INTRODUCTION

Developmental aspects of sleep and cognition
The present thesis focuses on the interaction between sleep, most commonly occurring at night, and cognitive functions, most commonly occurring during the day, in the developing human brain during the childhood and adolescent years.

**SLEEP**

Whereas infants spend approximately 60% of each day asleep, this percentage declines to 40% in early adolescence, and to a mere 33% in adults (Iglowstein, Jenni, Molinari, & Largo, 2003; Ohayon, Carskadon, Guilleminault, & Vitiello, 2004). Interindividual differences in sleep duration, however, occur through variations in sleep need, sleeping problems, and sleep restriction through exogenous factors and/or endogenous factors (Jenni, Molinari, Caflisch, & Largo, 2007; Pesonen, et al., 2010). Sleep efficiency, defined as the percentage of time in bed actually spent asleep, is typically higher than 95% in school-age children and remains near 90% until it drops when people reach the age of about 50 years (Montgomery-Downs, O’Brien, Gulliver, & Gozal, 2006; Ohayon, et al., 2004).

Sleep profoundly changes brain activity, and this process is thought to be essential for the maintenance of optimal daytime cognitive and emotional functioning. The gold standard for the assessment of sleep is polysomnography (PSG). PSG reveals electrophysiologically distinct stages of brain activity during sleep based on an electroencephalogram (EEG), an electromyogram (EMG) and an electrooculogram (EOG). These stages have historically been divided into one stage of rapid eye movement (REM) sleep and four stages (Stages 1–4) of non-rapid eye movement (NREM) sleep of increasing sleep depth; deeper NREM sleep Stages 3 and 4 are collectively referred to as slow wave sleep (Rechtschaffen & Kales, 1968). The current consensus sleep classification discriminates only three stages of NREM sleep: lighter sleep Stages N1 and N2, and deeper sleep Stage N3 (Iber, Ancoli-Israel, Chesson, & Quan, 2007). REM sleep constitutes 50% of total sleep time during early infancy, declining to 5%–20% in older children and adults (Hoban, 2010).

The sleep EEG furthermore shows characteristic phasic events, notably the spindles and slow waves, both reflecting neuronal oscillations within the thalamocortical system. The sleep spindle, a waxing and waning of a prominent 11 to 15 Hz oscillation that lasts for 0.5–1.5 s, is seen mostly in Stage 2 sleep. Slow waves of 0.5 to 4.0 Hz occur either as isolated K complexes during Stage 2 sleep or in more continuous sequences during Stages 3 and 4. Both spindles and slow waves represent key phenomena involved in the role of sleep for maintenance of brain function and cognition. They may facilitate synaptic downscaling (Tononi & Cirelli, 2006) or reactivate memory traces (Wilson & McNaughton, 1994), as described below.

Both spindles and slow waves develop during the first six months of life (De Weerd & Van den Bossche, 2003). Whereas sleep duration drops considerably
during the period that children go to primary school (from 5–6 to 11–12 years old), the expression of slow waves increases and peaks in early adolescence at a level higher than that seen in adults (Feinberg, 1982). After the age of about 11 or 12 years, slow wave activity initially declines steeply, followed by a slower ongoing decline with ageing (Campbell & Feinberg, 2009).

**Sleep Supports Daytime Cognition**

Sleep appears important to cognition. Sleep is important for both explicit memory, the memory for facts and figures, and implicit memory, memory gained with little or no conscious effort. An elegant, frequently reported study is Walker et al.’s finger-tapping task (Walker, Brakefield, Morgan, Hobson, & Stickgold, 2002). Human adults learnt to tap a particular sequence of keys with their non-dominant hand, and were retested after either a period of wakefulness or an equivalent period of sleep. Retesting after sleep showed a 20% increase in motor speed without loss of accuracy, whilst retesting after remaining awake showed no significant benefit. Furthermore, the overnight improvement in finger-tapping performance correlated specifically with the amount of late night Stage 2 NREM sleep.

One of the key methods to test the relationship between sleep and daytime performance is application of sleep deprivation or sleep restriction. Experimentally induced partial and total sleep deprivation in healthy adults can lead to a host of negative consequences within the affective, cognitive, and motor domains (Pilcher & Huffcutt, 1996), suggesting that an adequate amount of sleep is essential to maintain optimal daytime functioning. In a recent meta-analysis, Lim and Dinges (2010) aggregated past studies in adults addressing the consequences of total sleep deprivation on several cognitive domains and revealed considerable performance deficits in simple attention, moderate deficits in complex attention and working memory, and small detriments in short-term memory, whereas measures of mental processing speed and crystallised intelligence remained intact. At present, it is not clear whether sleep restriction similarly affects these domains in children, because a comprehensive meta-analysis is lacking.

