figure 6 illustrates the topical relations between the respective publications.

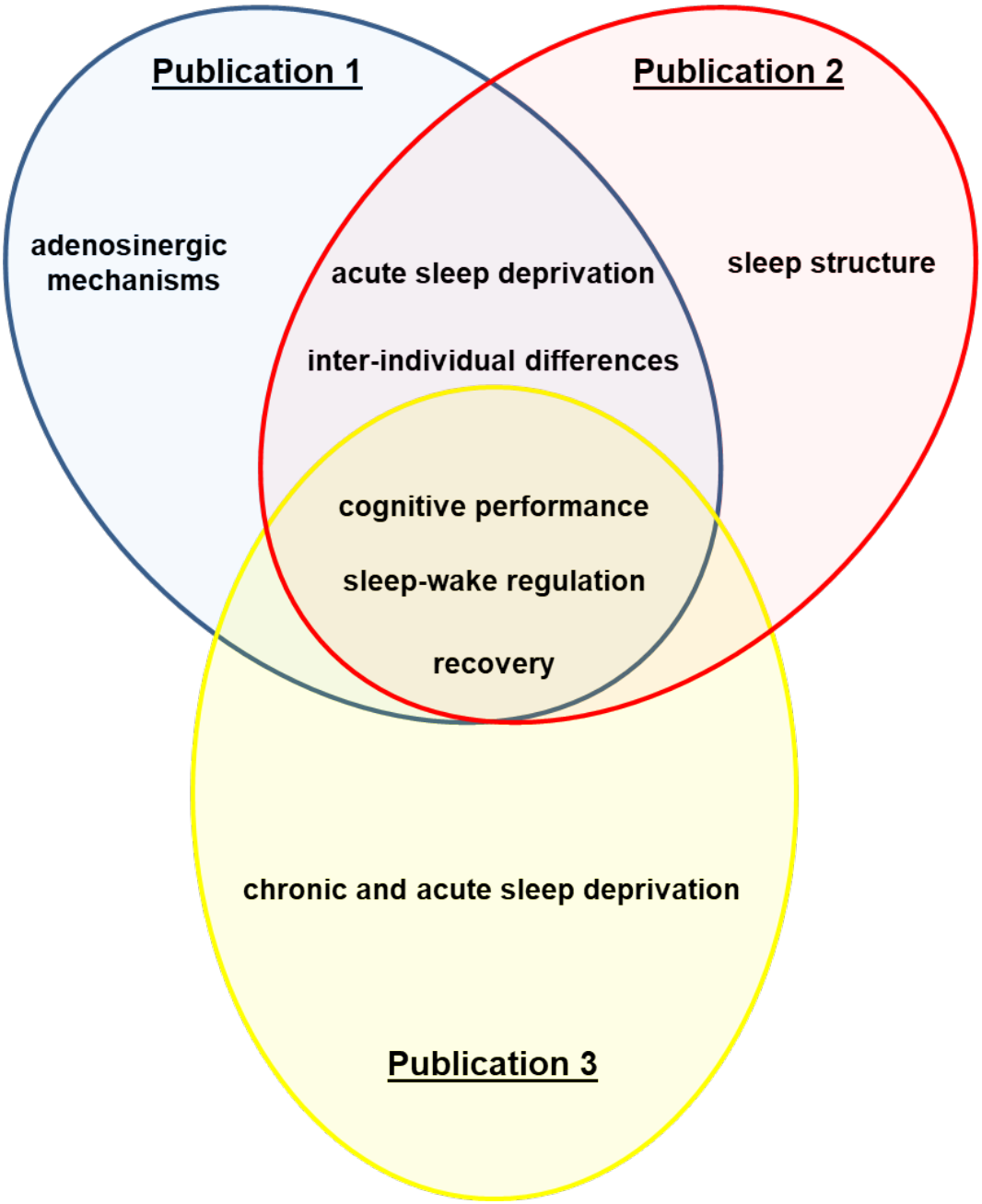

Figure 6: Overview of topical overlap of the three publications. All three publications focus on sleep-wake regulation, cognition and recovery from sleep loss effects. Publication 1 and 2 are additionally concerned with effects of acute sleep deprivation and inter-individual differences in the sleep loss response. The publications diverge by their main focus on adenosinergic mechanisms (publication 1 only), sleep structure (publication 2 only) and the assessment of combined effects of chronic and acute sleep deprivation (publication 3 only).

3.1 Overview publication 1 'Recovery sleep after extended wakefulness restores elevated A1 adenosine receptor availability in the human brain'

Elmenhorst, D., Elmenhorst, E.-M., Hennecke, E., Kroll, T., Matusch, A., Aeschbach, D., Bauer, A. (2017). Recovery sleep after extended wakefulness restores elevated A1 adenosine receptor availability in the human brain. Proceedings of the National Academy of Sciences, 114 (16) 4243-4248. https://doi.org/10.1073/pnas.1614677114. Epub 2017 Apr 3.

Adenosine has been proposed as a key component of the homeostatic sleep-wake regulation. Studies in rodents and cats showed that endogenous adenosine and A1AR availability increase during wakefulness and decrease during sleep (Porkka-Heiskanen et al., 2000). D. Elmenhorst et al. (2007) support the role of adenosine also for human sleep-wake regulation. In their experiment, human participants were exposed to one night of sleep deprivation and A1AR availability was quantified. The authors found an upregulation of A1AR after 24 h of wakefulness.

A question that has not yet been investigated is whether adenosine levels saturate during prolonged wakefulness and decrease to well-rested levels after recovery sleep in accordance with predictions of sleep pressure based on the two process model (Borbély, 1982). Therefore, the SC-5 project aimed at investigating A1AR availability after prolonged wakefulness as well as after recovery sleep. We hypothesized a decrease of A1AR to well-rested levels after recovery sleep from extended wakefulness. Furthermore, we aimed at investigating the contribution of the adenosinergic system to inter-individual performance differences in response to sleep loss.

Fourteen men (mean age 27.7 ± 5.4 years) were included in the analyses. After an adaptation and a baseline night (TIB: 23:00 – 7:00 hours), they were exposed to 58 hours of sleep deprivation and had a 14-h recovery sleep opportunity (TIB: 17:00 – 7:00 hours). After 52 hours of wakefulness and after 14 hours of recovery sleep, [^{18}F]CPFPX positron emission tomography was applied to quantify A1AR availability. As the number of possible scans was limited due to radiation protection, rested baseline data for A1AR availability after 8 hours of

sleep were obtained from an independent sample and compared to the before mentioned data. Furthermore, a cognitive test battery was performed every 6 hours during wakefulness, consisting of a PVT and an N-back task.

Compared to A1AR availability after 52 hours of wakefulness, our results showed a reduction in A1AR availability after recovery sleep, ranging from 11 % (insula) to 14 % (striatum). After recovery sleep from extended wakefulness, A1AR availability was reduced to baseline levels. The association of A1AR availability with neurobehavioral performance outcomes showed counterintuitive results. Individuals with a high increase of A1AR availability during prolonged wakefulness were more resilient to the sleep loss effects on performance than individuals with only a slight increase. Although the exact mechanism underlying these observations in unknown, we speculated that in both vulnerable as well as less vulnerable individuals, A1AR were upregulated in response to sleep loss. However, we suggested that in contrast to the less vulnerable individuals, this upregulation was accompanied by a substantial increase in endogenous adenosine levels in vulnerable individuals. In turn, increased receptor activation might have led to the performance impairing effects.

