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If only I could sleep, maybe I could remember

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Abstract
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Memory lies the ground for human cognitive skills, enabling complex social interaction, abstract thinking, and execution of precise motor skills. Development of these memory functions can be modified by several factors, including previous knowledge, reward, and sleep. In Paper I, skill level already when learning a motor skill determined whether the newly encoded memory would be enhanced during a subsequent post-learning period without training. Those already performing at a high level during learning gained less until recall, whereas those who performed at a lower level during learning demonstrated an enhanced improvement at recall.

Thus, in Paper I we determined modulators of skill enhancement. In Paper II, we actively intended to modulate subsequent motor skill gain by delivering a praise immediately following learning. We found that praise had a positive effect on performance gain, which demonstrates that there are interventions that can easily be applied to enhance motor skill learning across time.

Sleep is vital for healthy cognitive functions, and sleep disruption has not only been correlated with impaired cognitive function in the short-term, it has also been implicated as a risk factor for development of neurodegenerative disorders such as Alzheimer's disease. In paper I, nighttime sleep between learning and recall of a motor memory was beneficial for learning compared to a daytime wake period. In Paper III, depriving participants from sleep negatively influenced performance on a working memory task; as did auditory distractions, but independent from sleep deprivation. However, working memory functions were not equally effected in women and men; working memory functions in women were more affected by sleep deprivation.

Although it is well-known that sleep is good for health and well-being, in today's modern society, most people have access to electricity and internet 24/7, and it is not uncommon to exchange sleep time with spending time in front of screen-based devices, such as smartphones. Access to screen-based devices in the evening and during the night are negatively correlated with a good night's rest. In Paper IV, we did not find support for that the light emitted from those screens play a role for this negative correlation.

Keywords: Sleep, Memory, Learning, Motor skills, Praise, Reward, Sleep deprivation, Sex-differences, LED-screens, Circadian rhythm, Competence-based self-esteem

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In dedication to Millie Eleonora,

For you, I want to be the best and the most courageous I can be,
even when it is hard and I have to fight for it.
For you, I want to show you what it means to follow your dreams
and to stand up for what you believe in.
For you, I want to show you how much it means to have a team around you
that truly believes in you and loves you for who you are.
For you, I want to show you how much love there is in this world,
if we decide to see it and to spread it.
For you, I want to show you what it can mean to be a human in this world,
a woman.
For you, I want to show you that expressing your emotions is a strength.

For you, I want to be brave.

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I Rångtell, F.H., Karamchedu, S., Andersson, P., van Egmond, L., Hultgren, T., Broman, JE., Cedernaes, J., Benedict, C. (2017) Learning performance is linked to procedural memory consolidation across both sleep and wakefulness. *Sci Rep*, 7(1):10234

II Rångtell, F.H., van Egmond, L., Karamchedu, S., Boukas, A., Moulis, A., Ilemosoglou, M., Schmidt, F., Tan, X., Benedict, C. (2019) Praise and competence-based self-esteem alter offline gains in motor skills. *Manuscript*.

III Rångtell, F.H., Karamchedu, S., Andersson, P., Liethof, L., Olaya Búcaro, M., Lampola, L., Schiöth, H.B., Cedernaes, J., Benedict, C. (2019) A single night of sleep loss impairs objective but not subjective working memory performance in a sex-dependent manner. *J Sleep Res*, 28, 1-8

IV Rångtell, F.H., Ekstrand, E., Rapp, L., Lagermalm, A., Liethof, L., Olaya Búcaro, M., Lingfors, D., Broman. JE., Schiöth, H.B., Benedict, C. (2016) Two hours of evening reading on a self-luminous tablet vs. reading a physical book does not alter sleep after daytime bright light exposure. *Sleep Med*, 23:111-118

Contents

Preface

It had been a long day, full of exciting activities. As I was reading “Hattjakten”, she was babbling and pointing at the detailed drawings. As I turned the page, I could feel her breath become slow and heavy, accompanied by a sudden snore, a twitch. Her eyes rolled under her shut eyelids. After a few minutes, she did not react when I corrected her posture, put the pillow under her head, and put socks on her cold feet. I wondered what was going on in her mind, as her neurons were signaling in a synchronized manner. A few hours later when I lay down next to her, her eyes were moving rapidly, her muscles in the face and extremities twitching occasionally. I wondered what was going on inside her mind, as her neurons were signaling as if she was awake, but totally dissociated from the outside world. I drifted off and a vivid world of dreams appeared.

She woke me up as the sun was about to start lighting up the world.

“Mamma, is it morning?”

Without opening my eyes, I mumbled

“No, it’s still night” wishing I had gone to bed earlier the previous evening, and not getting stuck in PhD thesis writing.

Watching my daughter Millie sleep, grow, and learn how this world works, along with the dreams of my youth are what drives my curiosity to study sleep and my fascination for cognitive processes. Sleep is surrounded by mysticism – a time far away from the outside world, where a vivid and bizarre world appears in front of a dreamer’s eye. A world that is full of scary, sensual, happy, irrational, and dark emotions. But this world is not so independent of the external world as one might think; the “real” world impacts our sleep, and our sleep is absolutely vital for our daily function and health. Although sleep is such an integral part of our lives, we know astonishingly little about it. How could that be? Well, it is difficult to study sleep: most of today’s available methods to record brain activity during sleep can also easily disrupt sleep, for instance if the equipment is uncomfortable or makes noises. Despite these challenges, sleep research has virtually exploded in the past years, yet much knowledge is waiting to be unraveled. With this thesis, I aim to de-mystify certain aspects of sleep and the cognitive processes going on while we slumber.

Frida Rångtell
February 2019, Uppsala

Abbreviations

CBSE	Competence-based self-esteem
EEG	Electroencephalography
EMG	Electromyogram
EOG	Electrooculogram
FFT	Fast Fourier Transform
Hz	Hertz
KSS	Karolinska Sleepiness Scale
LED	Light-emitting diodes
N1	Sleep stage 1
N2	Sleep stage 2
NREM	Non-REM sleep
PSG	Polysomnography
REM	Rapid eye movement sleep
SCN	Suprachiasmatic nucleus
SOL	Sleep onset latency
SWA	Slow-wave activity
SWS	Slow-wave sleep
TST	Total sleep time
WASO	Wake after sleep onset

Glossary

Sleep
Although there is no precise definition of sleep, it is characterized by an increased threshold to external stimuli and a lower skeletal muscle activity compared to wakefulness. During sleep, there is also a lack of will-control behaviors (perhaps with an exception for lucid dreaming).

Wakefulness
As for sleep, we lack a proper definition for wakefulness. In general, wakefulness can be thought of as a time when the person, to a higher degree than during sleep, can receive, process, and react to external stimuli.

Sleep stage
Sleep is divided into four sleep stages, which are defined by characteristic patterns shown in a polysomnographic (PSG) recording.

Sleep onset latency
Sleep onset latency (SOL) is the time it takes to fall asleep after lying in bed with the intention of sleep.

Electroencephalogram frequency
The electroencephalogram (EEG) signal is composed of different frequencies, measured in Hertz (Hz). Hz is oscillations per second. Using a power spectral analysis, we can evaluate how much of each frequency that the signal is composed of.

Theta frequency band
Commonly defined as 4-7 Hz.

Sleep stage 1
Sleep stage 1 (N1) typically occurs in the transition from wakefulness to sleep and is the lightest sleep stage, i.e. the sleep stage from which it is easiest to wake someone up from. During N1, the EEG is to a large extent composed of frequencies within the theta frequency band.

Sleep stage 2

Sleep stage 2 (N2) is the most frequent sleep stage throughout a full night of sleep. During N2, the theta frequency is the most common background frequency detected by the EEG. Two characteristic EEG phenomena occur during N2: sleep spindles and K-complexes.

Sleep spindle

Sleep spindles occur mainly during N2, typically lasting for 0.5-2 seconds. A sleep spindle is a sudden burst of higher frequencies (usually 12-15 Hz) compared to the 4-7 Hz that otherwise dominates N2. Sleep spindles are considered important for sleep maintenance, i.e. preserve sleep and inhibit wakefulness, and for memory.

K-complex

A K-complex occurs during N2 and appears as a sudden peak and subsequent dip in the signal. K-complexes are hypothesized to protect sleep and promote a shift toward deeper sleep stages.

Slow-wave sleep and Slow-wave activity

Slow-wave sleep (SWS) is sometimes called deep sleep, as it is very difficult to wake someone up from SWS. SWS has been related to many functions, including to clean the brain and to process memories. The EEG activity during SWS is characterized by low frequencies (<4 Hz) with relatively high amplitude, which indicates that the measured electric activity of the brain is synchronized. The frequency band 1-4 Hz is called slow-wave activity (SWA). SWA is correlated to sleep pressure; higher pressure to sleep results in more SWA during subsequent sleep.

Rapid eye movement sleep

Based on EEG readings, the rapid eye movement (REM) sleep stage appears similar to wakefulness; however, the muscles are paralyzed and it is common to see rapid movements of the eyes; hence the name of the sleep stage: rapid eye movement sleep. REM is important for many functions, including processing emotions, motor memory, and pain sensitivity. During REM sleep, it is common to experience vivid and “movie-like” dreams that sometimes have bizarre and emotional content.

Sleep cycles

The four sleep stages (N1, N2, SWS, REM) oscillate in approximately 90-120-minute cycles across a night of sleep.

Circadian rhythm
Humans have “internal clocks” that follow the natural light-dark cycles of a day. These can be entrained by environmental cues, such as light, temperature, timing of feeding, and timing of activity/rest. These clocks are set to promote wakefulness and activity during the day, and help us sleep during the night.

Suprachiasmatic nucleus
The suprachiasmatic nucleus (SCN) in the hypothalamus is an intrinsic circadian pacemaker, which synchronizes physiological functions and behavior to follow the natural light-dark cycle. The SCN is entrained to the external environment by receiving information from cells in the retina of the eye about light exposure. In addition, SCN controls melatonin production.

Melatonin
Melatonin is a hormone released from the pineal gland in the evening to promote sleep behavior. Light exposure to the eye signals to the SCN, which in turn facilitates melatonin suppression. Darkness stimulates melatonin production.

LED-screens
LED-screens (light emitting diodes) are common technology for screens in smartphones, computers, and TVs. Screens with LED usually emit light with a high proportion in the blue-light spectra.

Sleep pressure
The circadian rhythm promotes sleep behavior during the night and wakefulness during the day. This process interacts with the process of built-up sleep pressure. As time passes since we last slept, the pressure to sleep builds up the longer one stays awake. Previous sleep and activities while awake impact sleep pressure. The exact mechanism behind sleep pressure is unknown, but adenosine has been speculated to be an important factor that builds up with sleep pressure.

Chronotype
Chronotype is the preference for staying up late and sleeping in (“evening-types”), or going to bed early and getting up early (“morning-types”). This preference is not only driven by environmental and cultural factors, but also by genetic components.

Adaption night
Sleeping in the laboratory and wearing the equipment that is used to study sleep is different than sleeping at home. Research shows that sleeping in a new place affects the brain activity during sleep, which keeps us more alert to the environment. Therefore, it is important that participants in a sleep study come

for a first visit (the adaption night) that is not part of the test sessions, during which they get used to the environment and the procedures.

Memory
Memory is the ability to encode, store, modulate, and recall information.

Short-term memory
The short-term memory is the ability to process and hold a limited amount of information for a shorter period of time, and is executed by the working memory system.

Working memory
Working memory is a brain system that can temporarily store and process information, which enables complex cognitive tasks such as planning, reasoning, and learning.

Long-term memory
Long-term memory is the ability to store information for a longer period of time.

Explicit long-term memories
Explicit memories are memories that can be retrieved consciously. Explicit memories can be divided into episodic and semantic memories.

Episodic memory
This is an explicit type of memory for time-related events and personal experiences, and includes information about time, place, and what occurred.

Semantic memory
This is an explicit type of memory for concepts, facts, and general knowledge.

Implicit long-term memory
Implicit long-term memories are memories that can be retrieved unconsciously. There are four types of implicit memories: *procedural*, *associative* (a memory that is associated with another memory, such as a cue that is linked to an event, and learning of consequences of a behavior), *non-associative* (sensitization and habituation due to repeated exposure), and *priming* (a first stimulus influencing the response to a secondary one).

Procedural memory
Procedural memory is implicit memories of motor and cognitive skills. These include motoric movements and language comprehensive skills.