Two main hypotheses exist on the supportive role of sleep in sustaining cognition, both propose an active role for sleep in the neuronal processing of information acquired during prior wakefulness, rather than merely providing rest or an absence of interference.

The trace reactivation or replay hypothesis (Born, Rasch, & Gais, 2006; Born & Wilhelm, 2012; Hoffman & McNaughton, 2002; Sejnowski & Destexhe, 2000; Sutherland & McNaughton, 2000; Wilson & McNaughton, 1994) proposes that sleep aids memory consolidation through reactivation of traces of neuronal activity patterns that encoded information during the prior wakeful period. The reactivation is proposed to aid transfer of information: from temporary hippocampus-dependent storage to long-term hippocampus independent neocortical storage. Whereas the hippocampus is initially essential to index (i.e., to provide “pointers”) to the coordinated patterns of activation of cortical modules, sleep is thought to promote the gradual strengthening of horizontal corticocortical connections that ultimately release memory traces from hippocampal involvement. Mechanistically both slow wave up -states and sleep spindles have been implicated in this strengthening (Rasch & Born, 2013). The trace reactivation hypothesis has focused mainly on consolidation, enhancement, and reorganisation of explicit memory processes that involve a dialogue between the hippocampus and the neocortex, but might apply as well to corticocortical connectivity of implicit memory traces, not involving hippocampal pointers.

The synaptic homeostasis hypothesis proposes that sleep is necessary to counterbalance the net increase in synaptic connectivity that occurs during wakefulness (Tononi & Cirelli, 2006). Wakeful information processing is associated with neuronal plasticity processes that adapt the synaptic strength of neuronal connections. Whereas synaptic strength can both increase and decrease, the former occurs more prominently during wakeful periods, leading to a net increase in synaptic strength by the end of the wakeful period. Sleep, and especially the slow cortical oscillation, a phasic electroencephalography (EEG) event typical of deep sleep, is proposed to underlie a general, homeostatic downscaling of synaptic strength. This is necessary to prevent saturation and preserve cost efficiency of the neuronal networks. In the synaptic homeostasis hypothesis, memory consolidation would occur through the sleep-dependent slow oscillations that act locally to reduce synaptic strength, retaining only the strongest synapses. The net effect would be that strong memories are spared and subsequently have a higher signal-to-noise ratio; in this framework, memory consolidation is passive and more or less a by-product of synaptic downscaling, rather than an active process of replay. The synaptic homeostasis hypothesis predicts that sleep deprivation will result in a synaptic overload of neocortical and limbic circuits, which could show in cognitive and emotional impairments.

**Sleep Supports Emotion**

The recently emerging overnight therapy hypothesis (Walker & Van der Helm, 2009) focuses more on the role of sleep in maintaining optimal emotional reactivity and emotional information processing, of which the derailment would show...
as internalising and externalising problems (Eisenberg, et al., 2001). On the basis of a review of the current literature on adult studies, Walker and Van der Helm (2009) proposed that sleep provides a window for a resetting of the neuronal systems involved in affect regulation and for the reprocessing of recent emotional experiences. These two processes result in maintenance of appropriate reactivity of limbic and associated autonomic networks. In support of this hypothesis, sleep-deprived adults show increased amygdala reactivity and an attenuation of control of the amygdala by the medial prefrontal cortex both involved in the regulation of emotion and the autonomic nervous system (Yoo, Hu, Gujar, Jolesz, & Walker, 2007). Walker and Van der Helm (2009) proposed an important role for rapid eye movement (REM) sleep, a stage of sleep that occurs more prominently at the end of the sleep period and may thus be curtailed considerably in case of restricted sleep duration.

Sleep and Daytime Performance in Children

These three hypotheses are not necessarily mutually exclusive, nor exhaustive. They are, furthermore, subject to ongoing discussion, elaboration, and refinement (e.g., Diekelmann, Wilheim, & Born, 2009; Stickgold, Whidbee, Schirmer, Patel, & Hobson, 2000; Yang, et al., 2014). The above-mentioned hypotheses received support from data on the effects of sleep and sleep deprivation in adults, yet inconsistencies and complications remain. When starting the experimental work in this thesis, this area was largely unexplored in children. Researchers’ understanding of the mechanisms and the validity of the hypotheses might profit from studies on the effects of sleep and sleep deprivation in children, for children are in a very different developmental stage regarding brain structure, physiology, and function.