We concluded that A1AR is upregulated during prolonged wakefulness and decreased to baseline levels after recovery sleep. We proposed that adenosinergic mechanisms contribute to inter-individual differences in the sleep-loss response. With regard to work and organizational settings, understanding of these mechanisms have the potential to enhance safety by identifying and protecting individuals with a high vulnerability to sleep loss effects on performance. With regard to clinical implications, the understanding of individual adenosinergic mechanisms might enhance therapeutic strategies for the treatment of depression. Given the well-established but short-lasting effect of acute sleep deprivation in major depression, possible mechanisms during chronic sleep restriction might be a future therapeutic target.

3.2 Overview publication 2 ‘Reestablishment of individual sleep structure during a single 14-h recovery sleep episode after 58 h of wakefulness’

Hennecke, E., Elmenhorst, D., Mendolia, F., Putzke, M., Bauer, A., Aeschbach, D., Elmenhorst, E.-M. (2017). Reestablishment of individual sleep structure during a single 14-h recovery sleep episode after 58 h of wakefulness. Journal of Sleep Research, 28(3). https://doi.org/10.1111/jsr.12641. Epub 2017 Nov 24.

Sleep EEG characteristics across nights differ between individuals but show trait-like agreement within an individual (Buckelmüller et al., 2006). Recovery sleep after sleep deprivation shows alterations in the individual sleep structure. In accordance with the two process model of sleep regulation (Borbély, 1982), a compensatory response to sleep deprivation is reflected in increased sleep intensity rather than in sleep duration. The increased sleep intensity is apparent in increased proportions of deep sleep during the first hours after sleep onset.

An unanswered question was to what extend the individual sleep structure during baseline sleep correlates with the structure of extended recovery sleep after sleep loss. We therefore aimed at assessing the robustness and recovery processes of the individual sleep structure to extended total sleep deprivation.

Seventeen healthy men (mean age 27 years ± 5 years) were included in the analysis. They spent one adaptation and one baseline night in the laboratory (TIB: 23:00 – 7:00 hours). Thereafter, they were sleep deprived for 58 hours and had a 14-h recovery night (TIB: 17:00 – 7:00 hours). Participants performed a cognitive test battery (including a PVT) every 6 hours. Sleep was recorded with polysomnography (EEG: C4-A1, O2-A1, F4-A1; EOG; EMG; ECG) and scored according to AASM criteria (Iber et al., 2007). Sleep stage proportions between baseline night and the extended recovery night were compared with intraclass correlation coefficients (ICCs). In detail, the sleep stage proportions were calculated in hourly steps and compared between the two nights.

As expected, our results showed a state-like compensatory sleep loss response in the sleep structure during the first hours of recovery sleep. In line with the predictions of the two process model (Borbély, 1982), slow-wave activity reached a plateau level after approximately 10 hours of recovery sleep. In contrast, the ICC of sleep stage proportions increased thereafter with every hour of additional sleep, suggesting ongoing recovery processes independent of process S. By the end of the recovery night, ICCs for NREM sleep stages N1, N2, and N3 were at least .62, which accounts for substantial agreement (Landis & Koch, 1977). In contrast, the agreement of the REM sleep proportion with an ICC of .38 was much lower. In addition, morning PVT performance was recovered to baseline levels after the 14-h night.

Given that especially the homeostatic mechanisms and neuromolecular basis of REM sleep and REM sleep recovery are not completely understood (for review see Aeschbach, 2011), our findings provide further evidence for a homeostatic REM sleep response and the need for extended recovery periods beyond those needed for deep sleep recovery.

To conclude, we found state-like changes in sleep structure during the first hours of recovery sleep. Trait-like sleep characteristics became evident in the course of extended recovery sleep. With every additional hour of sleep, the interclass correlation coefficients suggested that sleep structure approximated that of the baseline night. After 14 hours of recovery sleep, individual sleep structure was reestablished. Our results emphasized the robustness of individual sleep structure and provided insights in the recovery processes after prolonged wakefulness.

3.3 Overview publication 3 ‘Adverse interaction effects of chronic and acute sleep deficits on spatial working memory but not on verbal working memory or declarative memory’

Hennecke, E., Lange, D., Steenbergen, F., Fronczek-Poncelet, J., Elmenhorst, D., Bauer, A., Aeschbach, D., Elmenhorst, E.-M. (2020). Adverse interaction effects of chronic and acute sleep deficits on spatial working memory but not on verbal working memory or declarative memory. Journal of Sleep Research. https://doi.org/10.1111/jsr.13225. Epub2020 Nov 09.

Chronic sleep deficits are common in our society and caused by diverse reasons. Shift work and associated sleep at adverse circadian times, which often results in increased noise and light exposure during sleep, is one major contributor. Sleep deficits pose a risk to work safety. This risk is augmented by the finding that subjective ratings and objective measurements of sleepiness often deviate in the direction of a subjective underestimation of sleepiness (Van Dongen et al., 2003). In shift work settings chronic sleep loss is often combined with periods of acute sleep loss.

Combinations of chronic and acute sleep deprivation have been rarely investigated despite their relevance in occupational settings. We therefore assessed possible interaction effects of chronic sleep restriction and acute sleep deprivation on human cognitive performance and recovery sleep. Thirty-six women and men participated and were randomly assigned to a control (N = 15; mean age 28 ± 6 years; 5 females) or chronic sleep restriction group (N = 21; mean age = 26 ± 4 years; 9 females). After an adaptation and two baseline nights (8 hours TIB: 23:00 – 7:00 or 24:00 – 8:00 hours), participants underwent 5 nights with 5 hours TIB (2:00 – 7:00 or 3:00 – 8:00 hours; chronic sleep restriction group) or normal sleep (8 hours TIB: 23:00 – 7:00 or 24:00 – 8:00 hours; control group). After one 8-h night (TIB: 23:00 – 7:00 or 24:00 – 8:00 hours) in both groups, all participants underwent acute sleep deprivation for 38 hours and a final 10-h recovery night (TIB: 21:00 – 7:00 or 22:00 – 8:00 hours). A cognitive test battery was performed every three hours during wakefulness. Among other tests, it included a spatial and verbal N-back task. For a detailed description of

the N-back task see section 2.4.2. Prior to bedtime and in the mornings, a word-pair test was administered (for a detailed description see section 2.4.3).

Data were analyzed with mixed models for repeated measures. Our results showed decreased spatial N-back performance during sleep restriction compared to baseline. Letter N-back and word-pair recall were not affected during chronic sleep restriction. During acute sleep deprivation, spatial N-back performance was more affected in the chronic sleep restriction than in the control group. No group differences appeared concerning letter N-back or word-pair recall.

In sum, our results provided evidence for interaction effects of chronic and acute sleep deprivation on spatial working memory performance. These effects appeared despite a recovery night between chronic and acute sleep loss. As performance was temporarily recovered after the recovery night from chronic sleep loss, individuals might get a false sense of recuperation but with further performance impairments during the additional sleep loss. Our results supported and complemented the work of Cohen et al. (2010) who suggested a second homeostatic process acting on a longer time scale.

4. Discussion

Recuperative sleep is a prerequisite to good cognitive performance. Shift work poses a challenge to recuperative sleep and herewith influences work safety. However, inter-individual differences in the neurobehavioral response to sleep loss exist (E.-M. Elmenhorst et al., 2018; Goel et al., 2009; Leproult et al., 2003; Van Dongen et al., 2003, 2004, 2005; Wilkinson, 1961). Furthermore, cognitive domains are differentially affected by sleep loss (Lim & Dinges, 2010; Lo et al., 2012). This dissertation combines results of two elaborative laboratory research projects and aims at contributing to the understanding of the neuro-molecular basis of individual differences in the sleep loss response, of sleep-wake regulation under different sleep-wake schedules and its association to cognitive functioning.

