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Sleep to grow smart?

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ABSTRACT

Sleep is undisputable an essential part of our life, if we do not sleep enough we feel the consequences the next day. The importance of sleep for healthy brain functioning has been well studied in adults, but less is known for the role of sleep in the paediatric age. Childhood and adolescence is a critical phase for brain development. The increased need for sleep during this developmental phase fosters the growing recognition for a central role of sleep during development. In this review we summarize the findings that demonstrate a close relationship between sleep and brain maturation, discuss the consequences of insufficient sleep during childhood and adolescence and outline initial attempts that have been made in order to improve sleep in this age range.

Key words

EEG • Sleep Slow Waves • Development • Sleep regulation

Introduction

Major components of sleep EEG during development

The electroencephalogram (EEG) is an important tool widely used in sleep research. The sleep EEG signal changes as a function of the non-rapid eye movement/ rapid eye movment sleep cycle (alteration of non-REM sleep and REM sleep across the night) and as a function of age across our life. However, the most dramatic changes take place during development. At the time of birth, the sleep EEG is widely indefinable but rapidly develops distinct EEG characteristics before the age of two years (Feinberg, 1982). Infants spend more time asleep than in any other period of life. Moreover, sleep architecture differs remarkably from those in adults: infants spend about 50% of their total sleep time in REM sleep. This proportion of REM sleep decreases to about 25% in adults (Feinberg, 1982; Roffwarg et al., 1966). Furthermore, in infancy REM sleep episodes occur with random durations at any time of the night, whereas adults show a cyclic sleep pattern with alternating episodes of non-REM (NREM) and REM sleep (Feinberg, 1973). With increasing age, children and adolescents spend more time awake and both the total amount of sleep and the percentage of REM sleep diminish (Roffwarg et al., 1966). From early childhood throughout adolescence the most prominent changes that take place are observed during slow wave sleep, a major EEG component during deep NREM sleep. Slow waves have their origin in slow oscillating activity patterns of cortical neurons, which alternate between a phase of depolarisation (on state) and a silent phase of hyperpolarisation (off state) with a frequency <1 Hz (Steriade et al., 1993). When this alternating neuronal firing pattern is synchronous across large populations of neurons it becomes visible in the surface EEG as waves with high amplitude, commonly over 75μV, and low frequency, commonly below 4.5 Hz (Vyazovskiy et al., 2009). Slow wave activity (SWA, EEG spectral power in the 0.5-4.5 Hz band) has been shown to be a marker of sleep depth (Blake and Gerard, 1937) and sleep need (Borbély, 1982). More

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recently, evidence has accumulated that sleep slow waves are involved in brain plasticity processes (Born et al. 2006; Steriade, 1999; Tononi and Cirelli, 2006). Throughout development, SWA undergoes major changes: the activity increases in early childhood, reaches its maximum before puberty and decreases during adolescence (Feinberg, 1982; Gaudreau et al., 2001; Jenni and Carskadon, 2004). Longitudinal data shows similar age-related changes in SWA. Overall SWA increases until the age of about 8 years, plateaus thereafter and shows the most rapid decline between the ages 12 and 16.5 years (Feinberg and Campbell, 2012). Additionally, SWA reveals region specific changes in the course of early childhood to late adolescence (Kurth et al., 2010). Using high density EEG, Kurth and colleagues demonstrated that locations showing maximal SWA shift along a posterior-anterior axis from childhood through adolescence. Thus, the topography of maximal SWA shows an age-specific distribution: in pre-school children (2-5 years) maximal SWA occurs over the occipital lobe and in older adolescents SWA is maximal over the frontal lobe (Kurth et al., 2010). Importantly, these changes are specific for the frequency band of slow waves (Kurth et al., 2010).