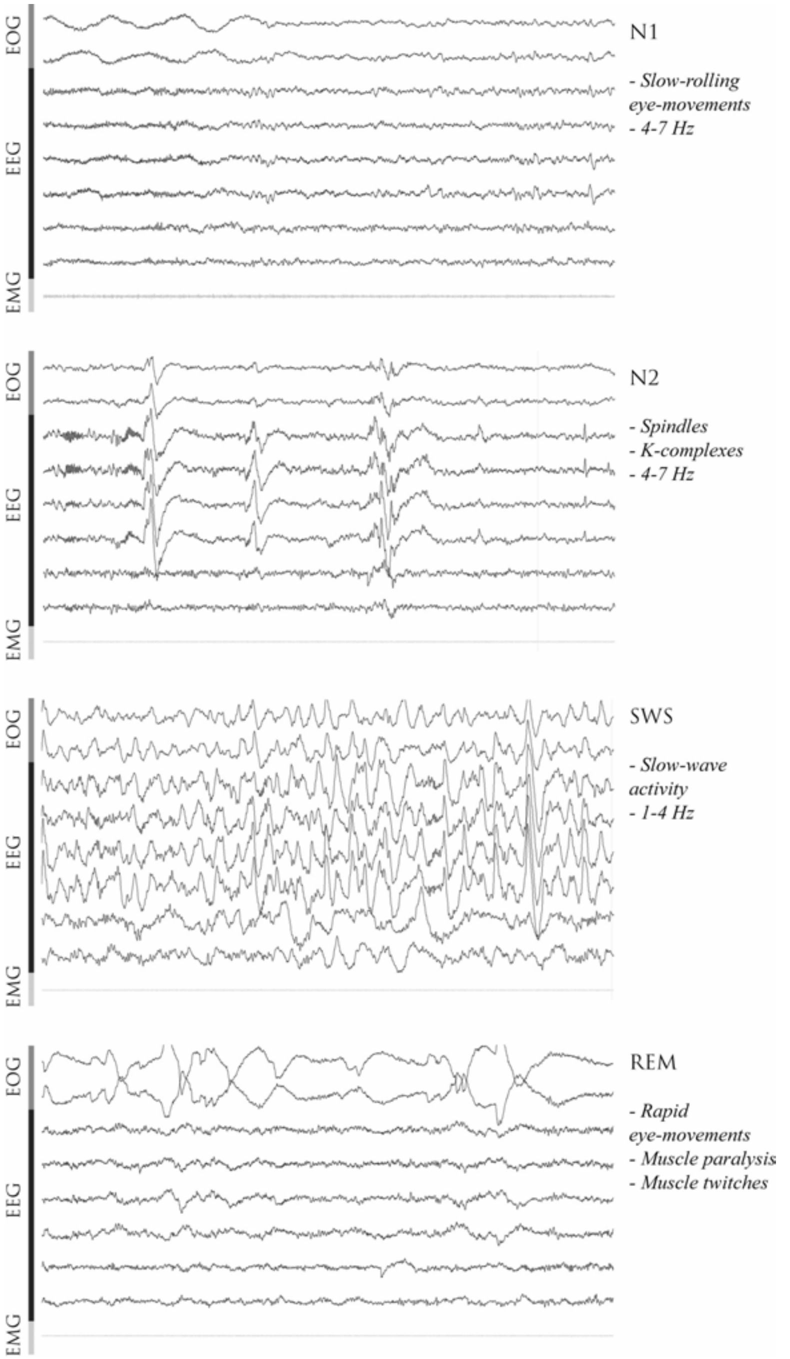
Introduction

Sleep

Sleep is characterized by a loss of attention to the external world. As we snooze, our brain and body are not simply resting. Activity is still ongoing, but very different from wakefulness. This sleep-specific activity and the functions it serves seems to rely on a dissociation from the external world; otherwise the vulnerable and possibly dangerous state of sleep would likely have been selected out across years of evolution. For example, sleepers, compared to non-sleepers, could have been more likely to be eaten by lions.

So what are the characteristics of human sleep? According to the US National Sleep Foundation, an adult (26-64 years old) should get approximately 7 to 9 hours of sleep per night in order to promote good health[1]. However, sleep is much more than a number of hours. During sleep, we cycle through four different sleep stages. These stages have been defined by observing the brain activity during sleep using electrodes placed on different places on the head, as well as eye-movements measured by electrodes near the eyes, and muscle activity[2]. Combined, these measurements are called polysomnography (PSG). *Figure 1* is an example of what the different sleep stages can look like in the PSG. The brain activity is typically measured by electroencephalography (EEG); that is, electrodes placed on the outside of the scalp, recording the sum activity of millions of neurons[3]. When determining the sleep stages, the sleep period is typically divided into 30-second epochs, and each epoch assigned a sleep stage. This is common practice for clinical and research purposes, but it is important to keep in mind that sleep is in reality not divided into epochs or sleep stages; it forms a continuum.

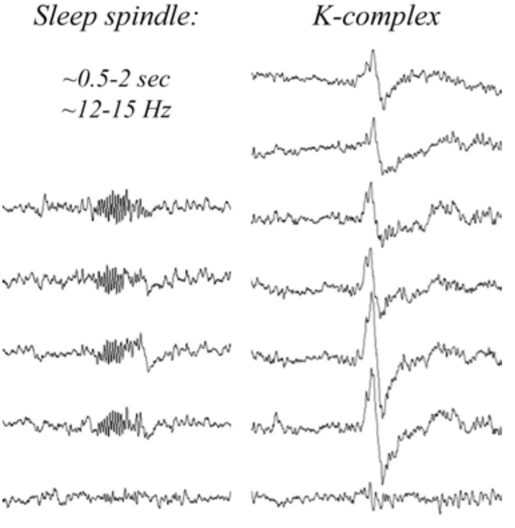
Figure 1. Sleep stages; PSG examples. In each subfigure, the top two signals are for the eyes (electrooculogram, EOG); the following six signals are EEG signals (more frontal signals on the top and signals from the back of the head at the bottom); the bottom signal is muscle movements (electromyogram, EMG). Time window is 30 sec.



Sleep stage 1

The first sleep stage (N1) usually occurs during the transition from wake to sleep[2]. Typically, a full night of sleep is only composed of a few minutes of N1. N1 is characterized by slow-rolling eye movements and slower frequencies in the brain activity compared to wakefulness, with a dominance of 4-7 hertz (Hz), also referred to as the theta frequency band. Hallucinations, called hypnagogic experiences, are relatively common during this transition from wakefulness to sleep, and possibly related to previous experiences[4,5].

Figure 2. Example of a sleep spindle and a K-complex in the EEG signals



Sleep stage 2

Sleep stage 2 (N2) is the most frequent sleep stage during the night, constituting approximately 50% of the time[6]. During N2, the theta activity is still the most pronounced frequency, but is interrupted by two types of EEG events: sleep spindles and K-complexes[2]. Both are thought to protect, maintain, and deepen sleep, for instance by inhibiting processing of sensory stimuli sent to the brain from the external world[7-9]. *Figure 2* shows an example of a sleep spindle (left) and a K-complex (right). A sleep spindle is a burst of higher frequency in the 12-15 Hz band (sigma frequency band) and lasts about 0.5-2 seconds. The sleep spindle is also associated with learning and memory and more sleep spindles correlate with higher consolidation of certain memory tasks[10,11], such as procedural memories. K-complexes are a sudden peak followed by a dip in the signal, as visualized in *Figure 2*.

Slow-wave sleep

Sleep stage 3, or slow-wave sleep (SWS), is also commonly called deep sleep since it is very difficult to wake someone up from this sleep stage[12]. During SWS, slow frequencies below 4 Hz dominate, typically with high amplitude of the oscillations[2]. These slow waves of 1-4 Hz are called slow-wave activity (SWA). The presence of slow waves with high amplitude indicates that there is a high degree of synchronization of the electrical brain activity[13,14]. The SWA seems to serve many functions. For instance, SWA correlates with sleep pressure[15]; that is, the built up pressure to sleep the longer one stays awake. If you have been awake a full night, you will have a higher sleep pressure, and the recovery sleep will thus contain more SWA to compensate.

In recent years, SWA has been implicated in promoting healthy cognitive function by cleaning the brain from toxins and decay after neuronal signaling[16]. Issues with this cleaning process may be related to development of degenerative diseases such as Alzheimer's disease[17,18]. SWA is also important for memory processing and consolidation; it has been proposed that SWA is important for strengthening the important memory traces formed during day (and removing the less important) and transfer them to long-term memory sites[14,19].

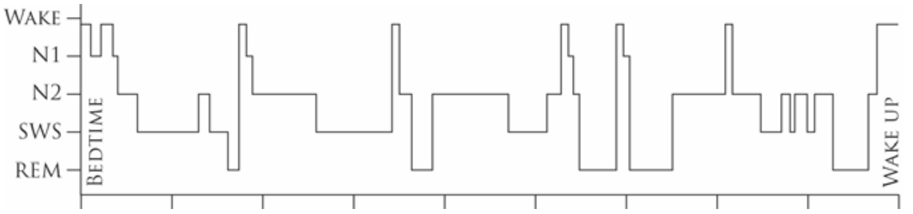
Combined, N1, N2, and SWS are called non-rapid eye movement sleep (NREM).

Rapid eye movement sleep

Finally, the fourth sleep stage is called rapid eye movement sleep (REM). Although the EEG during REM is composed of mixed frequencies and looks similar to wakefulness, REM sleep is characterized by muscle paralysis and vivid dreams, disconnected from the external world. Further demonstrating the paradoxical properties of REM sleep, cerebral blood flow during REM sleep is similar to levels seen during wakefulness; in contrast to SWS, where cerebral blood flow is decreased[20,21]. During REM, our skeletal muscles are paralyzed, with the exception of occasional muscle twitches. These muscle twitches have been implicated to play a role for motor control and development[22,23], but their functions are still largely unexplored. In addition to the muscle twitches and paralysis, during some parts of REM sleep, we can detect rapid eye movements, measured by the electrooculogram (EOG) which measures eye movements.

REM is sometimes called dream sleep, which to some extent is misleading. We can dream during all sleep stages; however, the REM dreams are perhaps the most bizarre, vivid, and movie-like dreams compared to the dreams in NREM[24]. Even though we do not know why we dream or how dreams are produced, dreams seem to play a role for memory processes[24-27]. Dreaming of a memory task can improve learning during sleep[26,27]. Further, REM sleep is probably important to process emotions and emotional memories[28]. In addition to learning, dreams, and emotions, REM appears to be involved in pain control[29].

Figure 3. Schematic hypnogram exemplifying how sleep stages alternate during a night of sleep



Sleep cycles

Together, these sleep stages cycle in a particular pattern, each with an approximate length of 90-120 minutes in adults. *Figure 3* is a schematic overview of how the sleep stages can alternate during one night. Note the short periods of wakefulness that occur at several occasions, which likely goes unnoticed by the person sleeping. Whether noticed or not, waking up several times per night is a part of a normal sleep.

Earlier in the night, SWS is more abundant, but decreases with time. At the same time, the amount of REM sleep increases throughout the night, with most REM occurring toward the end of sleep. As mentioned earlier, the sleep stages seem to serve different functions, but cation should be taken when treating them as separate units; by observing how the sleep stages cycle during a sleep period, it is more likely that they serve complementary functions. For example, sleep has been proposed to promote creativity, and it has been debated which sleep stage that is the major contributor to this[30]. Creativity generally requires a reorganization of knowledge in order to reach novel solutions. Lewis et al.[30] suggest that the brain processes during NREM and REM work synergistically to complement each other and thereby to boost creativity. NREM sleep could be important for the construct of rules from learned information, while REM sleep supports associations of the learned information with previous knowledge, thus creating novelty. Therefore, the temporal order of the sleep stages and their duration is proposed to be critical. Processing of a memory during REM is dependent on its processing during prior NREM. Thus, how the sleep stage composition within each sleep cycle progress throughout a night is of importance.

Although there are some general features of human sleep, sleep composition can vary substantially between individuals, likely due to differences in genetic and developmental traits, age, sex, physical and psychological health status, lifestyle, and environment. Hence, an individual approach to sleep research and clinical work is warranted.

What is a good night's sleep?

In the previous section, several key features of normal sleep were described. But what does it mean to have a good night's sleep? This is a key question that we need to address when we want to study sleep and identify relevant outcome measures of improved or impaired sleep, for instance due to an experimental intervention. First, consider what happens when turning the question around: what is optimal wakefulness? How we spend our wake time varies immensely between people and between different days. Yet, there are some key things that we can identify to have a positive effect on our health, such as: sufficient physical activity, healthy food, free of diseases impacting our well-being, time with people that we care about and that makes us happy, time for contemplation, consistency of routines between days, and to engage in things that gives us meaning. With this in mind, measures of these key factors can be used to get a rough assessment of if a person is healthy during their wake time. However, identifying only few key factors about wakefulness that can be used to in full determine if a person is having a healthy and meaningful wake time is probably an impossible quest. There is a tendency and a desire, both among sleep researchers and among the public, to try to simplify sleep, searching to identify one or a few key variables to determine what is good or bad sleep. It is likely that sleep is just as complex and diverse as wakefulness, but we currently lack the tools or the conscious experience while sleeping to properly evaluate sleep. In this sense, trying to investigate how different factors impact sleep is, with our current techniques, a mission of simplifications. How can we explore effects of, for instance, lifestyle factors on sleep, when we do not have a consensus of what a good sleep is?

Sleep varies with culture, environment, age, and history. In a study on actigraphically measured sleep patterns in a hunter-gatherer community in Tanzania, this group of people were found to have short nocturnal sleep and poor sleep efficiency, while it was common that they were taking daytime naps when given the opportunity[31]. At the same time, their circadian rhythm was strongly entrained to the environmental cues. The authors concluded that sleep in this group showed signs of flexibility. They propose that the results from their and other's studies together indicate that human sleep is characterized by its flexibility to adapt in response to factors influencing sleep, such as environmental and social factors. If human sleep is characterized by its possibility to adapt, how can we reach a consensus for a definition of optimal sleep?

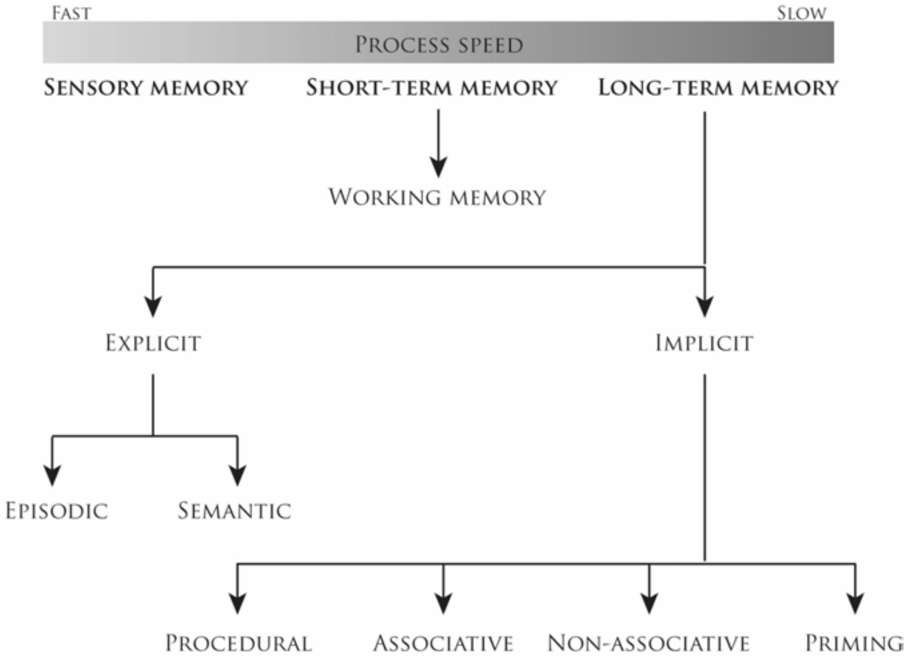
Without a golden standard for optimal sleep, when we study sleep we are limited to use characteristics of sleep that have been correlated to positive outcomes on health and cognitive functions, just as we do when studying wakefulness. Sleep characteristics that have been correlated to positive health effects, such as cognitive function, cardiovascular health, and immune function, include: sleep time 7-9 hours for adults; sufficient SWS, sleep spindles, and REM; in addition to a subjectively rated high sleep quality and low subjective daytime tiredness. It is important to keep in mind that the outcome measures we use to study sleep are still rough estimates of a good night's sleep, and the reality is much more complex. Thus, results such as "an intervention increases time in SWS" should be interpreted in a holistic manner, leaving space for uncertainty in how this actually impacts sleep and health, and not only interpreted in a binary manner (i.e. sleep was good/bad).