Adenosine has previously been suggested to be involved in sleep-wake regulation (Basheer et al., 2004; D. Elmenhorst et al., 2007; Landolt, 2008; Porkka-Heiskanen et al., 2000). D. Elmenhorst et al. (2007) already showed increased A1AR availability during prolonged wakefulness. Unknown were the adenosinergic dynamics in response to recovery sleep after prolonged wakefulness in humans, which we therefore investigated. Compared to cerebral A1AR availability after 52 hours of wakefulness, A1AR availability after 14 hours of recovery sleep was reduced by between 11 % in the insula and 14 % in the striatum. A1AR availability after recovery sleep furthermore was comparable to baseline levels from an independent rested sample.

Interestingly, individual differences in this decrease could be identified and linked to performance during prolonged wakefulness. Because of the finding of an association between A1AR availability and performance during sleep loss, we suggest an adenosinergic contribution to the individual sleep loss response. In contrast to our expectation, participants with a high receptor availability during prolonged wakefulness were more resilient to the sleep loss effects on performance. In the following we detail a possible explanation for this counterintuitive result. In humans, cerebral adenosine cannot be quantified easily. Therefore,

the quantification of cerebral A1AR is applied to infer possible underlying adenosinergic mechanisms. It is suggested that A1AR is upregulated along with increasing levels of endogenous adenosine. Thus, we infer that increased receptor availability is accompanied by an increase in endogenous adenosine. We therefore expected individuals with a high receptor availability to be especially affected by sleep deprivation with regard to cognition. We cannot prove the exact underlying mechanisms for the presented finding. However, we speculate that in both vulnerable and less vulnerable individuals, A1AR availability increased during prolonged wakefulness. While also endogenous adenosine levels were likely increased in both groups, we suggest that this increase was much more pronounced in the vulnerable group. We suggest that in the vulnerable group, a huge increase in endogenous adenosine levels led to high receptor activation which in turn induced the performance impairing effect. In the less vulnerable group, more receptors might have been available for the PET ligand to bind, giving the impressions of a more increased receptor density in this group.

The two process model (Borbély, 1982) provides an influential theoretical framework for the regulation of sleep and wakefulness. However, the detailed mechanisms underlying the homeostatic sleep-wake regulation as well as underlying the regulation of chronic sleep loss are unknown. Previously, increasing and decreasing adenosine levels during wakefulness and sleep were shown in cats and rodents (Porkka-Heiskanen et al., 2000). Our findings support the role of adenosine as a sleep factor contributing to the homeostatic process of sleep-wake regulation (Borbély, 1982) also in humans. Previously, D. Elmenhorst et al. (2007) already showed increasing A1AR availability after 24 hours of wakefulness as compared to baseline. The result presented in our research is the first evidence for decreasing A1AR availability after recovery sleep from prolonged wakefulness in humans. Furthermore, the comparable A1AR availability after recovery sleep to rested baseline values suggests a decline of adenosine levels during sleep which parallels the exponential decline of SWA in the recovery night which we also reported. These dynamics fit the suggested decline of homeostatic sleep

pressure in the two process model, which predicts SWA recovery in our experimental design after approximately 9-10 hours (Borbély, 1982). In contrast, comparing sleep stage proportions between the baseline and the recovery night on an hourly basis, we found increased agreement between sleep stage proportions of the two nights even after the 10 hours, suggesting ongoing recovery processes and the robustness of individual sleep structure to the experimental challenge. PVT performance in the morning after the 14-h night was recovered to baseline performance. The underlying biological mechanisms for potential ongoing recovery processes which here became visible in the approximation of sleep stage proportions after 10 hours of recovery sleep need further investigation. Especially, our study design did not exclude the interference of circadian influences at the end of the recovery night, when baseline and recovery night fell on the same circadian phase. Further experiments with a manipulation of circadian times would be necessary to disentangle the role of homeostatic and circadian factors regarding recovery processes. Moreover, the evaluation of neurobehavioral performance and A1AR availability throughout the recovery day, and the sleep structure during a second recovery night would give further insights on sleep-wake regulation and recovery needs.

The question of recovery needs was also addressed concerning combined effects of chronic and acute sleep deprivation. We provide evidence for a carry-over effect of performance impairing influences from chronic to acute sleep deprivation. Although divided by one recovery night, spatial working memory performance during acute sleep deprivation was more affected in individuals with prior chronic sleep loss (5 nights á 5 hours) than in individuals without prior sleep loss. This impairment was initially covered after the recovery night and unveiled during additional wakefulness. These dynamics pose special risks with regard to work safety, where individuals might initially get a false sense of recovery from sleep loss. This might be exacerbated by the subjective underestimation of sleepiness compared to objective indicators of sleepiness (Van Dongen et al., 2003).

Our findings support previous results of differential sensitivities of cognitive domains to sleep deprivation (Lim & Dinges, 2010; Lo et al., 2012). Interestingly, we found the verbal and spatial component of working memory to be differentially affected by sleep deprivation. Our results on working memory support the multi-component model of Baddelely and Hitch (1974). The impairment in spatial working memory but not in verbal working memory might be explained by the lateralization of these functions to mainly the right and left hemisphere respectively (Smith et al., 1996).

The regulation of chronic sleep restriction is poorly understood. Cohen et al. (2010) previously suggested a second homeostatic process acting on a longer time-scale in an experiment concerning PVT performance. Our results complement their work and suggest this process also to be involved in the mediation of spatial working memory performance. Future experiments with an increased number of participants and tests of multiple cognitive processes might further elucidate cognition and individual differences in response to varying sleep-wake schedules.

A further aim of the project was to investigate the adenosinergic mechanisms in sleep-wake regulation during chronic sleep deprivation and its combination with acute sleep deprivation. Furthermore, individual differences in the susceptibility to sleep deprivation induced performance impairments and the link to biomarkers was of interest. The extensive analyses of the data on A1AR availability during chronic sleep deprivation is part of another dissertation project.

In the long run, the results should contribute to the elucidation of neuromolecular sleep-wake regulation during chronic and acute sleep restriction and its association with inter-individual differences in the sleep loss response. With regard to implications and future directions, knowledge about individual vulnerabilities could advance the employee selection and the development of assistance systems in the organizational setting. With regard to the clinical setting, acute sleep deprivation is known as an effective but short-lasting treatment for

depression (Hemmeter et al., 2010). The present findings contribute to the understanding of the underlying neuromolecular basis. Furthermore, with the presented evidence for individual differences in sleep-loss responses we suggest possible implications also for depressive treatment.

Moreover, the understanding of adenosinergic sleep-wake regulation during chronic sleep deprivation might enhance the development of future therapeutic targets for depression. Furthermore, experiments involving caffeine as a non-selective adenosine antagonist might provide additional insights into inter-individual differences in sleep-wake regulation and dynamics of neuro-behavioral performance under varying sleep-wake schedules.

5. References

Aeschbach, D. (2011). REM-sleep regulation: Circadian, homeostatic, and non-REM sleep-dependent determinants. In B. N. Mallick, S. R. Pandi-Perumal, R. W. McCarley, & A. R. Morrison (Eds.), *Rapid Eye Movement Sleep* (pp. 80–88). Cambridge University Press. https://doi.org/10.1017/CBO9780511921179.011

Agnew, H. W., Webb, W. B., & Williams, R. L. (1966). The first night effect: An EEG study of sleep. *Psychophysiology*, *2*(3), 263–266. https://doi.org/10.1111/j.1469-8986.1966.tb02650.x

Bachmann, V., Klaus, F., Bodenmann, S., Schäfer, N., Brugger, P., Huber, S., Berger, W., & Landolt, H.-P. (2012). Functional ADA Polymorphism Increases Sleep Depth and Reduces Vigilant Attention in Humans. *Cerebral Cortex*, *22*(4), 962–970. https://doi.org/10.1093/cercor/bhr173

Baddeley, A. D. (2010). Working memory. *Current Biology*, *20*(4), R136–R140. https://doi.org/10.1016/j.cub.2009.12.014

Baddeley, A. D., Eysenck, M. W., & Anderson, M. C. (2009). *Memory*. Psychology Press.