Slow wave activity parallels brain and skill maturation

Changes in grey matter volume

Sleep slow waves exhibit the most dramatic changes during a time window that is marked by intense alterations in brain function and morphology (Johnson, 2001). A key alteration concerns changes in synaptic density: the first decade of life is lined up with an extensive increase in the number of cortical synapses, which reaches its peak shortly before puberty and decreases exponentially during adolescence (Huttenlocher, 1979; Huttenlocher and Dabholkar, 1997). Thus, during childhood more synapses are formed than eliminated and, contrarily, during adolescence more synapses are eliminated than formed (i.e. pruned; Zuo et al., 2005). Magnetic resonance imaging (MRI) studies have shown a consistent picture: cortical grey matter volume (an indirect measure of cortical synapse density) exponentially increases before puberty and subsequently decreases after puberty (Giedd et al., 1999; Giedd et al., 1999; Gogtay et al., 2004; Pfefferbaum et al., 1994). Moreover, these changes are region specific and follow a posterior anterior direction, i.e. lower order somatosenory and visual cortices mature before higher order association cortices (Giedd, 2004; Gogtay et al., 2004, Shaw et al., 2008; Tamnes et al., 2010). Given that these changes in cortical grey matter closely resemble the time course and region-specific changes in SWA, SWA might reflect the underlying processes of cortical maturation (Campbell and Feinberg, 2009; Feinberg, 1982; Kurth et al., 2010). Such a relationship between synaptic changes and SWA was shown using a large-scale computer model: a lower number of synapses / weaker synapses led to a reduction of the amplitude and the slope of sleep slow waves, which resulted in decreased SWA (Esser et al., 2007). Notably, a combination of structural imaging and high-density EEG demonstrated a positive correlation between SWA and grey matter volume in adolescents, most prominently in regions that undergo cortical reorganization at this age (Buchmann et al., 2011). Thus, sleep slow waves seem to mirror the maturation of cortical grey matter.

Changes in white matter volume

Along with changes in grey matter volume, there is a steady and linear increase of white matter volume throughout the first three decades of life (Giedd, 2004; Giedd et al., 1999, Lebel et al., 2008; Lebel and Beaulieu, 2011; Tamnes et al., 2010). The increase in white matter has been interpreted as a developmental progression in axonal myelination (Paus et al., 2008) which is provided by oligodendrocytes and is necessary for the integrity of white matter pathways and for the augmentation of neural transmission. On a cellular level, there is evidence that sleep promotes myelination by enhancing genes involved in membrane synthesis, myelination and proliferation of oligodendrocytes (Bellesi et al., 2013). Myelination in turn contributes to the development of functional connectivity. The observation of an intra-hemispherical increase in sleep EEG coherence that was associated with increased white matter development in early childhood (Kurth et al. 2013) and adolescence (Tarokh et al., 2010) is in line with the proposed relationship between myelination and brain activity during sleep. Moreover, a longitudinal study using diffusion tensor Imaging (DTI),

an MRI-based technique used to track and identify microstructural properties of white matter (Le Bihan et al., 2001) provided evidence for a link between sleep and white matter maturation during brain development (Telzer et al., 2015). In this study, a high variability in sleep duration 1.5 years before a DTI scan in adolescents was associated with lower measures of fractional anisotropy (FA; a measure of myelin level), suggesting that poor sleep may impair white matter development.

Development of skill maturation

Brain maturation is a complex process involving dynamic changes of conjoint white and grey matter volume (Bray et al., 2015) with high impact on the development of brain functions (for comprehensive reviews see: Johnson, 2003; Blakemore and Choudhury, 2006). However, only few longitudinal studies exist which provide a direct link between cortical reorganisation and the maturation of specific skills: a greater decrease in cortical grey matter in the frontal and parietal regions is associated with better performance in a verbal intellectual task (Sowell et al., 2004) and improvement in verbal working memory (Tamnes et al., 2013). The rate of improvement in cognition corresponds to the rate of increase in intra-hemispheric sleep EEG coherence (Tarokh et al. 2014) which can be used as a marker for white matter integrity. Further, Shaw et al. (2006) observed that intelligence depends on dynamic changes of cortical grey matter in frontal regions, rather than the absolute volume at a given age. Recently, Kurth et al. (2012) have integrated these findings by using a combination of structural imaging (MRI), high density sleep EEG and tests of cognitive abilities. All three measures follow a similar, age dependent trajectory: children exhibiting a more mature SWA topography (i.e. more frontal) performed better in a finger-tapping task. Interestingly, maturation of SWA preceded maturation of skills by 3.7 years.