With this in mind, several of the studies in this thesis are using a within-subject design; that is, the same person underwent both an intervention condition and a control condition, enabling to compare outcomes within each person. This method can to some extent control for between-individual variances in sleep and memory that are otherwise difficult to control for.

Memory

Memory serves many functions for survival and interactions in society. We have different types of memories, which are learned, processed, stored, and retrieved in different ways and locations in the brain. In addition, the processing of memory has different time-windows, such as processing of sensory information (fast process), short-term memory (temporary holding something in memory), and long-term storage (slow process)[32]. Short-term memory is the ability to keep information accessible in mind for a shorter period of time and to process and act on this information. The working memory system includes the structures and processes that enable short-term memory. It also facilitates the processing and execution of complex cognitive tasks, such as to plan, reason, learn, and perform goal-directed behavior[32-35]. *Figure 4* demonstrates how the different memory types can be classified.

Figure 4. Overview of how memory can be divided into different types with different functions. Inspired by Camina and Güell[32].



Long-term memory can hold memories for longer periods of time, sometimes even a whole life-time. Long-term memory is divided into two categories: explicit (also called declarative) and implicit (also called non-declarative)[32]. Explicit memories can be retrieved consciously and includes episodic and semantic memories; that is, memories of past events and experiences, as well as general knowledge and concepts including factual knowledge.

When implicit memories have been learned, they can be retrieved automatically, without requiring consciousness[32,36]. Implicit knowledge includes four sub-categories (see *Figure 4*), of which procedural skills is most relevant for this thesis. Procedural skills include perceptual skills, cognitive skills, and motor skills[37]. Perceptual skills include language comprehension, both written and spoken. The implicit component of language comprehension is very important in order to effectively, and with less effort, understand and speak language; for instance, without the need to consciously remember grammar when listening to someone talking. Procedural memories also include cognitive skills. Cognitive skills involve problem-solving, which require involvement of a combination of several cognitive skills. Finally, motor skills are the motoric action required to perform a desired movement.

The explicit and implicit memory systems are separated, both functionally as well as brain location-wise[36]. However, when we learn new skills and encounter new situations, the two memory systems most likely interact. The implicit memory system can respond fast and use incredible amounts of information, and it is thus very effective[36]. This is in part due to its ability to work automatically, without the need for prefrontal involvement, and thus without the need for consciousness[36]. In implicit memory tasks, even if the person selects the correct answer, they can usually not explain why they responded as they did. The explicit memory system on the other hand is dependent on the prefrontal cortex and working memory to function. It requires more resources and thus has a more limited capacity[36]. It mediates conscious thoughts and reflection, which is an important part of being human.

Learning a new language is a good example of how these two memory systems function and how they cooperate. Learning a language as a toddler only depends on the implicit memory system[36]. The toddler learns by hearing other people speak, thus generating concepts and rules for how the language is structured. The toddler also practices the sounds of the language, which can then be put into words, and then those words become sentences, in a trial-and-error manner. Immediate feedback is given about the sounds they make in a binary manner: "yes, the sound I made is the same sound as I heard my parent make when talking", or "no, I need to adjust it". In contrast, to learn a new language as an adult can require much more effort, and rarely results in the notion that "I use this grammatical rule because it just feels right", without really knowing why. Learning a new language as an adult is more dependent on the conscious explicit memory system, and is thus more ineffective and slow[36]. Nevertheless, an adult can learn a new language and form implicit memories of it, enabling efficient comprehension, even if it is a slower process. Thus, when beginning to learn a new language as an adult, the memories are more explicit, whereas with learning, the memories become more implicit and there is a higher degree of automatized processing[36]. The same learning pattern applies to many other skills, such as motor skill learning of playing soccer, playing guitar, or dancing ballet; the list could be as long as this thesis!

Processing of motor skill memories involves several stages, including: initial training of the skill (online processing), offline consolidation occurring after training, and retrieval of the skill[38]. In other words, training and repetition of a task can increase performance, but processing of the task can also continue offline. Offline processing does not involve active training and repetition of the memory, and can include periods of both sleep and wakefulness. Newly acquired motor skills can be stabilized or even enhanced during an offline period, for instance including sleep[39-43]. This offline processing is thought to stabilize the memory that is initially rather fragile. Two of the studies included in this thesis (Paper I and Paper II) focus on motor skill learning and offline processing.

Sleep and motor memory

During recent years, the role of sleep in memory processing has received increased attention. For instance, sleep can be important for newly acquired explicit memories and emotional memories[14]. There is also evidence that sleep could positively contribute to procedural memory processing[41,44,45]. However, whether and how sleep affects procedural memories is still up for debate[43,46,47]. While sleep can substantially enhance skill gain from a learning session to a delayed recall session[14,40,44,45] (the sessions divided by a period of sleep), a meta-analysis did not conclusively support an enhancement effect by sleep on procedural skill gain[48]. Further complicating the matter, increases in motor skill performance also occur after shorter periods of rest even if the rest period does not include sleep, suggesting that sleep may not be a prerequisite for offline motor skill enhancements[43,49,50]. Nettersheim et al.[43] contributed to the debate with an elegant study which showed that there is a short-term boost in performance gain that occurs 30 min after training. The levels of performance enhancement were comparable to those commonly seen after an offline period of sleep. However, four hours after training, task performance was not better compared to the learning session; thus, the early enhancement effect was abolished. If sleep occurred within 30 minutes after training, enhancement levels similar to those seen after 30 minutes were preserved. If sleep occurred four hours after training, performance was restored and recovered to performance gains similar to those seen during the early enhancement period 30 minutes after the learning session. This indicates that perhaps sleep stabilizes and restores, rather than enhances, motor skill learning. However, as the next section describes, there are several possible explanations for the outcome variability between studies on motor skill gain and sleep.

Determinants for motor skill learning during sleep

The discrepancies in the literature regarding the effects of sleep on motor skill learning could be driven by several contributing factors. First, the extent of skill gain after sleep seems to depend on certain aspects of sleep. For instance, sleep spindles and REM are positively correlated with a higher procedural skill gain after sleep[45,51-53]. It is also possible that other, currently unknown, sleep-related variables on the macro and micro architecture levels are important for sleep's role in motor skill processing. Differences in sleep spindles and REM sleep between studies may contribute to different results of sleep on motor skill gain.

Second, not all memories and experiences from a day are equally consolidated during subsequent sleep. Which memories are prioritized to be processed during sleep and how is that determined? There are several factors that can impact sleep's role for motor memory processing; including possible rewards[54,55] and emotions related to the task[56], as well as if the knowledge gain from the task is expected to be relevant in the future[57]. Further, initial level of expertise and difficulty of a motor skill task may modulate subsequent gain after sleep. In line with this, offline processing of a more difficult and complex motor skill task has been shown to be prioritized over an easier one[58]. Another study showed that restricted learning before sleep resulted in motor skill improvements after sleep[59]. Whether (and how) task difficulty affect subsequent performance gains is still up for debate, but variations in task difficulties or participants' baseline performance could to some extent explain between-study differences in the role of sleep for motor skills. This topic is in part addressed in Paper I of this thesis, where the aim was to investigate how participants' motor skills during an evening learning session impact subsequent offline gains across sleep. We found that those who performed at a lower level at learning gained more from the offline period.

Self-esteem is the personal evaluation of one's own value[60]. Self-esteem can to different degrees rely on achievements and success. This component of self-esteem is termed competence-based self-esteem (CBSE)[61]. The self-esteem of a person with high CBSE is vulnerable to variability in performance and success; thus, a self-esteem that is more internal, and to a lesser extent rely on CBSE is believed to be preferred[60,61]. We hypothesize that self-esteem, and particularly self-esteem related to competence and achievements, could influence learning processes. However, to our best knowledge, no study to date has investigated how competence-based self-esteem relates to acquiring new skills and knowledge. With this in mind, in Paper II, the impact of CBSE on motor skill learning was investigated. We are the first to show that a low CBSE relates to greater offline gains in finger skill.

Furthermore, reward, possibly driven by increases in the neurotransmitter dopamine in reward- and motor learning-related brain areas, can boost motor skill learning[54,55]. Thus, inconsistencies between studies in the context in which a motor skill task is performed could result in variability in the rewards related to task performance that participants may perceive, and could therefore affect performance gain after sleep. Most studies that investigate the effect of reward on performance gain over sleep have utilized a monetary reward. However, there are many situations where enhancing motor skill learning could be of value, but where it is not appropriate to use monetary rewards, such as in schools or during rehabilitation of motor skills. Sugawara et al.[62] instead investigated the effect of a verbal praise (delivered as a pre-recorded video) on subsequent offline gains in motor skills. All participants were praised for their performance at learning, irrespective of their actual performance. Sugawara et al.[62] demonstrated that performance gain to the next day was enhanced in those who received the praise after learning. In Paper II, we studied the effect of praise on motor skill learning, while removing possible confounding effects of human experimenter-participant interactions that are otherwise difficult to control for. Therefore, the praise was administered as a text displayed on the screen in the same program as the task was performed. Additionally, the aim was not only to study short-term effects on motor skills, but also to see how motor memories develop over time using both a 12-hr as well as a one-month delayed recall. In Paper II, we show that a text-based praise can enhance motor skill learning in the long-term.

In summary, the extent of motor skill gain during sleep are dependent on several factors, which in human experimental studies could partly explain inconsistencies between studies on sleep and motor skill processing. For instance, participants' sleep composition, initial skill level, competence-based self-esteem, and perceived rewards may contribute to variations in overnight skill gain.

Sleep deprivation and working memory

As discussed earlier in this thesis, it is difficult to study sleep and to define representative outcome measures. One way to tackle that challenge is to instead study what happens when we do not sleep. In this way, we increase our understanding of why and how sleep is important. Sleep is undoubtedly vital for survival; for example, when rats were kept awake, death occurred already after 11-32 days[63]. In the short term, acute sleep deprivation makes it more difficult to handle stress[64] and process emotions[65,66], increases pain sensitivity[29], promotes increased food intake and weight gain[67-69], and affects immune cells[70], and in general puts the body in a stress-reactivity mode. Chronic sleep disruption has been linked to increased risks of a variety of different diseases such as cardiovascular issues, obesity, type-2 diabetes, cancer, and neurodegenerative diseases such as Alzheimer's disease[71-73].

Sleep deprivation can also impact memory processes. Working memory is key in higher executive functions such as complex reasoning and planning[33-35]. Vigilance and decision-making, which are components of working memory, can be impaired by acute sleep loss[74-76]. An impaired working memory could be annoying to a person trying to plan the day or reflect on life. It could also be potentially dangerous; for instance, when entering a round-about in traffic and trying to pay attention to other cars as well as potential pedestrians, and at the same time planning where to drive and coordinate proper movements. What happens to working memory functions when an auditory distraction is added in addition to the load from sleep deprivation? Again, consider the driving scenario: imagine that at the same time as the driver is entering the busy round-about, a person sitting in the back of the car is simultaneously talking to the sleep-deprived driver and giving (bad) driving directions. There are indications that task-irrelevant auditory distractions can impair working memory performance[77]. To the best of our knowledge, in Paper III, we were the first to show that task-irrelevant auditory distractions and sleep deprivation both impair working memory performance, but in a separate manner.

Sleep deprivation and working memory: sex-differences

Why should potential sex-differences be investigated in studies on cognitive consequences of sleep deprivation? First, it is not necessarily the case that women and men respond in the same way to sleep disruption. In fact, women and men can differ in how they are affected by sleep disruption, such as with regards to metabolic functions[78,79] and pain sensitivity[80]. Second, in support of sex-differences in sleep, women and men are differently affected by sleep problems. Women are more likely to suffer from insomnia than men[81], to perceive their sleep quality as less satisfactory[82], to report a longer sleep requirement, and to wish to receive treatment for sleep issues[83]. There are indications that sleep architecture on the macro and micro level differ between women and men[84]. Although studies are sparse, women might have more SWS compared with men[84], and with age, SWS decreases more in men than in women[6]. The etiology behind these differences is unknown, but it is plausible that women and men have different sleep requirements. With this background, it is quite surprising that there are relatively few studies that investigate sex-differences in sleep and effects of sleep deprivation.

As suggested earlier, sleep deprivation might impair important working memory functions that are vital for conscious cognition. For certain aspects of working memory functions, men and women seem to differ in their performance under normal sleep conditions[85,86]. A study investigating working memory in aging found that working memory functions declined more in men than in women as they aged; whereas working memory functions increased more with increasing education levels in women compared to men[87]. A possible explanation for these sex-differences in working memory could be that women and men activate different brain areas during working memory performance, as suggested by Hill et al.[88]. Related to this, working memory performance was found to deteriorate more in women than in men under extended wakefulness[89]. Thus, there is indication that women and men might react differently to sleep deprivation with respect to working memory functions. Therefore, Paper III additionally investigated whether effects of sleep deprivation and auditory distraction on working memory differed between women and men.

Technology use, sleep, and circadian rhythm?