Baddeley, A. D., & Hitch, G. (1974). *Working Memory* (G. H. Bower, Ed.; Vol. 8, pp. 47–89). Academic Press. https://doi.org/10.1016/S0079-7421(08)60452-1

Banks, S., & Dinges, D. F. (2007). Behavioral and physiological consequences of sleep restriction. *Journal of Clinical Sleep Medicine: JCSM: Official Publication of the American Academy of Sleep Medicine*, *3*(5), 519–528.

Banks, S., Van Dongen, H. P. A., Maislin, G., & Dinges, D. F. (2010). Neurobehavioral Dynamics Following Chronic Sleep Restriction: Dose-Response Effects of One Night for Recovery. *Sleep*, *33*(8), 1013–1026. https://doi.org/10.1093/sleep/33.8.1013

Barger, L. K., Flynn-Evans, E. E., Kubey, A., Walsh, L., Ronda, J. M., Wang, W., Wright, K. P., & Czeisler, C. A. (2014). Prevalence of sleep deficiency and use of hypnotic drugs

in astronauts before, during, and after spaceflight: An observational study. *The Lancet Neurology*, *13*(9), 904–912. https://doi.org/10.1016/S1474-4422(14)70122-X

Basheer, R., Strecker, R. E., Thakkar, M. M., & McCarley, R. W. (2004). Adenosine and sleep–wake regulation. *Progress in Neurobiology*, *73*(6), 379–396. https://doi.org/10.1016/j.pneurobio.2004.06.004

Basner, M., Hermosillo, E., Nasrini, J., McGuire, S., Saxena, S., Moore, T. M., Gur, R. C., & Dinges, D. F. (2018). Repeated Administration Effects on Psychomotor Vigilance Test Performance. *Sleep*, *41*(1). https://doi.org/10.1093/sleep/zsx187

Basner, M., Rubinstein, J., Fomberstein, K. M., Coble, M. C., Ecker, A., Avinash, D., & Dinges, D. F. (2008). Effects of night work, sleep loss and time on task on simulated threat detection performance. *Sleep*, *31*(9), 1251–1259.

Bauer, A., Holschbach, M. H., Cremer, M., Weber, S., Boy, C., Shah, N. J., Olsson, R. A., Halling, H., Coenen, H. H., & Zilles, K. (2003). Evaluation of 18F-CPFPX, a novel adenosine A1 receptor ligand: In vitro autoradiography and high-resolution small animal PET. *Journal of Nuclear Medicine: Official Publication, Society of Nuclear Medicine*, *44*(10), 1682–1689.

Bauer, A., Holschbach, M. H., Meyer, P. T., Boy, C., Herzog, H., Olsson, R. A., Coenen, H. H., & Zilles, K. (2003). In vivo imaging of adenosine A1 receptors in the human brain with [18F]CPFPX and positron emission tomography. *NeuroImage*, *19*(4), 1760–1769. https://doi.org/10.1016/s1053-8119(03)00241-6

Bauer, A., Langen, K.-J., Bidmon, H., Holschbach, M. H., Weber, S., Olsson, R. A., Coenen, H. H., & Zilles, K. (2005). 18F-CPFPX PET identifies changes in cerebral A1 adenosine receptor density caused by glioma invasion. *Journal of Nuclear Medicine: Official Publication, Society of Nuclear Medicine*, *46*(3), 450–454.

Belenky, G., Wesensten, N. J., Thorne, D. R., Thomas, M. L., Sing, H. C., Redmond, D. P., Russo, M. B., & Balkin, T. J. (2003). Patterns of performance degradation and

restoration during sleep restriction and subsequent recovery: A sleep dose-response study. *Journal of Sleep Research*, *12*(1), 1–12. https://doi.org/10.1046/j.1365-2869.2003.00337.x

Benington, J. H., Kodali, S. K., & Heller, H. C. (1995). Stimulation of A1 adenosine receptors mimics the electroencephalographic effects of sleep deprivation. *Brain Research*, *692*(1–2), 79–85. https://doi.org/10.1016/0006-8993(95)00590-m

Bergum, B. O., & Lehr, D. J. (1962). Vigilance performance as a function of interpolated rest. *Journal of Applied Psychology*, *46*(6), 425–427. https://doi.org/10.1037/h0043505

Borbély, A. A. (1982). A two process model of sleep regulation. *Human Neurobiology*, *1*(3), 195–204.

Boy, C., Meyer, P. T., Kircheis, G., Holschbach, M. H., Herzog, H., Elmenhorst, D., Kaiser, H. J., Coenen, H. H., Haussinger, D., Zilles, K., & Bauer, A. (2008). Cerebral A1 adenosine receptors (A1AR) in liver cirrhosis. *European Journal of Nuclear Medicine and Molecular Imaging*, *35*(3), 589–597. https://doi.org/10.1007/s00259-007-0586-z

Breslau, N., Roth, T., Rosenthal, L., & Andreski, P. (1996). Sleep disturbance and psychiatric disorders: A longitudinal epidemiological study of young adults. *Biological Psychiatry*, *39*(6), 411–418. https://doi.org/10.1016/0006-3223(95)00188-3

Brown, R. E., Basheer, R., McKenna, J. T., Strecker, R. E., & McCarley, R. W. (2012). Control of sleep and wakefulness. *Physiological Reviews*, *92*(3), 1087–1187. https://doi.org/10.1152/physrev.00032.2011

Buckelmüller, J., Landolt, H.-P., Stassen, H. H., & Achermann, P. (2006). Trait-like individual differences in the human sleep electroencephalogram. *Neuroscience*, *138*(1), 351–356. https://doi.org/10.1016/j.neuroscience.2005.11.005

Byrne, E. M., Johnson, J., McRae, A. F., Nyholt, D. R., Medland, S. E., Gehrman, P. R., Heath, A. C., Madden, P. A. F., Montgomery, G. W., Chenevix-Trench, G., & Martin, N. G. (2012). A genome-wide association study of caffeine-related sleep disturbance:

Confirmation of a role for a common variant in the adenosine receptor. *Sleep*, *35*(7), 967–975. https://doi.org/10.5665/sleep.1962

Carskadon, M. A., & Dement, W. C. (1985). Sleep loss in elderly volunteers. *Sleep*, *8*(3), 207–221. https://doi.org/10.1093/sleep/8.3.207

Carskadon, M. A., & Dement, W. C. (2000). Normal Human Sleep: An Overview. In M. H. Kryger, T. Roth, & W. C. Dement (Eds.), *Principles and Practice of Sleep Medicine* (pp. 15–25). W. B. Saunders.