Of relevance to the hypotheses mentioned previously, first, synaptic downsizing is thought to be more abundant in children than in adults (Huttenlocher, 1979; Huttenlocher & de Courten, 1987; Paus, Keshavan, & Giedd, 2008), and its occurrence may not be predominantly during sleep, as it is suggested to be the case in adults (Tononi & Cirelli, 2006). Second, the process of memory trace reactivation in adults involves connections between the hippocampus and neocortex, notably the medial prefrontal prefrontal cortex, whilst these connections are still immature in children (Abrahám, et al., 2010; Benes, Turtle, Khan, & Farol, 1994; Fair, et al., 2008; Kelly, et al., 2009; Power, Fair, Schlaggar, & Petersen, 2010). Third, the involvement of the frontoparietal network in the effects of sleep deprivation on sustained attention in adults may likewise be different in children, because this network is also still quite immature (for reviews, see Daniels, Frewen, McKinnon, & Lanius, 2011; Uddin, Supekar, & Menon, 2010). A critical question therefore is whether (Diekelmann & Born, 2010; Stickgold, et al., 2000; Yang, et al., 2014) there are differences in the effects of sleep restriction on cognition along the developmental trajectory, and if so, how these differences impact hypotheses on the tentative neurobiological substrates of the involvement of sleep in cognition and behavioural problems.

Therefore, there are valid applied and fundamental reasons to study the relationship between sleep and cognition earlier in development. From an applied point of view, studies spanning a full century indicate a disquieting reduction in the habitual sleep duration of children (Galland, Taylor, Elder, & Herbison, 2012; Iglowstein, et al., 2003; Terman & Hocking, 1913). It is important for parents, teachers, clinicians, and policy makers to know how this change of habits may be involved in cognitive and behavioural problems in children. If, as is the case in adults, specific subdomains turn out to be more sensitive to sleep restriction, a focused applied approach would be to first evaluate the efficacy of sleep interventions in those children who both perform suboptimally in these domains as well as have relatively short sleep durations. Early detection and treatment may be important as detrimental effects of a period of curtailed or disturbed sleep in children could have more, and possibly irreversible, long-term consequences than is the case in adults (Beebe, 2011; Touchette, et al., 2007), a contention that is supported by animal studies (e.g., Frank, Issa, & Stryker, 2001; Seugnet, Suzuki, Donlea, Gottschalk, & Shaw, 2011).

From a fundamental scientific point of view, studies in adults are beginning to define likely candidates for the neurobiological mechanisms by which sleep restriction affects brain function, cognition and behaviour. For example, as described in the previous section of this introduction, likely mechanisms involved in the adverse effect of sleep deprivation on cognition are interference with synaptic scaling (Tononi & Cirelli, 2006) as well as with the reactivation (Wilson & McNaughton, 1994) and reorganisation (Frankland & Bontempi, 2006; Takashima, et al., 2006) of memory traces. Because brain structure, physiology, and function are different in children, defining differences and similarities in the effects of sleep restriction on cognition and behavioural problems along the developmental trajectory provides a unique opportunity to further elucidate these tentative neurobiological substrates of vulnerability to sleep restriction. This in turn will aid our understanding of the functions of sleep for the both the developing and mature brain.

Given these important reasons, we will examine this relationship between sleep and cognition using a range of different techniques.
Chapter 1

Introduction

Developmental aspects of sleep and cognition

SCOPE

Based on past knowledge and the gaps within it, it appears timely to investigate the following questions regarding the relationship between sleep and cognition:

- Is sleep (duration, efficiency) related to cognition or behavioural performance in children? More specifically, which consequences can we expect following sleep restriction?
- To what extent does children's sleep change in response to a shortening of its duration? Do children show a similar compensatory sleep response to sleep restriction as adults? Does this compensatory response persist in the face of prolonged stress?
- Looking at children's sleep in more depth, can we find evidence of wake-like cognitive activity, specifically during slow waves? A potential mechanism behind sleep-dependent memory consolidation is the co-occurrence of electrophysiologically measured wake-like cortical high frequency (gamma) oscillatory activity and sleep's slow oscillations. This mechanism has been difficult to verify in adults, due to the low amplitude of their cortical gamma activity. Children may provide an optimal situation to investigate this, due to the larger amplitude of their cortical oscillations, across the frequency spectrum.
- Can we find direct evidence for a relationship between sleep and memory performance in children? Furthermore, can we find evidence for a relationship between sleep spindles or slow waves and cognitive performance, similar to that previously suggested in adults?

These questions are addressed in the following chapters.