As highlighted earlier in this thesis, sleep is vital for health and well-being. Though, in our modern society, access to internet and electricity facilitate wakeful activity on a 24/7 basis. There is a negative correlation between evening and night access to screen-based media devices, such as smartphones, but it is currently unknown what drives this negative correlation. One of the hypotheses is that evening exposure to the light emitted from these screens can delay our circadian rhythm.

Circadian rhythm

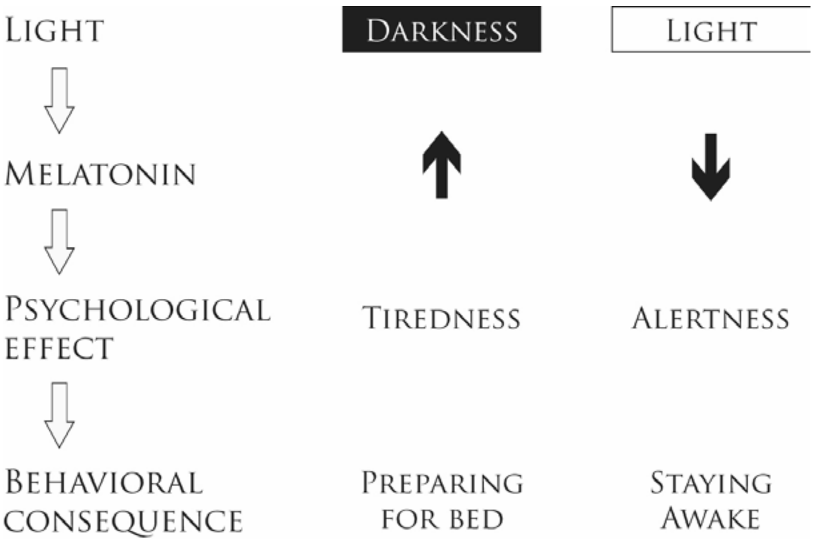
Our sleep and wake rhythm during the day is thought to be controlled by two main biological processes: sleep pressure and the circadian rhythm[15]. Sleep pressure increases with increased time spent awake. An increased sleep pressure results in compensatory increases in SWA[15]. Hypotheses for the mechanisms behind the building up of sleep pressure range from increases in adenosine[15] to build-up of increased synaptic strength in certain neuronal circuits during wakefulness (based on a study in fruit flies)[90]. Yet, the mechanisms behind sleep pressure in humans have yet to be revealed.

More is known about the other process controlling timing of sleep and wakefulness: the circadian rhythm. Our bodies have an intrinsic clock setting our inner time. This clock is entrained to the external world by different cues, of which light is one of the strongest driving forces[91]. Through this system, we can adapt our biological processes and behavior to the natural conditions that we live in, to promote wakefulness and activity during the day, and sleep and rest during the night[91,92]. The entrainment by light is mediated by light exposure to the eye, relaying the information to the suprachiasmatic nucleus (SCN) in the hypothalamus. The SCN can be thought of as the major central pacemaker for circadian rhythms[91-93], although it has been speculated that other central circadian pacemakers may also exist[94]. The SCN pacemaker can oscillate independently with a near 24-hour rhythm, even if the cells are isolated from the SCN and put in cell culture[91,95]. All cells in the body have their own clocks, resulting in daily fluctuations in activity, gene expression, and other biological processes, which ultimately influence behavior[94]. SCN plays a very important role for synchronization of all the clocks in both central and peripheral structures. This is done in part by SCN-induced control on the pineal gland synthesis of melatonin[92-94,96].

Melatonin is a hormone involved in a diversity of functions, of which we have likely just scratched the surface[97]. Among those are antioxidant actions and sleep-promoting properties. Melatonin synthesis is stimulated by darkness, and inhibited by light exposure to the eyes[92,93,96,98] (see *Figure 5*). When melatonin is released into the blood-stream, it is subsequently spread throughout the body, however it is metabolized rather rapidly. Melatonin levels typically display a steep rise in the evening and are high during the night, while plasma melatonin levels are low during the day, especially if exposed to bright natural light. Thus, blood concentrations of melatonin exhibit a clear circadian rhythm[92,93,96]. The circadian rhythm, mediated by SCN output, controls circadian rhythms of sleep and wakefulness, body temperature, timing of feeding, timing of activity and rest, and a host of other functions to match the natural light–dark cycle[98].

Sleep is most probable when a high sleep pressure coincides with circadian signals indicating night time. Thus, the processes of sleep pressure and circadian rhythm interact[15]. In the next section, evening use of media devices with light-emitting diode (LED) screens will be discussed from a circadian point of view.

Figure 5. Melatonin and light.



Screens, light and circadian rhythm

One of the major challenges in today's society is to understand how developments in technology and how we use technological devices impact us and our health, both in the short and long term. As technological developments and human behavior patterns have been rapidly changing, it has been a challenge for scientists to address the effects of these devices and behavior changes on sleep and well-being.

Use of technological screen-based devices are common in the evening[99], but studies are increasingly associating evening use of screen-based media devices with impaired nocturnal sleep in both children, adolescents, and adults[99-104]. However, as most studies have been observational cross-sectional studies, it is difficult to ascertain causality. Information about the etiology behind this relationship of evening use of media devices and sleep is sparse; one of the proposed hypotheses has been that evening exposure to the light that media devices emit could be a hazard for sleep. These devices commonly have LED screens, with light enriched in the blue-light spectra. Since inhibition of melatonin production is most sensitive to short wavelengths[91], a plausible hypothesis is that screen-based devices may alter the ability to fall and stay asleep. Studies on exposure to short-wavelength light in the evening have detected suppressed melatonin levels, decreased subjective sleepiness, delays in sleep onset time, prolonged SWS latency, and increased time in N2, but decreased REM[105,106]. Studies have also tested the effect of evening tablet screen exposure on sleep and circadian rhythm[107,108]. In one study, participants either read on a tablet or on physical books for four hours in the evening during five consecutive days. Tablet exposure resulted in delayed evening rise of melatonin, accompanied by decreased subjective sleepiness and increased sleep onset latency (SOL). In addition, REM sleep time was reduced. Although this study has received much attention, there are other studies that show contradicting results. For instance, in a study with adolescents, one hour of evening tablet exposure was compared to the same intervention, but with a short-wavelength filter applied to the tablet light[109]. In contrast to the study by Chang et al.[107], they did not find any effects on evening tiredness or SOL. Neither did they see any differences between the interventions with respect to minutes spent in SWS and REM (this was only reported for the two first sleep cycles). Additionally, in a study from Norway[108], participants read on a tablet in bed for half an hour right before bedtime, which resulted in reduced evening sleepiness and early-night SWA; however, neither sleep-onset latency nor time spent in the different sleep stages were altered by screen exposure. Given the contradictory results in the field, Paper IV aimed to clarify the effects of screen light exposure in the evening compared to physical book reading on sleep and circadian outcome measures.

Research questions and hypotheses

Overall aim:
In general, my studies aimed to further elucidate 1) the connection between sleep and memory, and determinants of learning, 2) factors impacting sleep, and 3) effects on our cognitive ability when we do not sleep. In addition, one of my aims has been to include both female and male participants, and when possible investigate sex-differences. Addressing this question is important, since previous work has provided evidence for sex-differences in sleep and memory, which could impact health and everyday functions, yet has not received sufficient recognition in sleep research. Taken together, my work aims to increase knowledge about sleep and memory, and factors that influence these brain processes. *Figure 6* is an overview of the hypotheses for the studies where a regular night's sleep was employed (Papers I, II, and IV), whereas *Figure 7* is an overview of the study including sleep deprivation (Paper III).

Research question paper I:
Does initial skill level on a motor task impact the degree of performance gain to a delayed recall after a night of sleep and a day of wakefulness?

Hypothesis paper I:
We hypothesized that performance levels at learning would correlate with overnight performance gains, insofar that those with higher initial skills would gain less from a night of sleep compared to those with a lower motor skill performance at learning. Sleep may play a particularly important role when a motor skill memory is converted from needing a high degree of conscious top-down activity when performing the movement, to a more automatized skill. Therefore, a memory that has already undergone the automatized process may be more robust and may not require an offline period of sleep to the same extent. Based on previous studies, we also hypothesized that a retention interval of sleep would be more beneficial than wakefulness.

Research questions paper II:
Could a text-based praise after learning have short- and long-term consequences on motor skill gain across time? Is an effect of praise modulated by competence-based self-esteem?

Hypothesis paper II:
Previous studies indicate that human memory processing is sensitive to praise; thus, we hypothesized that a text-based praise could elicit positive effect on skill gain from learning to short-term recall, and potentially also to long-term recall a month later. In addition, we hypothesized that an effect of praise may be enhanced in participants with a higher competence-based self-esteem, which is a self-esteem more dependent on one's abilities and external input.

Research questions paper III:
How does sleep deprivation impact working memory? Does auditory distraction impair performance on a working memory task equally after a night of sleep as after a night of sleep deprivation? Are females and males equally affected by sleep deprivation with respect to working memory?

Hypothesis paper III:
Considering previous research on the effects of sleep deprivation on cognitive function, we hypothesized that sleep deprivation would impair working memory. Further, sound distraction during a working memory task may impair working memory performance; however, whether a person is more or less prone to working memory impairment by sound distraction after sleep deprivation is unexplored. We hypothesized that a sleep deprived person is 1) either more sensitive to a sound distraction due to a generally worse ability to inhibit their response to an incoming stimulus, 2) or, conversely, better at shutting out sound distraction if the working memory task is engaging enough since they may have difficulty focusing attention on two things at once.

Although sex-differences in effects of sleep loss is still a topic in need of further exploration, a previous study indicate that females and males react differently to sleep disruption with respect to working memory. We therefore hypothesized that there might be sex-differences in working memory performance after a night of sleep deprivation.

Research question paper IV:
Does evening exposure to light emitted from LED screens impact evening tiredness and melatonin, as well as sleep variables and morning tiredness?

Hypothesis paper IV:
Previous studies indicate that evening exposure to LED screen light could impact melatonin release, which in turn can reduce evening tiredness, delay SOL, and increase morning tiredness. We therefore hypothesized that reading on a tablet in the evening, compared to reading the same book as a physical book (thus, the light from the tablet the only thing differing between conditions), could increase alertness and SOL, while decreasing melatonin levels.

Figure 6. Overview of the studies that include a full night of sleep. In Paper IV, exposure to LED screen light in the evening was hypothesized to impact sleep. In turn, in Paper I, sleep, as well as performance at the initial training session, were hypothesized to impact offline gain in finger tapping skills. In Paper II, a self-esteem to a high degree dependent on one's competence was hypothesized to influence offline processing in finger tapping skills. In addition, an active intervention with the aim to improve finger tapping skills was applied in Paper II: half of the participants received a text praise immediately after initial training.

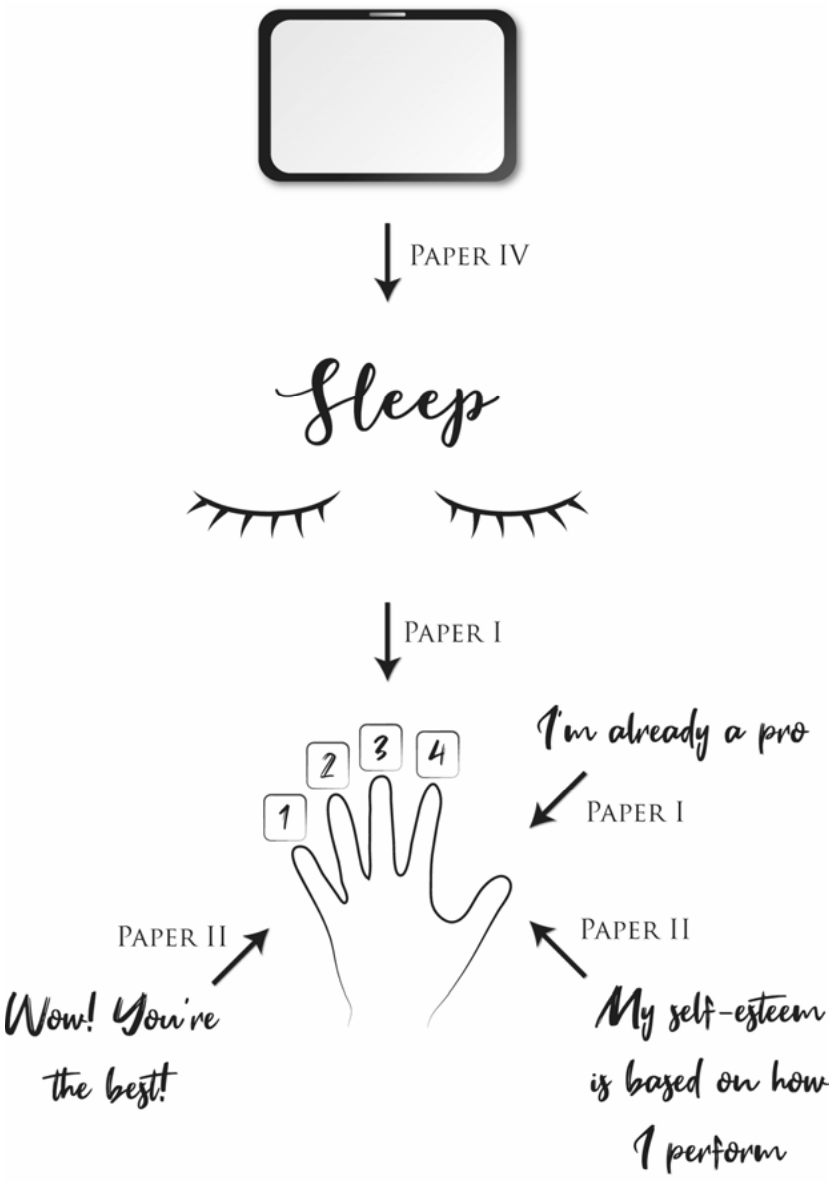
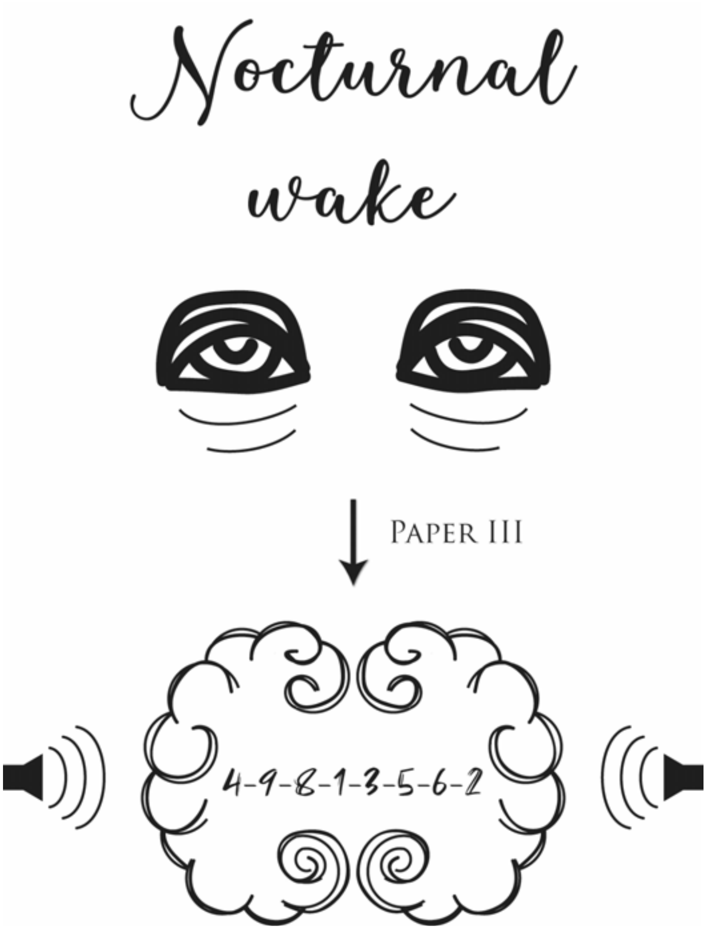