Chun, M. M., Golomb, J. D., & Turk-Browne, N. B. (2011). A taxonomy of external and internal attention. *Annual Review of Psychology*, *62*, 73–101. https://doi.org/10.1146/annurev.psych.093008.100427

Cohen, D. A., Wang, W., Wyatt, J. K., Kronauer, R. E., Dijk, D.-J., Czeisler, C. A., & Klerman, E. B. (2010). Uncovering residual effects of chronic sleep loss on human performance. *Science Translational Medicine*, *2*(14), 14ra3. https://doi.org/10.1126/scitranslmed.3000458

Cowan, N. (2008). What are the differences between long-term, short-term, and working memory? *Progress in Brain Research*, *169*, 323–338. https://doi.org/10.1016/S0079-6123(07)00020-9

Czeisler, C. A., Weitzman, E. d, Moore-Ede, M. C., Zimmerman, J. C., & Knauer, R. S. (1980). Human sleep: Its duration and organization depend on its circadian phase. *Science*, *210*(4475), 1264–1267. https://doi.org/10.1126/science.7434029

Daan, S., Beersma, D. G., & Borbely, A. A. (1984). Timing of human sleep: Recovery process gated by a circadian pacemaker. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, *246*(2), R161–R183. https://doi.org/10.1152/ajpregu.1984.246.2.R161

De Gennaro, L., Marzano, C., Fratello, F., Moroni, F., Pellicciari, M. C., Ferlazzo, F., Costa, S., Couyoumdjian, A., Curcio, G., Sforza, E., Malafosse, A., Finelli, L. A.,

Pasqualetti, P., Ferrara, M., Bertini, M., & Rossini, P. M. (2008). The electroencephalographic fingerprint of sleep is genetically determined: A twin study. *Annals of Neurology*, *64*(4), 455–460. https://doi.org/10.1002/ana.21434

Dijk, D.-J., Brunner, D. P., Beersma, D. G. M., & Borbély, A. A. (1990). Electroencephalogram Power Density and Slow Wave Sleep as a Function of Prior Waking and Circadian Phase. *Sleep*, *13*(5), 430–440. https://doi.org/10.1093/sleep/13.5.430

Dijk, D.-J., & von Schantz, M. (2005). Timing and Consolidation of Human Sleep, Wakefulness, and Performance by a Symphony of Oscillators. *Journal of Biological Rhythms*, *20*(4), 279–290. https://doi.org/10.1177/0748730405278292

Dinges, D. F., Pack, F., Williams, K., Gillen, K. A., Powell, J. W., Ott, G. E., Aptowicz, C., & Pack, A. I. (1997). Cumulative sleepiness, mood disturbance, and psychomotor vigilance performance decrements during a week of sleep restricted to 4-5 hours per night. *Sleep*, *20*(4), 267–277.

Dinges, D. F., & Powell, J. W. (1985). Microcomputer analyses of performance on a portable, simple visual RT task during sustained operations. *Behavior Research Methods, Instruments, & Computers*, *17*(6), 652–655. https://doi.org/10.3758/BF03200977

Doran, S. M., Van Dongen, H. P., & Dinges, D. F. (2001). Sustained attention performance during sleep deprivation: Evidence of state instability. *Archives Italiennes De Biologie*, *139*(3), 253–267.

Edgar, D. M., Dement, W. C., & Fuller, C. A. (1993). Effect of SCN lesions on sleep in squirrel monkeys: Evidence for opponent processes in sleep-wake regulation. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *13*(3), 1065–1079.

Ellis, N. C., & Hennelly, R. A. (1980). A bilingual word-length effect: Implications for intelligence testing and the relative ease of mental calculation in Welsh and English.

British Journal of Psychology, *71*(1), 43–51. https://doi.org/10.1111/j.2044-8295.1980.tb02728.x

Elmenhorst, D., Bier, D., Holschbach, M., & Bauer, A. (2014). Imaging of Adenosine Receptors. In R. A. J. O. Dierckx, A. Otte, E. F. J. de Vries, A. van Waarde, & P. G. M. Luiten (Eds.), *PET and SPECT of Neurobiological Systems* (pp. 181–198). Springer Berlin Heidelberg. https://doi.org/10.1007/978-3-642-42014-6_7

Elmenhorst, D., Elmenhorst, E.-M., Luks, N., Maass, H., Mueller, E.-W., Vejvoda, M., Wenzel, J., & Samel, A. (2009). Performance impairment during four days partial sleep deprivation compared with the acute effects of alcohol and hypoxia. *Sleep Medicine*, *10*(2), 189–197. https://doi.org/10.1016/j.sleep.2007.12.003

Elmenhorst, D., Meyer, P. T., Matusch, A., Winz, O. H., & Bauer, A. (2012). Caffeine occupancy of human cerebral A1 adenosine receptors: In vivo quantification with 18F-CPFPX and PET. *Journal of Nuclear Medicine: Official Publication, Society of Nuclear Medicine*, *53*(11), 1723–1729. https://doi.org/10.2967/jnumed.112.105114

Elmenhorst, D., Meyer, P. T., Winz, O. H., Matusch, A., Ermert, J., Coenen, H. H., Basheer, R., Haas, H. L., Zilles, K., & Bauer, A. (2007). Sleep deprivation increases A1 adenosine receptor binding in the human brain: A positron emission tomography study. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *27*(9), 2410–2415. https://doi.org/10.1523/JNEUROSCI.5066-06.2007

Elmenhorst, E.-M., Elmenhorst, D., Benderoth, S., Kroll, T., Bauer, A., & Aeschbach, D. (2018). Cognitive impairments by alcohol and sleep deprivation indicate trait characteristics and a potential role for adenosine A1 receptors. *Proceedings of the National Academy of Sciences of the United States of America*, *115*(31), 8009–8014. https://doi.org/10.1073/pnas.1803770115

Elmenhorst, E.-M., Elmenhorst, D., Luks, N., Maass, H., Vejvoda, M., & Samel, A. (2008). Partial sleep deprivation: Impact on the architecture and quality of sleep. *Sleep Medicine*, *9*(8), 840–850. https://doi.org/10.1016/j.sleep.2007.07.021

Elmenhorst, E.-M., Hörmann, H.-J., Oeltze, K., Pennig, S., Vejvoda, M., & Wenzel, J. (2013). Measuring cognitive performance in space: Validity of a 3-min PVT administered on a handheld computer. *Humans in Space Symposium*. https://elib.dlr.de/84521/

Everson, C. A., Bergmann, B. M., & Rechtschaffen, A. (1989). Sleep deprivation in the rat: III. Total sleep deprivation. *Sleep*, *12*(1), 13–21. https://doi.org/10.1093/sleep/12.1.13

Ferrara, M., De Gennaro, L., & Bertini, M. (1999). Selective slow-wave sleep (SWS) deprivation and SWS rebound: Do we need a fixed SWS amount per night? *Sleep Research Online: SRO*, *2*(1), 15–19.

Flynn-Evans, E. E., Barger, L. K., Kubey, A. A., Sullivan, J. P., & Czeisler, C. A. (2016). Circadian misalignment affects sleep and medication use before and during spaceflight. *NPJ Microgravity, 2,* 15019. https://doi.org/10.1038/npjmgrav.2015.19

Ford, D. E., & Kamerow, D. B. (1989). Epidemiologic study of sleep disturbances and psychiatric disorders. An opportunity for prevention? *JAMA*, *262*(11), 1479–1484. https://doi.org/10.1001/jama.262.11.1479

Gais, S., Lucas, B., & Born, J. (2006). Sleep after learning aids memory recall. *Learning & Memory*, *13*(3), 259–262. https://doi.org/10.1101/lm.132106

Gevins, A., & Cutillo, B. (1993). Spatiotemporal dynamics of component processes in human working memory. *Electroencephalography and Clinical Neurophysiology*, *87*(3), 128–143. https://doi.org/10.1016/0013-4694(93)90119-g

Goel, N., Banks, S., Mignot, E., & Dinges, D. F. (2009). PER3 polymorphism predicts cumulative sleep homeostatic but not neurobehavioral changes to chronic partial sleep deprivation. *PloS One*, *4*(6), e5874. https://doi.org/10.1371/journal.pone.0005874

Gregory, A. M., Rijsdijk, F. V., Lau, J. Y. F., Dahl, R. E., & Eley, T. C. (2009). The direction of longitudinal associations between sleep problems and depression symptoms: A study of twins aged 8 and 10 years. *Sleep*, *32*(2), 189–199. https://doi.org/10.1093/sleep/32.2.189

Harrison, Y., Horne, J. A., & Rothwell, A. (2000). Prefrontal neuropsychological effects of sleep deprivation in young adults–a model for healthy aging? *Sleep*, *23*(8), 1067–1073.