In chapter 2 we start out by systematically summarising all of the past relevant studies relating sleep (duration and efficiency) to cognition and behavioural problems in children. We perform an all-comprising meta-analysis, a scientific method to systematically and statistically evaluate all past studies and their outcomes, and aim to answer the following questions:

- Is there an overall association between duration and efficiency of sleep, cognition and behavioural problems?
- Do different subdomains of cognition and behavioural problems show different sensitivities to sleep?
- Does the profile of these subdomains' sensitivities to sleep match the profile seen in adults?
- How do the summarised findings fit within previously proposed neurobiological models?

- Which particular aspects of past studies are the most effective at studying the relationship between sleep, cognition, and behavioural problems and could therefore provide a roadmap for the next wave of research on this topic?

We hypothesise that sleep duration and efficiency in children are positively associated with cognitive performance and negatively with behavioural problems, and we expect these relationships to extend across the same subdomains as reported in adults.

In chapter 3 we wish to further investigate the main aspects of sleep in children, sleep duration and sleep efficiency (the two main outcome measures in the meta-analysis), and the changes that occur following sleep restriction. Past studies in adults have shown that a curtailment of sleep duration results in a partially compensating sleep efficiency response (Levine, Lumley, Roehrs, Zorick, & Roth, 1988; Sadeh, Gruber, & Raviv, 2003). We wish to investigate whether we can find this in a naturalistic setting in adolescents. In particular, we wish to investigate the effects on objectively measured sleep outcomes that occur when adolescents attend school and thus are subjected to sleep restriction due to set morning get-up times. Second, we wish to determine the additional effects a daily stressor will have on these children's sleep patterns. Therefore, we perform a naturalistic ecologically valid quasi-experimental actigraphy study in which we contrast three different conditions of sleep curtailment and stress levels. We compare sleeping patterns during a week's holidays (extended-sleep low-stress) to those in a normal week of school (restricted-sleep low-stress) and subsequently to the patterns during stressful examination-weeks (restricted-sleep high-stress). We hypothesise that a shortening of sleep duration will result in an increase in the efficiency of sleep. We further hypothesise that this relationship will collapse when faced with a chronic challenge to the system.

In chapter 4 we further investigate the potential mechanisms behind the relationship between sleep and cognition in children. We wish to investigate how neuronal networks communicate and memory traces are consolidated during sleep (see Diekelmann & Born, 2010; Mölle, Bergmann, Marshall, & Born, 2011; Schwindel & McNaughton, 2011; Van Someren, Van der Werf, Roelfsema, Mansvelder, & Lopes da Silva, 2011). Past studies have shown that the co-occurrences of high frequency oscillations—spindle activity between 10 and 15 Hz, and gamma activity >30 Hz—and slow waves may be how new memories are transferred from the short term store to a more long term neocortical representation (Mena-Segovia & Bolam, 2011; Mena-Segovia, Sims, Magill, & Bolam, 2008; Rosanova & Ulrich, 2005; Steriade, Amzica, & Contreras, 1996). Thus far only
animal studies, human intracortical studies and a single adult MEG study have found evidence for this co-occurrence. Yet, children provide an optimal situation to test for wake-like neuronal activity during sleep EEG as their developmental stage displays more pronounced electrophysiologically detectable oscillations and a thus a better signal-to-noise capacity in detecting each of the waves of interest. Therefore, we evaluate the time course of spectral power of higher frequencies along the development of a slow wave in children. As children’s sleep is still in development their high amplitude slow wave sleep might reveal particular features that might be harder to find later in development. We hypothesise that slow waves may play a particularly important role in driving spindles and gamma activity.

Finally, in chapter 5 we wish to further study the relationship between sleep and cognition by looking at more detailed aspects of sleep and their relationship to motor skill performance. For this purpose we use a complex repeated-measures design in which children are tested on a motor skill-learning task—the finger-tapping task—across different consolidation periods (i.e., containing wakefulness, sleep, or a combination of states), and we obtain a full night of sleep-EEG. Next, we relate different aspects of sleep, both on macroscopic and microscopic levels, to skill performance and overnight improvements to determine if there are any direct links between cognition and sleep, and specifically sleep spindles. We hypothesise that skill performance will improve more over sleep and that sleep spindles occurring in association with slow oscillations will be involved. Furthermore, we attempt to influence children’s expression of slow waves and associated spindles through acoustic stimulation specifically occurring during slow wave sleep. By contrasting this group of children with slow wave suppression to a yoked control and a regular control group, we hope to reveal to what extent consolidation processes depend on slow oscillations and associated spindles.

Following the meta-analysis in chapter 2, the observational study in chapter 3, and the experimental studies in chapters 4 and 5, chapter 6 provides a general discussion summarising the findings.

REFERENCES


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