Figure 7. Overview of the study including a full night of sleep loss. In Paper III, sleep deprivation was hypothesized to impair working memory function. Auditory distraction was also hypothesized to impact working memory, possibly interacting with the effect of sleep loss.



Methods

All the studies included in this thesis were performed at the Department of Neuroscience at Uppsala University.

In short, the four studies were planned as follows:

Paper I The key outcome measure in this study was offline improvement on the motor sequence finger tapping task. Data on improvement over nocturnal sleep was combined from several studies previously performed in our lab, forming the sleep condition group. A wake condition group instead performed the task in the morning and was tested in the evening (that is, an offline period of wake instead of sleep). Participants in the sleep group slept in the lab.

Paper II The main outcome measure in this study was again the motor sequence finger tapping task. Half of the participants were given praise directly following learning on the task, and half did not receive this praise. The learning session was scheduled in the evening, a retest the following morning, and a delayed retest a month later. Participants slept at home in the night between experimental sessions.

Paper III This study had two conditions: a full night of wakefulness (sleep deprivation) and a night of sleep. Comparisons were made within each subject. In the morning, participants were tested on a working memory task with a sound distraction component. The participants were kept in the lab throughout both of the conditions.

Paper IV In this study, each participant took part in two study conditions: reading a book on a tablet for two hours in the evening, or reading the same book as a physical book for the same duration of time. Outcome measures were evening tiredness, evening melatonin, sleep composition, and morning tiredness. The participants were kept in the lab throughout both conditions.

Participants

The participants in the studies included in this thesis were all: assessed to have a good general health and normal sleep habits, young adults, and free of medications, with exception for the females, who were all using combined hormonal contraceptives. The reason why the included females were supposed to use hormonal contraceptives is because there is an indication that both sleep and memory performance can vary across the menstrual cycle[110-112]. In addition, experimental sessions of the female subjects were scheduled on days when they were taking the active contraceptives (and e.g. not during the week of taking sugar pills), reducing the likelihood that fluctuating sex hormone levels would differ between sessions. All participants provided written informed consent and the studies were conducted according to the Declaration of Helsinki and approved by the Regional Ethical Review Board in Uppsala, Sweden. The number of included participants in each study in this thesis are stated in *Table 1*.

Table 1. Number of participants in the studies. N = number of participants

Study	*N, Females*	*N, Males*	*N, Total*
Paper I	35	79	114
Paper II	38	40	78
Paper III	12	12	24
Paper IV	6	8	14

Adaption night

All participants that were to spend an experimental night in the sleep laboratory, participated in an adaption night in the sleep laboratory prior to the experimental nights. This was to reduce possible bias from the first-night effect on sleep maintenance, and to increase quality in the experimental sleep night[113].

Assessing sleep

In the four papers in this thesis, sleep was evaluated in several complementary dimensions. Questionnaires were used for different purposes such as, estimating participants' sleep habits and sleep quality, their chronotype[114,115], their daytime sleepiness[116], as well as current sleepiness[117,118]. In the days leading up to the experimental sessions, participants were usually given instructions to maintain specific bedtime routines. In order to validate that the participants had adhered to our instructions, they were asked to fill in a sleep diary, sometimes in combination with a wrist actigraph (wActiSleep+, ActiGraph LLC, Pensacola, FL, USA) or an Actiheart recording (Cambridge Neurotechnology, Cambridge, United Kingdom) to confirm the reporting from the sleep diary. Actigraphies and Actiheart are small devices that can easily be applied and worn for longer periods of time. Actigraphy measures movements and the Actiheart device measures variables related to heart activity. Both can be used to evaluate periods of rest/wakefulness.

PSG is the most reliable measurement we have of sleep today, but also the method that is the least easy to apply and to wear for longer periods of time. PSG is also the method that is most disruptive to a person's sleep compared to questionnaires and actigraphy. Nonetheless, it is the only validated measure we currently have to determine sleep stages and it is the golden standard in measuring sleep. A PSG requires at least these three signals: EEG for measuring the brain activity (placed on the scalp in certain positions, based on a standardized system), EOG for the eye movements, and electromyogram (EMG) for the muscle movements. The EEG signals are typically placed over the frontal, central, and occipital areas. It is important to keep in mind that EEG is precise in measuring events in real time, but the spatial resolution is low compared to measuring brain activity using functional magnetic resonance imaging (a method that instead has a lower time resolution). These three signals enable scoring of sleep stages. In studies where PSG was recorded, visual scoring of the PSG data was done in 30-second epochs. The output included minutes until sleep onset (SOL), minutes from sleep onset to the first epoch of SWS or REM (SWS/REM sleep latency), total sleep time (TST), time awake after sleep onset (wake after sleep onset, WASO), and time in sleep stages (N1, N2, SWS, and REM) or their relative percentages out of TST.

Dividing sleep into sleep stages result in a quantitative measure of sleep composition. Further, the EEG signals can be analyzed in a qualitative manner in order to measure how much power there is in each frequency band. This gives a more detailed view of the microarchitecture of what happens in the brain during sleep. For instance, this method can be applied in order to get a measure to how deep the SWS is; that is, how much power there is in the SWA frequency band. Power is measured in μV, and thus takes into account the amplitude and the abundance of a frequency band within a certain time frame. Since evening exposure to blue-enriched light has been found to impact SWA during NREM sleep[108,119,120], in Paper IV, a Fast Fourier Transform (FFT) was applied to the EEG signals during SWS in the first 90 minutes to calculate the power spectral density.

Measuring memory functions

As described in the introduction, there are many different types of memories with different functions in our everyday life. These memory types can be tested using a range of different memory tests. In the papers included in this thesis, a motor memory test and a working memory test (with a sound distraction) were used.

Motor memory test: the motor sequence finger tapping task

The motor sequence finger tapping task is a test where the participant is supposed to tap a certain 5-digit sequence (e.g. 4-1-3-2-4) on a keyboard as fast and as accurate as possible. The task is performed during 30 seconds, followed by 30 seconds of rest, which together constitutes one trial. Each session is composed of several trials. During the learning session, the test usually consists of 12 trials. During the initial training session, participants typically increase their performance across trials. Traditionally, the retest session consists of three trials. Performance is then defined as the mean of the last three trials at learning and the mean of the three trials at retest. However, comparing the mean of three trials where the participant has been performing nine trials before that, is not necessarily comparable to the mean of three trials with no preceding trials. It must also be noted that averaging scores from the final three learning trials (out of 12 learning trials) may mask a participant's actual learning performance[121]. Thus, it is possible to define performance on this task in alternative ways, such as instead calculating the mean of the three best trials (as applied in Paper I and II). Depending on how performance is defined, the impact of sleep on skill improvement can differ. In fact, the traditional way to estimate performance on the finger tapping task has recently been questioned by our (Paper I) and other groups[121].

In Paper I, the finger tapping task was used in order to assess the potential impact of a person's initial performance level on the degree of gain in performance after sleep (learned in the evening, tested in the morning) and daytime wake (learned in the morning, tested in the evening). In Paper II, we investigated whether giving a text-based praise ("Wow, very well done! This was one of the best performances we have ever seen") immediately following learning on the task could impact the performance gain after a night of sleep, as well as in the longer term (after one month).

Working memory test with sound distraction

In Paper III, working memory was assessed using a test where participants were presented with a sequence of numbers (digits 1–9), which had to be encoded and retrieved in the order in which they were initially presented. This was done in 16 trials. During the entire working memory task, participants wore headphones. All trials started with a 24-second long priming phase when an 8-second long Russian phrase was played (repeated three times). The phrases were taken from literature, popular science papers, and news articles. Importantly, none of the participants reported to understand Russian.

After the priming phase, the eight digits (ranging from 1–9) that the participant was supposed to encode were presented, one digit at a time, during the 8-second digit encoding phase. Half of the digit encoding phases was accompanied by auditory verbal distraction (using the same phrase as presented during the priming phase), and half were presented under silence.

In the retrieval phase, participants were prompted to input the eight-digit sequence in the same forward order as it was presented during encoding. No sound was played during retrieval. Once participants had completed the retrieval, they were requested to self-estimate their working memory performance for the completed trial by rating how certain they were about the correctness of their digit input. Thus, the output from the test is both a measure of the ability to encode and keep information in mind (working memory), with and without sound distraction, as well as a subjective rating of how they perceive their performance. In Paper III, this memory test was administered after a night of nocturnal wakefulness, as well as after a night of sleep.

Biological markers: melatonin

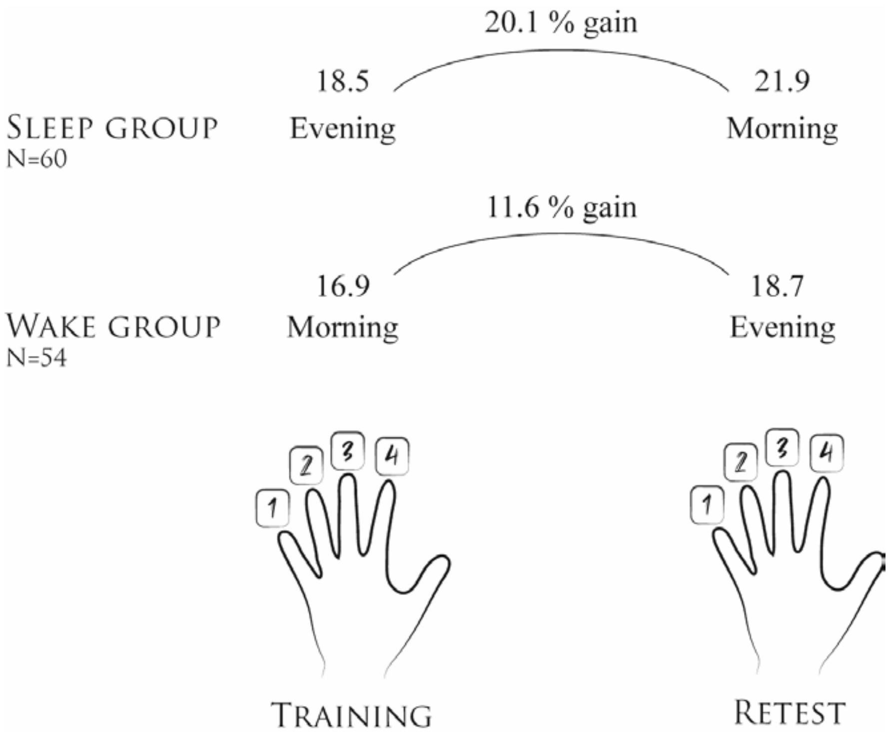
In Paper IV, saliva melatonin was measured in a subsample (N = 10) in order to evaluate the effect of screen light on melatonin release. Saliva was sampled during the book reading intervention at 30-minute intervals, starting from onset of the intervention. Together with saliva collection, the Karolinska Sleepiness Scale (KSS) was administered in order to measure sleepiness.

Paper I

Study design

In paper I, comparisons were made between a sleep group that learned the finger tapping task in the evening and were tested in the morning, and a wake group that learned the task in the morning and was re-tested in the evening. Data for the sleep group was derived from four separate in-lab studies previously performed in our group. In all of the studies included in the sleep group, the finger tapping task was administered in the evening, and again in the morning, and all participants slept the night in our sleep laboratory. *Figure 8* is an overview of the study design for Paper I, and also demonstrates the mean performance values obtained at learning and recall sessions.

Figure 8. Study design for Paper I. The numbers in the figure are the mean for all participants in the two groups regarding performance on the finger tapping task (here calculated as the mean of the last three trials).