Hemmeter, U.-M., Hemmeter-Spernal, J., & Krieg, J.-C. (2010). Sleep deprivation in depression. *Expert Review of Neurotherapeutics*, *10*(7), 1101–1115. https://doi.org/10.1586/ern.10.83

Hibi, M., Kubota, C., Mizuno, T., Aritake, S., Mitsui, Y., Katashima, M., & Uchida, S. (2017). Effect of shortened sleep on energy expenditure, core body temperature, and appetite: A human randomised crossover trial. *Scientific Reports*, *7*, 39640. https://doi.org/10.1038/srep39640

Hirshkowitz, M., Whiton, K., Albert, S. M., Alessi, C., Bruni, O., DonCarlos, L., Hazen, N., Herman, J., Adams Hillard, P. J., Katz, E. S., Kheirandish-Gozal, L., Neubauer, D. N., O'Donnell, A. E., Ohayon, M., Peever, J., Rawding, R., Sachdeva, R. C., Setters, B., Vitiello, M. V., & Ware, J. C. (2015). National Sleep Foundation's updated sleep duration recommendations: Final report. *Sleep Health*, *1*(4), 233–243. https://doi.org/10.1016/j.sleh.2015.10.004

Hohoff, C., Garibotto, V., Elmenhorst, D., Baffa, A., Kroll, T., Hoffmann, A., Schwarte, K., Zhang, W., Arolt, V., Deckert, J., & Bauer, A. (2014). Association of adenosine receptor gene polymorphisms and in vivo adenosine A1 receptor binding in the human brain. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*, *39*(13), 2989–2999. https://doi.org/10.1038/npp.2014.150

Holschbach, M. H., Fein, T., Krummeich, C., Lewis, R. G., Wutz, W., Schwabe, U., Unterlugauer, D., & Olsson, R. A. (1998). A1 adenosine receptor antagonists as ligands for positron emission tomography (PET) and single-photon emission tomography (SPET). *Journal of Medicinal Chemistry*, *41*(4), 555–563. https://doi.org/10.1021/jm9705465

Hudson, A. N., Van Dongen, H. P. A., & Honn, K. A. (2020). Sleep deprivation, vigilant attention, and brain function: A review. *Neuropsychopharmacology*, *45*(1), 21–30. https://doi.org/10.1038/s41386-019-0432-6

Iber, C., Ancoli-Israel, S., Chesson, A. L., & Quan, S. F. (2007). *The AASM Manual for the Scoring of Sleep and Associated Events; Rules, Terminology and Technical Specifications* (1st ed.). Westchester, IL: American Academy of Sleep Medicine.

Jasper, H. H. (1958). The ten-twenty electrode system of the International Federation. *Electroencephalography and Clinical Neurophysiology*, *10*, 371–375.

Jessen, N. A., Munk, A. S. F., Lundgaard, I., & Nedergaard, M. (2015). The Glymphatic System: A Beginner's Guide. *Neurochemical Research*, *40*(12), 2583–2599. https://doi.org/10.1007/s11064-015-1581-6

Kim, Y., Elmenhorst, D., Weisshaupt, A., Wedekind, F., Kroll, T., McCarley, R. W., Strecker, R. E., & Bauer, A. (2015). Chronic sleep restriction induces long-lasting changes in adenosine and noradrenaline receptor density in the rat brain. *Journal of Sleep Research*, *24*(5), 549–558. https://doi.org/10.1111/jsr.12300

Kitamura, S., Katayose, Y., Nakazaki, K., Motomura, Y., Oba, K., Katsunuma, R., Terasawa, Y., Enomoto, M., Moriguchi, Y., Hida, A., & Mishima, K. (2016). Estimating individual optimal sleep duration and potential sleep debt. *Scientific Reports*, *6*, 35812. https://doi.org/10.1038/srep35812

Komaki, J. (1967). Signal-source switching in human vigilance. *Japanese Psychological Research*, *9*(2), 49–57. https://doi.org/10.4992/psycholres1954.9.49

Krueger, J. M., Rector, D. M., Roy, S., Van Dongen, H. P. A., Belenky, G., & Panksepp, J. (2008). Sleep as a fundamental property of neuronal assemblies. *Nature Reviews Neuroscience*, *9*(12), 910–919. https://doi.org/10.1038/nrn2521

Krystal, A. D. (2012). Psychiatric disorders and sleep. *Neurologic Clinics*, *30*(4), 1389–1413. https://doi.org/10.1016/j.ncl.2012.08.018

Kuna, S. T., Maislin, G., Pack, F. M., Staley, B., Hachadoorian, R., Coccaro, E. F., & Pack, A. I. (2012). Heritability of performance deficit accumulation during acute sleep deprivation in twins. *Sleep*, *35*(9), 1223–1233. https://doi.org/10.5665/sleep.2074

Landis, J. R., & Koch, G. G. (1977). The measurement of observer agreement for categorical data. *Biometrics*, *33*(1), 159–174.

Landolt, H.-P. (2008). Sleep homeostasis: A role for adenosine in humans? *Biochemical Pharmacology*, *75*(11), 2070–2079. https://doi.org/10.1016/j.bcp.2008.02.024

Leproult, R., Colecchia, E. F., Berardi, A. M., Stickgold, R., Kosslyn, S. M., & Van Cauter, E. (2003). Individual differences in subjective and objective alertness during sleep deprivation are stable and unrelated. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology*, *284*(2), R280-290. https://doi.org/10.1152/ajpregu.00197.2002

Lim, J., & Dinges, D. F. (2010). A meta-analysis of the impact of short-term sleep deprivation on cognitive variables. *Psychological Bulletin*, *136*(3), 375–389. https://doi.org/10.1037/a0018883

Linkowski, P., Kerkhofs, M., Hauspie, R., Susanne, C., & Mendlewicz, J. (1989). EEG sleep patterns in man: A twin study. *Electroencephalography and Clinical Neurophysiology*, *73*(4), 279–284. https://doi.org/10.1016/0013-4694(89)90106-5

Lo, J. C., Groeger, J. A., Santhi, N., Arbon, E. L., Lazar, A. S., Hasan, S., von Schantz, M., Archer, S. N., & Dijk, D.-J. (2012). Effects of partial and acute total sleep deprivation on performance across cognitive domains, individuals and circadian phase. *PloS One*, *7*(9), e45987. https://doi.org/10.1371/journal.pone.0045987

Ma, N., Dinges, D. F., Basner, M., & Rao, H. (2015). How Acute Total Sleep Loss Affects the Attending Brain: A Meta-Analysis of Neuroimaging Studies. *Sleep*, *38*(2), 233–240. https://doi.org/10.5665/sleep.4404

Mackworth, J. F. (1964). Performance decrement in vigilance, threshold, and high-speed perceptual motor tasks. *Canadian Journal of Psychology*, *18*, 209–223. https://doi.org/10.1037/h0083302

Mackworth, N. H. (1948). The Breakdown of Vigilance during Prolonged Visual Search. *Quarterly Journal of Experimental Psychology*, *1*(1), 6–21. https://doi.org/10.1080/17470214808416738