Sleep function

Sleep is found in all species studied so far (Cirelli and Tononi, 2008; Siegel 2009); still the question why we need to sleep cannot entirely be answered yet. Sleep probably serves many functions; however three commonly accepted core activities have been proposed and were intensely investigated during the last decade. First, sleep serves as a restorative process; second, sleep plays a crucial role in memory consolidation and third sleep facilitates the waste clearance pathway in the brain. The increased sleep need during childhood and adolescence may indicate that these sleep functions are even more important during these developmental periods.

The synaptic homeostasis hypothesis

The synaptic homeostasis hypothesis states that synaptic strength changes as a function of wakefulness and sleep, i.e. during the day, total synaptic strength is increased whereas during sleep synaptic strength is reduced (synaptic downscaling; Tononi and Cirelli, 2003). Synaptic downscaling is hypothesised to be a restorative process in which previously, learning related potentiation of synapses, is reduced, allowing the brain to retain the capacity and efficiency to learn (Tononi and Cirelli, 2006;Tononi and Cirelli, 2014). Sleep slow waves are thought to mediate the homeostatic reduction of synaptic strength (Tononi and Cirelli, 2006; Tononi and Cirelli, 2014), mainly based on the following observations: sleep slow waves are closely related to sleep regulation: SWA increases with the time spent awake and decreases gradually in the course of the night (Borbély and Achermann, 2005). SWA might not only reflect the changes in synaptic strength but also contribute directly to synaptic reorganization as the underlying slow oscillations have been shown to induce long term depression of excitatory postsynaptic potentials (Czarnecki et al., 2007). As development is characterized by vast learning, the need for downscaling might be increased as well. Indeed, studies in young, adolescent mice support the view that extensive modulation in synaptic density during development is influenced by sleep and wake: wakefulness is associated with a net increase in synaptic density, whereas sleep reduces cortical spines (Maret et al., 2011; Yang and Gan, 2011). No such changes were observed in adult mice. Additionally, the link between synaptic plasticity and slow waves has been shown locally: a specific learning task that depends on a particular brain region showed increased SWA after learning (Huber et al., 2004; Landsness et al., 2009) and this experience dependent local increase in SWA is largest in children compared to adolescents and adults (Wilhelm et al., 2014).

Sleep serves memory consolidation

There is a vast amount of literature that provides evidence for an active role of sleep in memory consolidation in healthy adults. More specifically, it has been shown that newly learned information can be recalled better when memory encoding is followed by a period of sleep (either night sleep or afternoon nap) compared to an equal time spent awake (for reviews see Diekelmann et al., 2009; Diekelmann and Born 2010). The theory suggests that during slow wave sleep the brain repeatedly reactivates neuronal activity patterns in the hippocampus and neocortex that are associated with the newly learned material and thereby enable long-term memory storage (for a review see Born and Wilhelm 2012). Since there are fundamental changes in sleep duration and sleep structure (e.g. increased SWA; Feinberg and Campbell, 2012; Kurth et al., 2010) during development, it is conceivable that sleep in children might have an even greater impact on memory consolidation than in adults (Wilhelm et al., 2012). A recent study indeed showed that children outperform adults in a visuomotor learning task after a night of sleep (Wilhelm et al., 2014). This sleep dependent memory consolidation was also related to SWA. However, studies of sleep-dependent memory consolidation in children are rather scarce and further experiments directly comparing different age groups and different tasks are needed.