Statistical analysis

In this study, we aimed to study motor learning by testing how initial skills impact subsequent performance gains across sleep and wake using the finger tapping task. Learning performance on the finger-tapping task was defined in two ways: mean of the final three learning trials (which is the more traditional way to assess performance on this task), and the mean of the three best learning trials. All statistical evaluations were applied to both of these data sets. Data from subjects whose performance (defined as the average of the final three trials) at learning or re-testing, or offline gain from learning to retesting differed from the group mean (sleep and wake group, separately) by more than two standard deviations were identified as outliers and excluded from analysis (N = 13; the initial sample consisted of a total of 127 subjects). This criterion applied to seven subjects of the sleep group and six subjects of the wake group. A repeated measures ANOVA was used to test if the performance would differ between the between-subjects factor *Condition* (sleep/wake) and *Sex*, as well as for the within-subject factor *Time* (learning/retesting). In addition, three univariate ANOVAs were used to test whether learning and retesting performance as well as offline gain varied with *Condition* and *Sex*. Spearman correlations were used to investigate if overnight gain in finger tapping skills correlated with sleep variables, such as percentage of N2 (of TST). A linear regression model was utilized to analyze possible associations between *Learning performance* (predictor) and offline gains in finger skill between learning and retesting (dependent variable), while controlling for *Condition* and *Sex*. An additional linear regression model investigated possible interactions using a full-factorial design including the interaction terms built by *Condition* (dummy coded), *Sex* (dummy coded), and *Learning performance* (entered as z-values).

Paper II

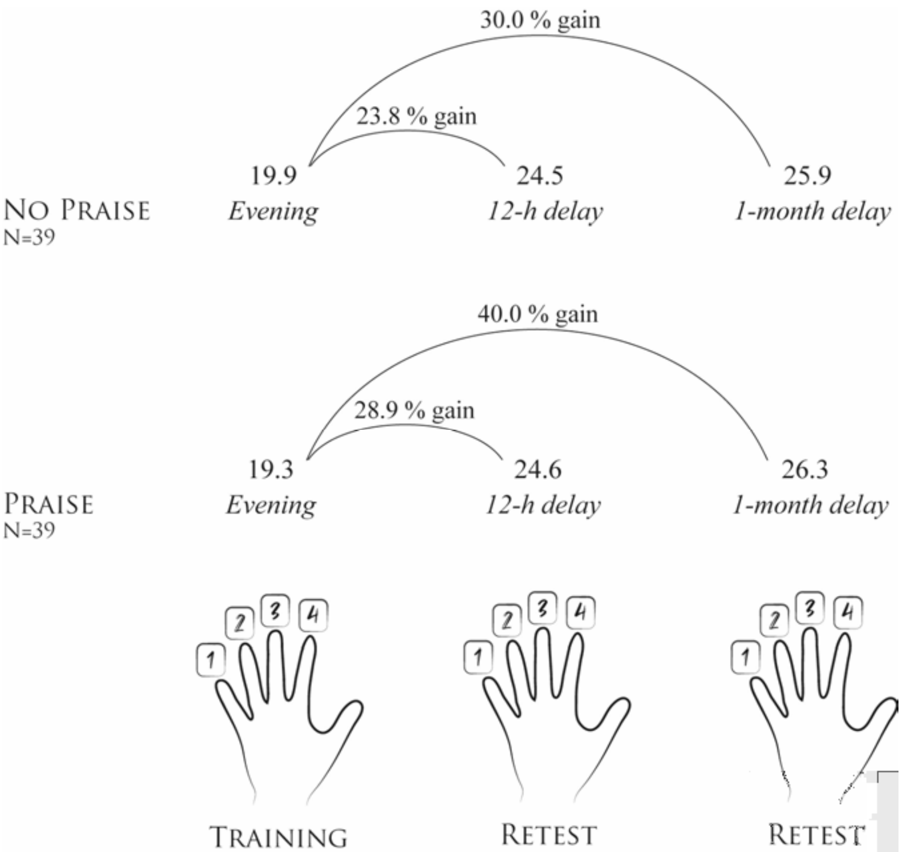
Study design

In Paper II, the finger tapping task was again used to test motor learning, but this time an intervention was applied in order to see if the offline improvement could be externally influenced (in contrast to Paper I where the difference in performance gain between participants was driven by internal individual differences in initial skills after learning). Therefore, immediately following evening learning on the task, half of the group was presented with a "feedback". However, this feedback was the same for all participants in the *Praise* group, and did in fact not reflect their actual performance. The praise was presented as a text within the program that was used for the finger tapping task.

After the evening learning session, participants went home and came back the next morning for the short-term retest session (12 hrs after the learning session). Sleep was assessed with actigraphy and a sleep questionnaire. Approximately one month later, a delayed retest (long-term session) was scheduled. No praise or other type of feedback were given at any other time points of the study than after learning. There were 39 participants in both the *Praise* and in the *No praise* groups, with 19 females and 20 males in each. *Figure 9* is an overview of the study design in Paper II, and visualizes the mean performance values and gain obtained for the learning and recall sessions.

Self-esteem can to varying extent rely on performance success and failure, which can be measured using the competence-based self-esteem (CBSE) questionnaire[61]. This questionnaire contains 12 questions, each rated from one (strongly disagree) to five (strongly agree), and total scores can range from 12 to 60. A high CBSE score indicates that self-esteem to a large extent rely on performance and achievement[60,61], and has been found to be related to a lower intrinsic self-esteem[61]. The CBSE questionnaire was used in Paper II in order to evaluate if this could modify motor skill learning.

Figure 9. Study design Paper II. The numbers in the figure are calculated using the mean of the best three trials for the correct number of sequences per trial. The numbers represent the means for all participants in the two groups (*No praise* and *Praise*).



Statistical analysis

Per trial performance was defined as the number of correctly tapped sequences per trial. Contrary to the traditional set-up for this task, we decided to use twelve trials at both learning and retesting in order to compare different ways to define performance. Performance was defined as the mean of the best three trials. Gain was defined as percentage change in performance from learning to retest. All analyses were performed in MATLAB (Mathworks, Inc., version R2018b). First, a linear mixed model was set up to investigate determinants of learning performance. In this analysis, *Sex* (females vs. males), and *CBSE score* were added as main fixed factors, and *Subject* was included as a random factor. Second, a linear mixed model was built to investigate determinants of finger skill gain to short- and long-term recall. *Condition* (*Praise* vs. *No* *praise*), *CBSE score*, and *Time* (change in finger skill from learning to short-term recall vs. change in finger skill from learning to long-term recall) were added as fixed factors, and *Subject* was included as a random factor. The model with the best model fit did not include the factor *Sex*, which was thus not included in the analysis (there was no main effect of *Sex* on finger skill gain). Two separate models investigated interactions: *Condition*, *CBSE score*, and *Condition* × *CBSE score* were added in one model, and *Condition*, *Time*, and *Condition* × *Time* into the second one. Group comparisons were performed by Student's t-test or Mann-Whitney U tests.

Paper III

Study design

Each participant came in for two study sessions: one night awake, and one sleeping (8-hour sleep opportunity). In the wake condition, participants were kept awake by the experimenters throughout the entire night. During the wake periods in the laboratory, participants were allowed to spend their time with sedentary activities, e.g. reading a book, when no study-related activities were scheduled. In the morning, the working memory task with sound distraction was administered. For an overview of the study design for Paper III, see *Figure 7*.

Statistical analysis

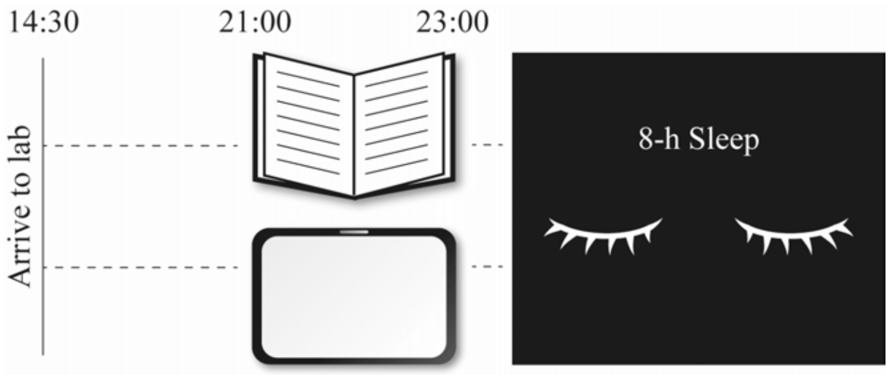
The effects of sleep loss and auditory verbal distraction on objectively measured and self-estimated working memory were analyzed by linear mixed models. Within-subject factors experimental *Condition* (i.e. being sleep-deprived versus being well-rested) and *Auditory distraction* (auditory distraction versus silence during digit encoding) were entered as repeated fixed factors into the analyses. *Sex* was considered as a fixed between-subjects factor. In addition, Bayesian statistics were applied (presented in Supplemental information to Paper III) in order to validate our findings. Sleep parameters were contrasted by sex using two-tailed independent Student's t-tests and Mann–Whitney U tests.

Paper IV

Participants

This study included 14 participants and the conditions were compared within each subject. Previous studies investigating similar research questions have included similar sample sizes. None of the participants reported any color blindness or visual acuity problems. None of the participants reported that they had read the book that was used in the study ("The Magicians" by Lev Grossman).

Figure 10. Study design Paper IV



Study design

There were two experimental conditions in this study, and all participants thus came in for two experimental sessions: one reading a traditional book ("The Magicians"), and one reading the same book, but as an eBook on a tablet. The intervention took place in the evening, right before going to bed, and the reading session lasted for two hours. The tablet that was used (ASUS Transformer Pad TF700) had an LED screen. During the reading intervention, the room was kept dark with the ceiling lights turned off and only a reading lamp turned on at the desk where the participant was sitting. Participants were exposed to a larger fraction of light in the blue-light spectrum in the tablet reading condition compared to the conventional book reading condition.

To ensure compliance, and to repeatedly collect saliva for melatonin measurement and sleepiness ratings, an experimenter stayed in the experimental room but remained quiet during the reading intervention. PSG was recorded during the night, and in the morning, sleepiness was again rated. Thus, outcome measures were evening melatonin levels, evening sleepiness, sleep latency, sleep composition, SWA power during early-night SWS, and morning sleepiness.

Even though the reading intervention took place in the evening, participants arrived to the sleep laboratory already at 14:30 in the afternoon. Experimental rooms were not equipped with windows, that is, room light conditions (~569 lux measured at the horizontal plane at the desk where participants were mainly seated) were kept constant for 6.5 hours prior to the reading intervention. *Figure 10* is an overview of the study design in Paper IV.

Statistics

Comparisons between the tablet reading and conventional book reading conditions were made for the melatonin, tiredness, and sleep variables. Linear mixed models were used, with the fixed repeated factor *Condition* (as well as the factor *Time* where appropriate), and fixed covariates *Sex* and log transformed *Chronotype*. The model also included *Condition* by *Time* interaction effects, where appropriate.

Results and Discussion

Paper I

In Paper I, we found that 1) sleep during the offline period (compared to wakefulness) resulted in increased skill gain; 2) performance at learning determined offline gain in that those who had a lower learning performance gained more; 3) results were affected by the method in which performance was defined.

In general, the sleep group performed better than the wake group, and also had a greater increase in performance with time (from learning to recall). This is in line with some but not all previous observations[14,40,41,43,45,47,48,122,123]. From our study design, it is impossible to disentangle if the motor skill gains during sleep is due to an enhancing effect of sleep, or a stabilizing effect of sleep on early post-learning gains occurring during wakefulness close in time after the learning session, as seen in previous studies[43].

Some previous studies have detected a link between procedural memory processing during sleep and certain sleep stages or sleep characteristics, for instance N2, REM, and sleep spindles[41,53]. In Paper I, we did not detect such links and performance gains in finger skills after sleep were not correlated to any of the measured sleep variables. Inability to detect such links are also found in previous literature[121,124].

In many activities involving motor learning, skilled performers commonly describe a "flow" when they had a really good performance, for instance among dancers and musicians. This "flow" is thought to depend almost exclusively, with the exception of pre-frontally derived directed attention, on the implicit memory system in a state of temporary frontal hypofunction[36]. But if the skill is not sufficiently learned yet, and/or the task is perceived as too challenging, then the explicit memory system with the prefrontal cortex might take a greater role when performing the task. This reduces the likelihood of "flow" perception and makes performance more inefficient. According to this proposed mechanism, the explicit memory system would be more involved during initial learning, but as the memory of the motor sequence gets stronger, the activity is rather shifted toward implicit performance, making performance of the motor sequence more automatic. The explicit memory system utilizes working memory during performance of the task, and the working memory has limited capacity. In order to circumvent this limitation, during initial learning of a motor sequence, it has been proposed that the sequence is tapped and encoded in "chunks" of smaller subunits[125,126]. During sleep, it has been suggested that these chunks are merged, resulting in a smoothing of performance at post-sleep recall[58]. Thus, sleep may play a role for shifting the memory from more explicitly to more implicitly performed. A higher level of implicit vs. explicit activity during performance is thought to improve performance.

In Paper I, we found that those who performed at a higher level at learning, gained less until recall; and vice versa, those who had a lower performance at learning exhibited an increased offline gain. It is possible that this difference in gain may be explained by differences in the quote between explicit vs implicit activity during performance. We speculate that those who perform at a higher level at learning, may also already have a higher degree of utilization of the implicit memory system during performance, perhaps as a result of extensive training of finger tapping on keyboards before participation in the study. Whereas those with lower performance may to a higher extent utilize the explicit conscious memory system during the task. If sleep plays a role for explicit-implicit shift, then those who to a higher degree utilize explicit activity during training may gain more from an offline period of sleep.

This study not only identified initial learning performance as a factor that impacts motor skill gain, it also highlights a methodological issue: how should we define performance on this task in order to most accurately reflect a participant's performance? Depending on how performance was defined, the effects of our findings varied. Thus, it is important to keep in mind that the choice of method that is used to estimate performance could partially account for different results on the impact of sleep on offline improvements in finger tapping skills. In Paper II, I revisit this methodological challenge.

Paper II

In Paper II, the finger tapping task was again (as in Paper I) used to measure fine motor skill learning. A text-based praise after initial training on the task had a positive impact on the magnitude of performance gain from learning to the short- and long-term recall sessions.