McCauley, P., Kalachev, L. V., Smith, A. D., Belenky, G., Dinges, D. F., & Van Dongen, H. P. A. (2009). A new mathematical model for the homeostatic effects of sleep loss on neurobehavioral performance. *Journal of Theoretical Biology*, *256*(2), 227–239. https://doi.org/10.1016/j.jtbi.2008.09.012

Meyer, P. T., Bier, D., Holschbach, M. H., Boy, C., Olsson, R. A., Coenen, H. H., Zilles, K., & Bauer, A. (2004). Quantification of Cerebral A_1 Adenosine Receptors in Humans using [^{18}F]CPFPX and PET. *Journal of Cerebral Blood Flow & Metabolism*, *24*(3), 323–333. https://doi.org/10.1097/01.WCB.0000110531.48786.9D

Meyer, P. T., Elmenhorst, D., Boy, C., Winz, O., Matusch, A., Zilles, K., & Bauer, A. (2007). Effect of aging on cerebral A1 adenosine receptors: A [18F]CPFPX PET study in humans. *Neurobiology of Aging*, *28*(12), 1914–1924. https://doi.org/10.1016/j.neurobiolaging.2006.08.005

Nir, Y., Andrillon, T., Marmelshtein, A., Suthana, N., Cirelli, C., Tononi, G., & Fried, I. (2017). Selective neuronal lapses precede human cognitive lapses following sleep deprivation. *Nature Medicine*, *23*(12), 1474–1480. https://doi.org/10.1038/nm.4433

Oken, B. S., Salinsky, M. C., & Elsas, S. M. (2006). Vigilance, alertness, or sustained attention: Physiological basis and measurement. *Clinical Neurophysiology*, *117*(9), 1885–1901. https://doi.org/10.1016/j.clinph.2006.01.017

Pellegrino, R., Kavakli, I. H., Goel, N., Cardinale, C. J., Dinges, D. F., Kuna, S. T., Maislin, G., Van Dongen, H. P. A., Tufik, S., Hogenesch, J. B., Hakonarson, H., & Pack, A. I. (2014). A Novel *BHLHE41* Variant is Associated with Short Sleep and Resistance to Sleep Deprivation in Humans. *Sleep*, *37*(8), 1327–1336. https://doi.org/10.5665/sleep.3924

Phillips, A. J. K., Clerx, W. M., O'Brien, C. S., Sano, A., Barger, L. K., Picard, R. W., Lockley, S. W., Klerman, E. B., & Czeisler, C. A. (2017). Irregular sleep/wake patterns are associated with poorer academic performance and delayed circadian and sleep/wake timing. *Scientific Reports*, *7*(1), 3216. https://doi.org/10.1038/s41598-017-03171-4

Phillips, A. J. K., & Robinson, P. A. (2007). A Quantitative Model of Sleep-Wake Dynamics Based on the Physiology of the Brainstem Ascending Arousal System. *Journal of Biological Rhythms*, *22*(2), 167–179. https://doi.org/10.1177/0748730406297512

Pilcher, J. J., Band, D., Odle-Dusseau, H. N., & Muth, E. R. (2007). Human performance under sustained operations and acute sleep deprivation conditions: Toward a model of controlled attention. *Aviation, Space, and Environmental Medicine*, *78*(5 Suppl), B15-24.

Plihal, W., & Born, J. (1997). Effects of early and late nocturnal sleep on declarative and procedural memory. *Journal of Cognitive Neuroscience*, *9*(4), 534–547. https://doi.org/10.1162/jocn.1997.9.4.534

Porkka-Heiskanen, T., Strecker, R. E., & McCarley, R. W. (2000). Brain site-specificity of extracellular adenosine concentration changes during sleep deprivation and spontaneous sleep: An in vivo microdialysis study. *Neuroscience*, *99*(3), 507–517. https://doi.org/10.1016/s0306-4522(00)00220-7

Rétey, J. V., Adam, M., Khatami, R., Luhmann, U. F. O., Jung, H. H., Berger, W., & Landolt, H.-P. (2007). A genetic variation in the adenosine A2A receptor gene (ADORA2A) contributes to individual sensitivity to caffeine effects on sleep. *Clinical Pharmacology and Therapeutics*, *81*(5), 692–698. https://doi.org/10.1038/sj.clpt.6100102

Rosenberg, M. D., Finn, E. S., Scheinost, D., Papademetris, X., Shen, X., Constable, R. T., & Chun, M. M. (2016). A neuromarker of sustained attention from whole-brain functional connectivity. *Nature Neuroscience*, *19*(1), 165–171. https://doi.org/10.1038/nn.4179

Rupp, T. L., Wesensten, N. J., Bliese, P. D., & Balkin, T. J. (2009). Banking Sleep: Realization of Benefits During Subsequent Sleep Restriction and Recovery. *Sleep*, *32*(3), 311–321. https://doi.org/10.1093/sleep/32.3.311

Sarter, M., Givens, B., & Bruno, J. P. (2001). The cognitive neuroscience of sustained attention: Where top-down meets bottom-up. *Brain Research. Brain Research Reviews*, *35*(2), 146–160. https://doi.org/10.1016/s0165-0173(01)00044-3

Schwierin, B., Borbély, A. A., & Tobler, I. (1996). Effects of N6-cyclopentyladenosine and caffeine on sleep regulation in the rat. *European Journal of Pharmacology*, *300*(3), 163–171. https://doi.org/10.1016/0014-2999(96)00021-0

Smith, E. E., Jonides, J., & Koeppe, R. A. (1996). Dissociating verbal and spatial working memory using PET. *Cerebral Cortex*, *6*(1), 11–20. https://doi.org/10.1093/cercor/6.1.11

Spiegel, K., Knutson, K., Leproult, R., Tasali, E., & Van Cauter, E. (2005). Sleep loss: A novel risk factor for insulin resistance and Type 2 diabetes. *Journal of Applied Physiology*, *99*(5), 2008–2019. https://doi.org/10.1152/japplphysiol.00660.2005

Squire, L. R., & Zola, S. M. (1996). Structure and function of declarative and nondeclarative memory systems. *Proceedings of the National Academy of Sciences of the United States of America*, *93*(24), 13515–13522. https://doi.org/10.1073/pnas.93.24.13515

Statistisches Bundesamt. (2019). Qualität Der Arbeit - Abend- Und Nachtarbeit. https://www.destatis.de/DE/Themen/Arbeit/Arbeitsmarkt/Qualitaet-Arbeit/Dimension-3/abend-nachtarbeit.html

Tucker, A. M., Whitney, P., Belenky, G., Hinson, J. M., & Van Dongen, H. PA. (2010). Effects of Sleep Deprivation on Dissociated Components of Executive Functioning. *Sleep*, *33*(1), 47–57. https://doi.org/10.1093/sleep/33.1.47

van Calker, D., Biber, K., Domschke, K., & Serchov, T. (2019). The role of adenosine receptors in mood and anxiety disorders. *Journal of Neurochemistry*, *151*(1), 11–27. https://doi.org/10.1111/jnc.14841

van Calker, D., Müller, M., & Hamprecht, B. (1978). Adenosine inhibits the accumulation of cyclic AMP in cultured brain cells. *Nature*, *276*(5690), 839–841. https://doi.org/10.1038/276839a0

Van Dongen, H. P. A. (2004). Comparison of mathematical model predictions to experimental data of fatigue and performance. *Aviation, Space, and Environmental Medicine*, *75*(3 Suppl), A15-36.