Glymphatic system

Neural activity during wake is associated with the accumulation of various metabolic waste products. Thus, the idea, that sleep may serve as a period to rest and to repair (including the elimination of neurotoxic waste products) is compelling (Vyazovskyi and Harris, 2013). It has been suggested previously that cerebrospinal fluid (CSF) and interstitial fluid (ISF) are in constant exchange to provide a clearance system to the brain, although the exact mechanisms were not clear yet (Schley et al., 2006). A recently proposed model (Iliff et al., 2012, Xie et al., 2013), called the "glymphatic system", provides evidence that this exchange of CSF and ISF is attributable to a convective bulkflow supported by astroglial processes. Importantly, this process is more active during sleep than during wakefulness (Xie et al., 2013). Two-photon-microscopy imaging revealed that in sleeping mice, interstitial space is increased by 60% which leads to a remarkable increase of the convective bulkflow and results in a higher metabolic clearance, including β-amyloid (Xie et al., 2013). So far, there is no study on the glymphatic sytem in humans, but there is evidence that β-amyloid concentration in humans and in mice increases during the day, with peak values in the evening and reduced levels during the night (Kang et al., 2009). Thus, sleep might be crucial for the waste clearance pathway in the brain. Again, as for the other proposed functions of sleep, the immense reorganization processes during development might be associated with an increased need for the elimination of neurotoxic waste products which in turn may necessitate increased sleep.

Consequences of insufficient sleep

Although the exact mechanisms of the function of sleep are still under debate, there is a clear association of sleep and brain function (Alkadhi et al., 2013). Childhood and adolescence constitute a vulnerable stage concerning brain development and together with the consideration that sleep contributes to brain maturation (Ringli and Huber, 2011) it appears to be likely that sleep disturbances at these ages have an impact on brain development. Moreover, disorders of brain development are often accompanied by disorders of sleep (Picchioni et al., 2014). Notably, around 30% of children and adolescents show sleep disorders including sleep-disordered breathing (such as sleep apnea and habitual snoring, 5 to 10%) or insomnia (Blader et al., 1997; Halbower and Marcus, 2003; Mindell et al., 1999). Sleep-disordered breathing is considered a spectrum of disorders which ranges from snoring to severe obstructive sleep apnea syndrome, which results in hypoxia, sleep fragmentation and day-time sleepiness (Walter et al., 2011). Sleep-disordered breathing was shown consistently to be related to behavioural disorders, reduced academic achievement and impairment of learning and memory (reviewed in Halbower and Mahone, 2006). In addition, habitual snoring, defined as snoring frequently or always, is found in 1 in 10 of primary school children (Urschitz et al., 2003) and is associated with sleep fragmentation (Halbower and Mahone, 2006). Children who snored habitually