Irrespective of praise, skill gain was greater to one-month recall compared to the 12-hour short-term recall. In addition, competence-based self-esteem was inversely correlated to skill gain. Specifically, those with high CBSE scores also improved less with time, compared with those who had a lower CBSE score. Self-esteem derived mainly from one's abilities is unstable and varies with the person's capability to succeed. It is thus an external source of self-esteem. However, a high CBSE has also been found to be linked to a lower intrinsic self-esteem[61]. In contrast to a self-esteem defined by a high CBSE, self-esteem to a large extent based on intrinsic or basic self-esteem is stable and preferred. Basic self-esteem is unconditional self-love, often derived from secure attachments during childhood[61]. High need to earn self-esteem by competence, in combination with a low basic self-esteem has been found to be disadvantageous when choosing strategy in response to false feedback during cognitive tasks[127]. Also in our study, it was found favorable to have a lower CBSE score. However, CBSE had a main effect on skill gain, but it did not modulate the effect of praise.

It might seem surprising that praise, even when given on false grounds and not reflecting actual performance as in the current study, still have the ability to enhance motor skill learning. Not even human-human interactions between an experimenter and participant were required to elicit an effect of praise, since even a text-based praise delivered by a computer improved motor skill gain. Considering human psychology, these findings are not so surprising. Humans are in fact biased toward accepting positive feedback compared to negative[128-131]. Further, encouraging feedback is perceived as more satisfying and useful than criticizing feedback[132-134]. Yet, one of our concerns when planning the study was whether the intervention would be strong enough to have an impact. We hypothesized that potential effects of a praise may require, or at least would be further enhanced by, human-human interactions between experimenter and participant. Human-human interactions are very important, but also difficult to control for in a study. Personality, gender, age, and a wide range of other factors may impact human-human interactions, and thus how praise is delivered and received. In the current study, the praise was therefore delivered as a text to keep the intervention as controlled as possible between participants. It is still possible that human-human interactions, or engaging other sensory modalities during praise delivery, would have resulted in even greater effects of praise on motor skill improvements.

A possible underlying mechanism for the effect of praise on motor skill learning could be mediated by increased dopamine activity in the striatum in the brain. The praise may act as a reward, and both reward as well as learning of a new motor skill is associated with increased dopamine activity in this structure[135-139]. Thus, it is possible that additional increases in dopamine due to a rewarding praise immediately following learning might increase consolidation and performance gain of the motor skill until the next recall session. It could also be speculated that the enhancement in performance gain driven by the praise could be the result of increased dopamine release when re-exposed to the situation (that is, during the recall session) where the rewarding praise was given.

Table 2. Performance at learning, short-term recall, and long-term recall. Performance was either defined as the mean of the best 3 trials, the mean of the first 3 trials, or the mean of the last 3 trials. P-values are derived from Student's t-tests.

		Mean ± SD	***P***
Learning Mean of the best 3	*Praise*	19.3±4.2	
	Control	19.9±5.0	0.513
Learning Mean of the last 3	*Praise*	17.3±4.2	
	Control	18.4±4.9	0.305
Short-term recall Mean of the best 3	*Praise*	24.6±4.9	
	Control	24.5±5.8	0.974
Short-term recall Mean of the first 3	*Praise*	21.0±5.8	
	Control	21.3±5.9	0.848
Short-term recall Mean of the last 3	*Praise*	22.0±4.7	
	Control	22.6±5.7	0.601
Long-term recall Mean of the best 3	*Praise*	26.3±5.6	
	Control	25.9±5.7	0.731
Long-term recall Mean of the first 3	*Praise*	23.4±5.6	
	Control	22.9±6.1	0.687
Long-term recall Mean of the last 3	*Praise*	23.6±5.3	
	Control	23.7±5.7	0.890

As in Paper I, how performance was defined had a major impact on the obtained results. *Table 2* displays the mean values split by group and time for the three ways in which performance was defined. Performance in Paper II was determined as the mean of the best three trials at learning and recall sessions, which resulted in a positive impact of praise on the magnitude of performance gain from learning to recall. When performance instead was determined in the traditional way, taking the mean of the last three trials at learning and the first three trials at recalls, then there was also an interaction between change over time and receiving the praise, in that the *Praise* group increased their gain more with time compared to the *No praise* group (*Table 3*). However, when the mean of the last three trials at both learning and recalls was used, then praise no longer showed a significant effect on gain in finger tapping skills (*Table 3*).

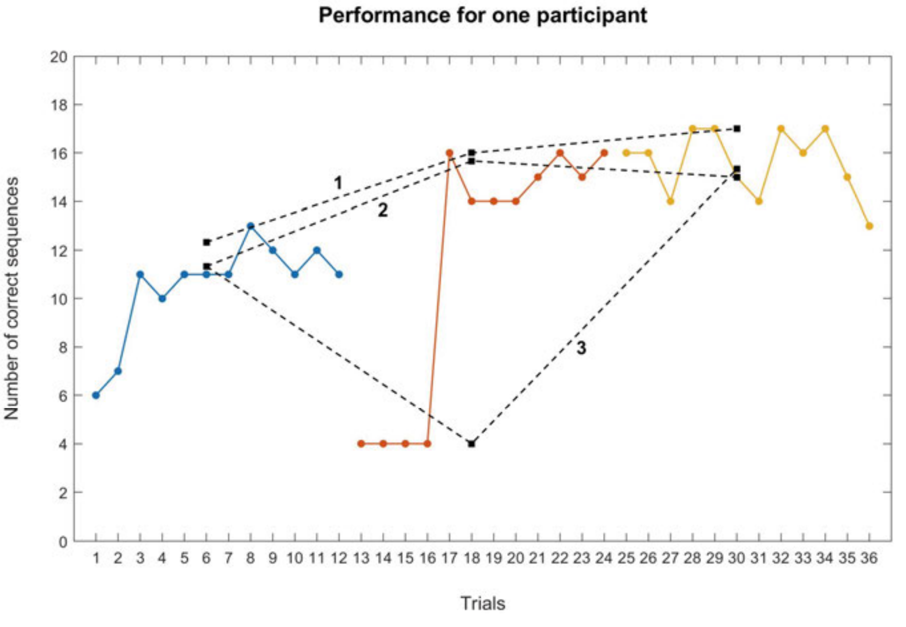
In the analyses presented in *Table 3*, there was one outlier appearing for the analyses with the mean of the last three trials at learning and the mean of the first three at recall. Removing this outlier from the analysis in *Table 3* had an impact on the outcomes by changing the P-value for the *Praise* × *Time* interaction from 0.041 to 0.083. In *Figure 11*, performance for this participant is plotted against time, shedding some light on why this participant was an outlier when performance was defined as the mean of the last three trials at learning and the mean of the first three trials at recall. This participant is a perfect example of how the different ways to define performance can impact the outcome from a study, and why it is important that we raise the question on how performance should be defined for this motor skill task. *Figure 11* clearly demonstrates the methodological issue of performance definition. Does the mean of the three first trials at the 12-hour recall really reflect short-term recall performance for this participant? Does the mean of the last three trials at the one-month recall reflect long-term recall performance?

In my opinion, using the mean of the best three trials out of 12 trials is the variable which probably best reflects the “true” performance capacity of a person. This way to measure performance is more robust toward temporary performance declines, driven for instance by fatigue, and unpredicted events such as a sneeze or a noise from outside. It also reduces the risk that worse performance in the beginning of a session might impact the results. Even a person that is highly skilled at a task might need some time to “warm up”; consider a professional athlete before a race, they always need warm-up.

Table 3. Analyses of gain in performance on the finger tapping task from learning to short-term and long-term recall. Two models were set up: one with main effects, and one including the interaction. Condition = *Praise* and *No praise* groups. One data point was an outlier when plotting the residuals, and was removed from all analyses. [1] = An additional data point was an outlier and removed from analysis; this did not change the outcome. [2] = The same outlier data point as in [1] was an outlier and removed from analysis, which changed the outcome: the new P for the interaction was 0.083.

Trials used to define performance		***Estimate***	***df***	***P***	***Lower***	***Upper***
Mean of the best 3	Main					
	Time	8.12	141	**<0.0001**	5.75	10.49
	Condition	6.23	141	**0.038**	0.33	12.12
	CBSE	-0.40	141	**0.034**	-0.78	-0.03
	Interaction					
	Time	6.65	141	**<0.0001**	3.46	9.83
	Condition	1.92	141	0.677	-7.16	11.00
	Time × Condition	3.22	141	0.175	-1.45	7.88
Mean of the last 3 at learning, mean of the first 3 at recall	Main[1]					
	Time	11.68	141	**<0.000.1**	7.34	16.03
	Condition	8.92	141	**0.044**	0.25	17.59
	CBSE	-0.50	141	0.073	-1.05	0.05
	Interaction[2]					
	Time	7.59	141	**0.010**	1.81	13.36
	Condition	-3.36	141	0.660	-18.46	11.73
	Time × Condition	8.77	141	**0.041**	0.34	17.20
Mean of the last 3	Main					
	Time	7.41	141	**<0.0001**	4.09	10.73
	Condition	7.01	141	0.097	-1.28	15.30
	CBSE	-0.43	141	0.107	-0.95	0.09
	Interaction					
	Time	6.01	141	**0.009**	1.50	10.52
	Condition	3.00	141	0.642	-9.74	15.74
	Time × Condition	3.03	141	0.365	-3.57	9.63

Figure 11. Example of performance across trials in one participant. The filled lines represent raw data for correct number of tapped sequences for the three different sessions (blue=learning session; orange=12-hr recall; yellow=1-month recall). The numbers 1, 2, and 3 for the dotted lines represent the different ways to define performance; 1=mean of the best three trials; 2=mean of the last three trials; 3=mean of the last three trials at learning and mean of the first three trials at recall. The black dots connected with dotted lines represent calculated performance at that session.



Paper III

In accordance with previous studies, we found that sleep deprivation impaired performance on a working memory task compared to a full night of sleep. However, the negative effect of sleep loss on working memory performance was seen in women but not in men (there was an interaction between *Condition* and *Sex*). This finding is in line with a previous study where sex-specific differences were seen for cognitive performance following sleep–wake disruption. In this study, a 28-h forced circadian desynchrony protocol was implemented, which impaired working memory to a greater extent in women than in men, particularly in the early morning hours[89]. On the contrary, a meta-analysis from 2017[140] found that restricted sleep impaired performance on measures of working memory, but this effect did not appear to be modulated by sex.

Are women more sensitive than men to experience negative effects on working memory after sleep loss? When extra stress is put on the working memory system, such as during sleep loss[74,76,141,142], there is an increased requirement for neurocognitive resources to maintain working memory performance. A neuroimaging study has shown that despite similar performances as men, women exhibited greater signal intensity changes — a measure of neuronal activity and engagement — in brain circuits such as the prefrontal cortex when performing a working memory task under well-rested conditions[143]. This could for instance indicate that women's processing of the memory recruited and integrated information from more brain areas, and therefor required more resources. However, the brain has limited resources, and in combination with sleep disruption, which already requires extra neuronal resources, working memory function in women could be more sensitive to sleep disruption-mediated declines in performance. Thus, it could be speculated that women compared to men require sleep to a greater extent with respect to working memory functions. This highlights the importance of an individualized approach, both in research and in clinical practice. There is a need to further develop our knowledge of how sleep and the functions of sleep differs between women and men in order to provide optimal clinical and medical support for both women and men experiencing sleep disruption.

It is important to keep in mind that the results from our study cannot be extrapolated to other types of working memory tests or to other cognitive functions (such as emotional processing, long-term memory formation), and sex-differences in other cognitive and physiological domains may vary. As an example, sleep loss is related to weight gain, but the mechanisms for this seems to vary between women and men. The hunger-promoting hormone ghrelin increases in the morning in men, but not in women after a night of shortened sleep[144]; while the satiety hormone glucagon-like peptide 1 decreases in the afternoon in women. On the other hand, in a study utilizing the same participant sample as in Paper III, morning enzymatic activity of the metabolism-related enzyme dipeptidyl peptidase 4 increased by about 14% in women due to sleep deprivation, whereas it decreased by about 11% in men following sleep loss[79].

It makes evolutionary sense that different people within a tribe would be better at some things and worse at others. In that way, people in a tribe could complement each other, increasing overall survival. Differences in sleep function and sleep need between people are probably a good thing for the human society, as some people would be more sensitive to sleep loss and have a higher sleep need (and perhaps have the potential to perform better at the things that sleep is good for), whereas others would be more robust toward sleep loss and could cope better with stressful and dangerous situations where it is not possible to sleep. However, research on potential benefits of different sleep need is lacking.

One thing to consider in this group of young students who participated in this study is that their performances were relatively high, increasing the risk of ceiling effects. This was also pointed out by one of the reviewers when we submitted the paper. This could affect the outcomes, and it is possible that we would have seen even stronger effects utilizing a more difficult working memory task, as suggested in Reed et al.[145]. They found that with increasing working memory task difficulty, the sex-difference increased in that men performed better relative to women.

Half of the working memory task was performed under auditory distraction. Auditory distraction was indeed disturbing for working memory functions, supporting previous findings[77], but the effect was not modulated by sleep. In the future, it would be interesting to see if an auditory distraction using a familiar language would disturb working memory performance more or less compared to an unfamiliar language (as employed in this study).

Paper IV

During the past couple of years there have been alarms in the media about how blue light emitted from screens could disrupt our sleep. More times than I can count, I have been asked the question if blue-light filtering apps and functions on smartphones and laptops in the evening can take away the possibly negative effects of LED-light exposure before sleep and if those functions are effective. Unfortunately, the scientific evidence for these blue-light filtering functions is more or less non-existent, and studies show that light of other wavelengths and light with low illuminance can also impact the circadian rhythm, even if to a lower extent than short-wavelength light[146]. The screen-based media devices that we have today are historically a very new invention, and how we use them has revolutionized modern day life. However, this also entails that we do not yet know the whole picture of how they affect human health and sleep. We know that there is a correlation between evening use of media devices and negative outcomes on sleep measures, but we do not know what is driving this correlation. Previous studies have hypothesized that the blue-enriched light emitted from LED screens could impact the circadian rhythm and shift the rhythm later, mediated by a suppression of melatonin. Recently, some studies also indicate that such a relationship could exist[107,147,148]. However, in Paper IV, we did not find support that evening exposure to a screen with blue-enriched light impacts evening melatonin levels, evening tiredness, sleep latency, sleep composition, sleep duration, SWA during SWS, morning ratings of sleep, or morning tiredness. None of these variables were altered by exposure to screen light in the evening.