Van Dongen, H. P. A., Belenky, G., & Krueger, J. M. (2011a). A local, bottom-up perspective on sleep deprivation and neurobehavioral performance. *Current Topics in Medicinal Chemistry*, *11*(19), 2414–2422. https://doi.org/10.2174/156802611797470286

Van Dongen, H. P. A., Belenky, G., & Krueger, J. M. (2011b). Investigating the temporal dynamics and underlying mechanisms of cognitive fatigue. In P. L. Ackerman (Ed.),

Cognitive fatigue: Multidisciplinary perspectives on current research and future applications. (pp. 127–147). American Psychological Association. https://doi.org/10.1037/12343-006

Van Dongen, H. P. A., & Dinges, D. F. (2005). Sleep, circadian rhythms, and psychomotor vigilance. *Clinics in Sports Medicine*, *24*(2), 237–249, vii–viii. https://doi.org/10.1016/j.csm.2004.12.007

Van Dongen, H. P. A., Maislin, G., & Dinges, D. F. (2004). Dealing with inter-individual differences in the temporal dynamics of fatigue and performance: Importance and techniques. *Aviation, Space, and Environmental Medicine*, *75*(3 Suppl), A147-154.

Van Dongen, H. P. A., Maislin, G., Mullington, J. M., & Dinges, D. F. (2003). The cumulative cost of additional wakefulness: Dose-response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. *Sleep*, *26*(2), 117–126. https://doi.org/10.1093/sleep/26.2.117

Van Dongen, H. P. A., Vitellaro, K. M., & Dinges, D. F. (2005). Individual differences in adult human sleep and wakefulness: Leitmotif for a research agenda. *Sleep*, *28*(4), 479–496. https://doi.org/10.1093/sleep/28.4.479

Viola, A. U., Archer, S. N., James, L. M., Groeger, J. A., Lo, J. C. Y., Skene, D. J., von Schantz, M., & Dijk, D.-J. (2007). PER3 polymorphism predicts sleep structure and waking performance. *Current Biology*, *17*(7), 613–618. https://doi.org/10.1016/j.cub.2007.01.073

Watson, N. F., Badr, M. S., Belenky, G., Bliwise, D. L., Buxton, O. M., Buysse, D., Dinges, D. F., Gangwisch, J., Grandner, M. A., Kushida, C., Malhotra, R. K., Martin, J. L., Patel, S. R., Quan, S. F., & Tasali, E. (2015). Recommended Amount of Sleep for a Healthy Adult: A Joint Consensus Statement of the American Academy of Sleep Medicine and Sleep Research Society. *Sleep*, *38*(6), 843–844. https://doi.org/10.5665/sleep.4716

Weis, S., Klaver, P., Reul, J., Elger, C. E., & Fernández, G. (2004). Temporal and cerebellar brain regions that support both declarative memory formation and retrieval. *Cerebral Cortex*, *14*(3), 256–267. https://doi.org/10.1093/cercor/bhg125

Wesensten, N. J., Belenky, G., Thorne, D. R., Kautz, M. A., & Balkin, T. J. (2004). Modafinil vs. caffeine: Effects on fatigue during sleep deprivation. *Aviation, Space, and Environmental Medicine*, *75*(6), 520–525.

Whitmire, A. M., Shea, C., Leveton, L. B., Barger, L., Brainard, G., Dinges, D. F., & Klerman, E. (2010). Risk of performance errors due to sleep loss, circadian desynchronization, fatigue, and work load. In C. J. McPhee JC (Ed.), *Human Health and Performance Risks of Space Exploration Missions: Evidence Reviewed by the NASA Human Research Program* (pp. 85–116).

Wilkinson, R. T. (1961). Interaction of lack of sleep with knowledge of results, repeated testing, and individual differences. *Journal of Experimental Psychology*, *62*, 263–271. https://doi.org/10.1037/h0048787

Williams, H. L., Lubin, A., & Goodnow, J. J. (1959). Impaired performance with acute sleep loss. *Psychological Monographs: General and Applied*, *73*(14), 1–26. https://doi.org/10.1037/h0093749

Wittmann, M., Dinich, J., Merrow, M., & Roenneberg, T. (2006). Social jetlag: Misalignment of biological and social time. *Chronobiology International*, *23*(1–2), 497–509. https://doi.org/10.1080/07420520500545979

Wolf, E., Kuhn, M., Normann, C., Mainberger, F., Maier, J. G., Maywald, S., Bredl, A., Klöppel, S., Biber, K., van Calker, D., Riemann, D., Sterr, A., & Nissen, C. (2016). Synaptic plasticity model of therapeutic sleep deprivation in major depression. *Sleep Medicine Reviews*, *30*, 53–62. https://doi.org/10.1016/j.smrv.2015.11.003

Yu, B., Zhang, W., Jing, Q., Peng, R., Zhang, G., & Simon, H. A. (1985). STM capacity for Chinese and English language materials. *Memory & Cognition*, *13*(3), 202–207. https://doi.org/10.3758/BF03197682

List of Figures

II Part 2: Publications

Publication 1

Title: "Recovery sleep after extended wakefulness restores elevated A1 adenosine receptor availability in the human brain."

Authors: David Elmenhorst, Eva-Maria Elmenhorst, Eva Hennecke, Tina Kroll, Andreas Matusch, Daniel Aeschbach, Andreas Bauer

Status: published

Citation: Elmenhorst, D., Elmenhorst, E.-M., Hennecke, E., Kroll, T., Matusch, A., Aeschbach, D., Bauer, A. (2017). Recovery sleep after extended wakefulness restores elevated A1 adenosine receptor availability in the human brain. *Proceedings of the National Academy of Sciences, 114* (16) 4243-4248. *https://doi.org/10.1073/pnas.1614677114. Epub 2017 Apr 3.*

Journal metrics:

- Impact Factor 2019: 9.4[1]

1 https://www.pnas.org/page/about/metrics

Publication 2

Title: "Reestablishment of individual sleep structure during a single 14-h recovery sleep episode after 58 h of wakefulness."

Authors: Eva Hennecke, David Elmenhorst, Franco Mendolia, Matthias Putzke, Andreas Bauer, Daniel Aeschbach, Eva-Maria Elmenhorst

Status: published

Citation: Hennecke, E., Elmenhorst, D., Mendolia, F., Putzke, M., Bauer, A., Aeschbach, D., Elmenhorst, E.-M. (2017). Reestablishment of individual sleep structure during a single 14-h recovery sleep episode after 58 h of wakefulness. *Journal of Sleep Research, 28*(3). *https://doi.org/10.1111/jsr.12641*. *Epub 2017 Nov 24.*

Journal metrics:

- Impact Factor 2019: 3.6[2]

2 https://onlinelibrary.wiley.com/journal/13652869

Publication 3

Title: "Adverse interaction effects of chronic and acute sleep deficits on spatial working memory but not on verbal working memory or declarative memory."

Authors: Eva Hennecke, Denise Lange, Florian Steenbergen, Judith Fronczek-Poncelet, David Elmenhorst, Andreas Bauer, Daniel Aeschbach, Eva-Maria Elmenhorst

Status: published

Citation: Hennecke, E., Lange, D., Steenbergen, F., Fronczek-Poncelet, J., Elmenhorst, D., Bauer, A., Aeschbach, D., Elmenhorst, E.-M. (2020). Adverse interaction effects of chronic and acute sleep deficits on spatial working memory but not on verbal working memory or declarative memory. *Journal of Sleep Research*. *https://doi.org/10.1111/jsr.13225. Epub 2020 Nov 09.*

Journal metrics:

- Impact Factor 2019: 3.6[3]

3 https://onlinelibrary.wiley.com/journal/13652869