had at least twice the risk of performing poorly at school. Notably, this association became stronger with increasing snoring frequency (Urschitz et al., 2003). The relationship between habitual snoring and poor academic performance did not appear to be mediated via intermittent hypoxia, since it was not diminished after excluding children with intermittent hypoxia in an overnight study (Urschitz et al., 2003). Therefore, the precise mechanism(s) responsible for neurocognitive impairment in sleep-disordered breathing remains unclear. Intriguingly, longitudinally investigations of children that underwent SDB treatment (e.g. Adenotonsillectomy or nasal steroids), have shown that recovery is confined to only some of the neurocognitive variables including nonverbal fluid reasoning, abstract thought and spatial visualisation, whereas behavioural measures showed no improvements (Biggs et al., 2014). The authors alluded to the link of CAP rate during slow wave sleep (cyclic alternating pattern; a measure of slow wave stability across the night) and fluid reasoning ability. Fluid reasoning ability was shown to be positively correlated with CAP rate, particularly during SWS in healthy children (Bruni et al., 2012) and was reported to be reduced in children with sleep disordered breathing (Kheirandish-Gozal et al., 2007). Thus, children with sleep disordered breathing show a reduction in the stability of slow waves, which seem to partially recover after treatment. Furthermore, several cross-sectional studies in healthy children and adolescents have shown an association of the quality or duration of sleep with cognitive measures such as executive functioning (Sadeh et al., 2002), intelligence (Gruber et al., 2010) and academic achievements (Dewald et al., 2010; Ravid et al., 2009). Nevertheless, it might be elusive to define a causal relationship of sleep quality or quantity and cognitive or behavioural functions outside of experimental settings, since reduced sleep efficiency might either be a cause or a consequence of observed impairments (Astill et al., 2012). So far, experimental sleep manipulation studies in children are rather sparse, but support a directional relationship between sleep quality or quantity and behavioural and cognitive performances. Especially sleep duration, sleep quality and sleepiness seem to be negatively correlated to cognitive abilities and school performance (Fallone et al., 2005; Astill et al., 2012; Dewald et al., 2011). Interestingly, even mild alterations in sleep duration of less than one hour have an impact on memory and attention (Sadeh et al., 2003). This study showed that setting bedtimes one hour earlier to the regular bed time for just 3 consecutive days resulted in an improved performance on memory and attention tasks, whereas one hour less sleep resulted in decreased test performances (Sadeh et al., 2003). Given this link between insufficient sleep and the drastic reduction in behavioural and cognitive performance, there is a growing body of literature investigating the impact of early or delayed school times on academic success. Early school start times might interfere with the recommended amount of sleep for children and adolescents; leading to sleep deprivation (Dexter et al., 2003) and daytime sleepiness, which has an high impact on daily functioning and school performance (Boschloo et al., 2013; Gradisar et al., 2011). Indeed, several studies have shown that early school start times raise fatigue levels due to a reduction in total sleep time, which was reflected in lower school performance (Owens et al., 2010; Wolfson et al., 2007). On the other hand, later school start times have been shown to improve sleep and daytime functioning, even if the delay is subtle (Boergers et al., 2014, Lufi et al., 2011; Perkinson-Gloor 2013). However, well controlled large scale interventional studies are missing. Nevertheless, this initial evidence indicates that sleep is substantial for health and cognition and appears to be particularly important during periods of brain maturation.

Manipulating sleep to improve behaviour and performance

Sleep problems in early childhood are frequently observed and are a typical feature of development (Alfano and Gamble 2009). However, when these problems become chronic, they can persist into adulthood and become an indicator for later emotional and behavioural problems (Alfano and Gamble 2009). Cognitive-behavioural treatment therapies (e.g. withdrawing excessive parental bedtime involvement, self-soothing strategies) have shown to improve bedtime problems and night wakenings in infants with additional improvement in other functional domains (for reviews see Mindell et al., 2006; Owens et al. 1999). In later child-