In close proximity in time to when Paper IV was published, two other similar studies were published. First, Chang et al.[107] found that four hours of evening screen light exposure during five consecutive nights had effects on melatonin, tiredness, sleep latency, and sleep composition. In this study, the participants stayed in the sleep lab throughout the whole study period. Just before we published Paper IV, a study from Norway came out showing that 30 min of evening reading on an iPad reduced early night SWA, while sleep onset latency and sleep composition remained unaltered[108]. This study was performed in the homes of the participants. With these two studies in mind, our study used a protocol that is similar to both, but differs in several aspects: in our study, participants spent the afternoon and whole night and morning in the sleep lab, aiming to control the environment and intervention as much as possible. Secondly, participants read the book for two hours. We aimed to develop a protocol that would be as realistic as possible, but still control the environment and the intervention. The findings in these three studies differ, and there could be several possible explanations to this. First, it is important to keep in mind that the few studies looking at screen light exposure and effects on circadian or sleep variables, including ours, are all small in magnitude (8-19 participants/study[107,108,149-151], 14 in our study), and statistical power can thus be questioned, increasing the risk for false positive and false negative findings. Second, study protocols differ vastly between studies, which make it difficult to get a good overview of the findings and to identify the roots to the conflicting results between studies. Yet, there are a few key variables differing between our studies that could be of high interest and possibly in part explain our different findings; these include: 1) duration of screen light exposure, 2) and previous light exposure during the previous day/-s. It is possible that our intervention of two hours of evening reading was not enough in order to elicit effects on the circadian rhythm and sleep. However, Grønli et al.[108] saw effects on evening tiredness and SWA after just 30 min of iPad reading.

An important, yet rather unexplored, aspect is the light preload. The impact of light preload on the suppressive effects of light on melatonin production in the evening is an understudied topic. A few studies indicate that bright light exposure during daytime over one to several days could attenuate the suppressive properties of evening short-wavelength-enriched light on evening melatonin levels[152-155]. In our study, participants were exposed to indoor bright light settings before the intervention period (light setting during intervention was instead relatively dark). This light-dark difference was greater in our study compared to that employed by Chang et al.[107] who used relatively dim light conditions throughout the study, and Grønli et al.[108] did not control for previous light exposure. Chang et al.[107] was also criticized for not taking light preload into account and the ecological relevance of their study was questioned[156]. Differences in light preload could partly explain discrepancies between the studies. Considering the light preload, it may also be of importance in future studies to take into account seasonal and latitudinal effects, which can impact ambient natural light availability. In line with this train of thought, when we submitted Paper IV to the journal, one of the reviewers asked whether the Actiheart device could measure free-living daytime light exposure. Unfortunately, this is not the case, but it would have been of high interest to measure light exposure during the days leading up to the study sessions in order to see if that would impact the effects of the intervention. Future studies should take light preload into account.

After Paper IV was published, a few newer studies have been published investigating the effects of screen light on sleep and circadian effects. These mainly include two studies from the same laboratory[150,151]. In these studies, 19 participants in each, were exposed to a 22'' computer screen in the evening. In their first study from 2017[151], the aim was to study both the effect of light composition as well as light intensity during computer screen exposure for two hours in the evening, on circadian, sleep, and cognitive outcomes. Participants were exposed to four conditions: low and high light intensity, as well as short and long light wavelength. They show that short-wavelength light disrupted sleep and circadian rhythm, as well as increased daytime sleepiness. Effects of light intensity were not as strong as the effects of light composition (wavelength). In their second study from 2018[150], they aimed to elucidate acute and chronic evening screen light exposure on sleep, circadian rhythm, and cognitive outcomes. They had three study sessions across six nights. The first night was a baseline night. In the baseline night, participants were sitting for two hours in a dark room with a turned-off computer screen. This was compared with two hours of evening screen exposure on night two, which was considered the acute intervention. During exposure time, participants were performing reading and writing tasks and solving cognitive tasks. During night three to five, participants slept in their homes, but came to the lab in the evening for a two-hour exposure. During the sixth night (again two hours of evening exposure), outcome measures were again studied and considered as chronic effects. They found that both acute and chronic evening screen light exposure negatively impacted sleep, altered circadian measures, and increased daytime sleepiness.

It is worth considering that the light exposure in the paper from 2018[150] was very strong (350 lux), and it is unclear whether their results can be extrapolated to realistic scenarios typically occurring in everyday life. It is also possible that the comparison between screen light exposure and baseline is driven by the change in activity between the conditions; it is rather different to sit in a dark room for two hours than to perform cognitive tasks and read for two hours. Further, there is no information on the participants' habitual evening use of technology stated in the paper. Thus, it is possible that some of the participants already before the baseline night were chronically using technology with LED screens in the hours before bedtime. Neither of the studies[150,151] took light history into account.

In 2017, another study was also published looking at blue-light filtering of the light emitted from smartphones used in the evening[157]. This study found that filtering out blue light emitted from a screen increased sleepiness compared to not using a blue-light filter, which instead depressed evening sleepiness. However, both this study and the studies by Green et al.[150,151] utilized the Epworth sleepiness scale to rate current sleepiness. The Epworth sleepiness scale is designed to be used to get a score for daytime sleepiness in everyday life, rating how likely one would usually be to fall asleep in different situations. The Epworth sleepiness scale cannot measure acute sleepiness. It is not clear why this questionnaire was used to study acute sleepiness before and after an intervention. There are questionnaires designed for that particular purpose, for instance the Karolinska Sleepiness Scale. With this in mind, it is problematic to draw any conclusions from these papers with respect to their results on sleepiness, and this uncertainty also puts into question the trustworthiness of these studies in general.

In summary, including studies published after our own study, the effect of the light emitted from screens on sleep is still debated and no consensus has been reached. Even though we did not detect an effect of screen light on circadian or sleep outcomes in Paper IV, it is still possible that screen light can increase alertness and suppress melatonin under certain conditions. In general, steps should be taken to reduce evening exposure to bright light, especially within the blue-light spectra, which could promote a better sleep hygiene.

Unfortunately, the sample size in Paper IV was too small to study potential sex-differences. It must also be kept in mind that people of different ages may be more or less sensitive to the effects of screen light in the evening[158].

In Paper IV, we took great care to standardize the conditions to be sure that any detected effects would be from the screen light, and not driven by, for instance, differences in the kind of online tasks that the technological device is used for if participants would have been allowed to do whatever they wanted with the tablet. However, since both groups were reading a book for two hours straight, the fatigue and effort used for reading[159,160] may have increased sleep pressure in both conditions and may thus have masked potential effects of the screen light.

Irrespective of the light, the available possibilities with media devices could still have a negative impact on sleep. Depending on how these devices are used, they could increase emotions, arousal, stress, reward, fear of missing out, and it can be difficult to quit and turn off. I speculate that exchanging sleep with screen time is probably a problem of a more behavioral character than mainly driven by the light exposure. Regardless, evening use of media devices can still prohibit a good night’s sleep, decrease sleep time, and delay circadian rhythm, which have all been related to negative health outcomes.

Summary and conclusions

- Post-learning skill gain of newly encoded motor skills is influenced by several factors:
    - Sleep
    - Performance at learning
    - Competence-based self-esteem
    - A text-based praise given after learning, irrespective of actual performance, is sufficient to enhance skill gain. Thus, a positive praise effect on motor skill learning is not only driven by human experimenter-participant interactions
    - How finger tapping performance is defined has an impact on the outcome
- These factors could account for some of the between-study variance in procedural offline gains observed in previous studies.

- Working memory is central in cognitive functioning. Thus, it is probable that a drop in working memory performance due to acute sleep loss increases the risk for accidents and mistakes. In some aspects, women and men seem to be affected by sleep loss in different ways; working memory can now be placed on that list

- It has been suggested that evening exposure to light from LED screens can impair sleep. We did not detect such a relationship, and the matter is still up for debate. It is possible that differences in study design and light preload before exposure could affect the outcomes in the different studies.

- In Paper I and II, we identified determinants for fine motor skill learning, including sleep

- In Paper III, we studied the importance of sleep for working memory functions by investigating the effects of sleep deprivation

- In Paper IV, we investigated how a hypothesized sleep disruptor (the light emitted from LED screens) impacts sleep

Why my research matters

During the course of PhD training, there are periods when one questions the relevance of one's research and why it matters. Talking to the public and putting together this thesis has helped me reflect on my work and to find motivation to pursue my line of research.

In my studies, I have 1) identified factors impacting motor memory functions (including sleep) and 2) tried to intervene with this process in order to boost motor skill learning, 3) investigated effects of sleep deprivation on working memory functions in women and men, and finally 4) studied how an important lifestyle-related factor (screen light) can impact sleep. So why is this important?

When we learn how to take our first trembling steps as a baby, ride a bike for the first time, learn how to handle a football on the soccer field, learn new dance moves or handcraft skills, and during motor rehabilitation, we are using our motor skill learning system. Even as I am typing on this keyboard, I am constantly using fine motor skills, even if my conscious thoughts are occupied with thinking about what I want to write. Motor skills are highly integrated in our lives, even if we do not always think about how much we use the motor skill system, since learned motor skills are performed more or less automatic without the need for conscious processing. Increasing the understanding of how motor skills are learned and processed and what can modulate motor skill learning is thus an important field of research. Additionally, if there are practical steps that we can take to further facilitate motor skill learning, this could have possible implications for motor skill learning in sports, in schools, as well as for rehabilitation of motor skills, for instance after a stroke.

Being awake during the night and to sleep during the day is required for many shift-workers. Understanding the cognitive effects of sleep deprivation is particularly important for this group of people. Additionally, this line of investigation helps to broaden our knowledge of all the diverse roles that sleep is serving for our well-being and psychological function. Throughout a day, we utilize our working memory system for a long list of purposes. Proper working memory function is vital for cognitive function as well as for personal and professional safety, for instance when operating vehicles where attention needs to be directed at the right things and a lot of different information needs to be integrated and kept in mind. We know that sleep disruption can increase the risk of accidents; thus, studying effects of sleep deprivation on cognitive function, especially under simultaneous sensory distraction, is an important field of research.

To some extent, women and men seem to sleep differently, possibly have different sleep needs, and be differentially affected by sleep deprivation. It is important that we can give appropriate advice, recommendations, and health care to everyone, irrespective of sex. Therefore, we need to a higher degree study potential differences between women and men in sleep and how we are affected by sleep loss.

Finally, the use of media devices is steeply increasing in our modern society, and it is of high importance that research tries to follow the pace of technology development, with studies investigating how these new functions and devices impact our sleep and health.

Future perspectives

I suggest that future studies on motor memory acquisition should:

- Have a long-term approach when studying motor skill development
- Further investigate determinants of degree of motor learning, for instance: does subjective rating of difficulty level after training impact offline gain?
- Identify sleep's role for automatization processes of skill memories; does sleep impact explicit-implicit shifting of a motor memory?
- Take into consideration how motor skill performance on the finger tapping task should be defined
- Apply praise to a study using a naturalistic scenario in order to investigate the relevance of our findings in Paper II for real-world applications

Future studies on sleep loss effects on cognitive functions:

- It will be important to perform additional studies focused on long-term effects of bad sleep habits (including shortened sleep, shifted sleep timing, and social jet lag) on cognitive functions such as working memory, preferably following people in their real life for a longer period of time
- Brain regions important for working memory differ between women and men, to some extent. It will be important to assess if sleep's role for working memory differ between women and men and if there are certain sleep characteristics (such as SWA) that relates to this
- We need to study sleep and effects of sleep loss in: women across the lifespan; women across the menstrual cycle, both for those using hormonal contraceptives and with natural cycles; women before, during, and after child bearing. Literature is sparse or completely lacking in these areas
- Our studies have looked at effects of sleep loss in young adults, this should be expanded to other age groups

Next step for studying the effects of our technological habits on sleep and health:

- We need to address mechanistic questions about the relationship between use of media devices and sleep in order to answer the questions: what is the underlying cause for negative effects of media device use on sleep? How can we prevent this?
- Regarding possible effects of screen light on sleep:
    - Future studies should include larger sample populations
    - Investigate the effect of light preload in a study designed for this purpose
    - Take season and latitude into account
    - Investigate potential individual differences, for instance age- and sex-differences, and variations depending on chronotype
- We need to further substantiate the correlation between media device use and worse sleep by utilizing intervention studies or longitudinal studies, in contrast to cross-sectional observational studies
- Future research should to a larger extent take into consideration what the technology is used for, in addition to how long it is used for, timing of use, and what type of device
- Many current studies are performed on adolescents; future studies should compare effects between different ages
- Finally, it is relevant to investigate possible counter-measures in order to see if there is anything we can do to reduce the risk that use of media devices will disturb our sleep, circadian rhythm, and health.

I wonder what we will know about sleep and cognition in hundred years from now. How will humans in the future think about today's knowledge about sleep?

If I would do it again…

The doctoral student time is an education in how to be a researcher, teacher, and project leader. Thus, it is obvious that as learning develops, one might identify things earlier on during the education that could have been done differently. An important part of learning is to identify those things in order to make further personal and professional progress. Therefore, I will here list some of the realizations I have made with time, and would try to do differently if I would do another PhD:

- Instead of several shorter studies, I would have wanted to focus on a few well-powered larger studies in order to be able to draw firmer conclusions.
- Allowed myself more time for reading, reflection, and planning
- Learned to program at an earlier stage in my education. Learning MATLAB has had a significant and highly positive impact on my work as a researcher, both on how I think about data processing as well as on my analyses.
- I wish I would have taken the time earlier to learn an illustration software. Looking back at the figures and tables in my previous papers, I see space for improvement. This is also helpful for sorting my thoughts and to make schematics over processes and hypotheses.
- I would have wanted to take a course in advanced statistics. I have had very fruitful discussions with Jenny Theorell-Haglöw and Pär Nyström about my analyses, which I am very thankful for. I find statistics challenging, and I still have a lot of learning left to do.
- I wish I would have slept more.

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