hood and adolescents, when the aetiology of sleep problems becomes more complex, the therapeutic approaches are very limited (Tikotzky, 2010), since pharmacological interventions for insomnia are only approved for adults (Pelayo and Dubik, 2008, Reed and Findling, 2002). Chronic sleep-onset insomnia, a common comorbidity in children diagnosed with attention-deficit/ hyperactivity disorder (ADHD; Corkum et al. 1999, Stein, 1999) leads to a persistent impairment of falling asleep, with a high impact on day time functioning and behavioural or cognitive problems (Sadeh et al., 2003). Studies investigating the impact of melatonin treatment in children with chronic sleep onset and attention-deficit/ hyperactivity disorder (Smits et al., 2003, Van der Heijden et al., 2007; Weiss et al., 2006) reported an increase in total sleep time, however failed to show improvements in behavioural and cognitive function. Moreover, melatonin treatment is not free of adverse events, such as cold feeling, dizziness, headache and decrease of appetite and mood (Hoebert et al., 2009, Smits et al., 2003). However, often not sleep disorders are the underlying problem of insufficient sleep but rather early school start times, the burden of homework, high caffeine consumption and the increased use of light-emitting (melatonin inhibiting) electronic devices (Alfano and Gamble 2009; Calamaro et al., 2009; Dworak et al., 2007; Orbeta et al., 2006). Since pharmacological treatment in otherwise healthy children or adolescents seems unethical and sleep medications are in general not approved for the pediatric use (Pelayo and Dubik, 2008) there is a high need for new non-drug interventions that result in cognitive or behavioural improvement. A very recent study demonstrated that blue-light blocking glasses, which are designed to block the blue-light emitted by electronic devices, extenuate the light-induced melatonin suppression in healthy male adolescents (van der Lely et al., 2015). Although the use of the glasses for one week was neither able to induce changes in sleep structure nor in performance of a vigilance test the next morning, participants reported a decreased alertness and increased sleepiness in the evening compared to the control condition (wearing glasses without blue-light block). Thus, blue light blocking glasses might be a suitable tool in order to sensitise adolescents for their own intrinsic sleep need, which in turn could result in a shift towards earlier bedtimes. A promising approach showing an improvement in cognitive performance comes from a study using transcranial oscillatory direct current stimulation (toDCS) during early sleep in children with ADHD (Prehn-Kristensen et al., 2014). Compared to healthy control subjects, children diagnosed with ADHD show a less mature topographical distribution of SWA (Ringli et al., 2013) and present diminished amounts of SWS (Prehn Kristensen et al., 2011), which has been significantly correlated with reduced sleep dependent consolidation of declarative memory (Prehn-Kristensen et al., 2011). Frontal bilateral application of an oscillating direct current at 0.75 Hz during the first part of the night led to a significant increase in SWA compared to the sham condition in the same subjects. Additionally, toDCS improved sleep-dependent declarative memory performance up to the level of healthy controls. Other studies have used auditory closed-loop stimulation, a technique in which tones (usually pink noise) are played time-locked to the upstate of individual slow waves (Ngo et al., 2013), which resulted in a profound increase in slow oscillations and was associated with increased performance in a declarative memory task (Ngo et al., 2013). So far, no study has probed closed-loop stimulation in the paediatric age group, although this group might highly benefit from this strategy, especially against the background that sleep disturbances are very prominent in this group and its high implication on brain development. On the other hand, modulations of slow wave sleep have not been limited to the effort to enhance, but also to reduce slow waves. Van Der Werf et al. (2009) used automated acoustic stimulation in which the stimulation was coupled to the occurrence of slow waves. Acoustic stimulation disrupted slow wave sleep and resulted in a decrease of SWA, which was directly related to reduced explicit but not to implicit memory performance. However, two very recent studies implementing the same paradigm in children (Astill et al., 2014; Piantoni et al., 2013) found no effects on the EEG activity, presumable due to the higher arousal threshold found in children. Notwithstanding, the non-invasive modulation of sleep seems to be a very promising method for future research as it can provide more direct evidence for a causal relationship between slow waves and brain maturation.

Summary and future directions

Overall, the literature discussed in this review provides substantial evidence for a close relationship between sleep and brain maturation and suggests that especially sleep slow waves might play an active role in brain plasticity processes that are of importance for a healthy brain development. The developmental remodelling of brain circuits goes along with the maturation of cognitive and emotional functions like reasoning processes, interpersonal interactions, recognition of conspecifics, attribution of mental states, cognitive control of emotion, evaluation of risk and reward, and motivation (e.g. Blakemore, 2008). It is therefore not surprising that this developmental period seems to be especially susceptible to interfering genetic, epigenetic or environmental factors, which may lead to an increased risk for the emergence of structural, functional and eventually behavioural abnormalities. This increased risk for deviant development of cognitive and emotional functions during adolescence is accompanied by an increasing incidence of psychiatric disorders, including mood, anxiety, eating, substance abuse and personality disorders as well as schizophrenia (Feinberg, 1982; Keshavan et al., 1994; Saugstad, 1994; Lewis and Levitt, 2002; Paus, 2005; Blakemore, 2008). As sleep and especially slow wave sleep seems to play an active part in these remodelling processes, the role of sleep during development should not be underestimated. Moreover, monitoring sleep slow waves during this particular important phase of brain development might constitute a marker of early atypical brain development. At the same time, the modulation of slow wave sleep might be beneficial in deviant brain maturation, but practical and clinical implementation in the paediatric age range need to be elucidated in the future.

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