E. J. W. Van Someren et al. (Eds.)
Progress in Brain Research, Vol. 193
ISSN: 0079-6123

CHAPTER 5

Developmental aspects of sleep slow waves: Linking sleep, brain maturation and behavior

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Abstract: Sleep slow waves are the major electrophysiological features of non-rapid eye movement (NREM) sleep. Although there is growing understanding of where slow waves originate and how they are generated during sleep, the function of slow waves is still largely unclear. A recently proposed hypothesis relates slow waves to the homeostatic regulation of synaptic plasticity. While several studies confirm a correlation between experimentally triggered synaptic changes and slow-wave activity (SWA), little is known about its association to synaptic changes occurring during cortical maturation. Interestingly, slow waves undergo remarkable changes during development that parallel the time course of cortical maturation. In a recent cross-sectional study including children and adolescents, the topographical distribution of SWA was analyzed with high-density electroencephalography. The results showed age-dependent differences in SWA topography: SWA was highest over posterior regions during early childhood and then shifted over central derivations to the frontal cortex in late adolescence. This trajectory of SWA topography matches the course of cortical gray maturation. In this chapter, the major changes in slow waves during development are highlighted and linked to cortical maturation and behavior. Interestingly, synaptic density and slow-wave amplitude increase during childhood are highest shortly before puberty, decline thereafter during adolescence, reaching overall stable levels during adulthood. The question arises whether SWA is merely reflecting cortical changes or if it plays an active role in brain maturation. We thereby propose a model, by which sleep slow waves may contribute to cortical maturation. We hypothesize that while there is a balance between synaptic strengthening and synaptic downscaling in adults, the balance of strengthening/formation and weakening/elimination is tilted during development.

Keywords: slow wave activity; sleep slow waves; topography; development; cortical maturation; plasticity.

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DOI: 10.1016/B978-0-444-53839-0.00005-3

Introduction

On the neuronal level, slow (<1 Hz) oscillations are the major electrophysiological features of deep non-rapid eye movement (NREM) sleep (Steriade et al., 1993; Fig. 1). When such slow oscillations are synchronized and involve the majority of cortical neurons in a certain brain area, they become visible in the surface electroencephalogram (EEG) as slow waves (Vyazovskiy et al., 2009a; Fig. 1). The activity of these slow waves is traditionally quantified by EEG spectral analysis. Sleep slow-wave activity (SWA; EEG power between 0.75 and 4.5 Hz) was shown to be a precise electrophysiological correlate of the homeostatic regulation of sleep. Sleep homeostasis is a well-characterized phenomenon with a strong impact on basic and clinical research (Borbély, 1982; Borbély and Achermann, 1999). In recent years, there is a growing understanding of where slow waves originate and how they are generated during sleep (Vyazovskiy et al., 2009a). However, the functions of the regulation of slow waves are still largely unclear. One interesting aspect is that the activity of slow waves undergoes remarkable changes during development (Campbell and Feinberg, 2009; Feinberg, 1982; Feinberg et al., 2006; Jenni et al., 2004; Kurth et al., 2010b). SWA increases in the first years of life, reaches a maximum before puberty, and then declines rapidly during adolescence into adulthood (Feinberg, 1982; Feinberg and Campbell, 2009). The understanding of mechanisms behind such developmental changes in the activity of slow waves may explain the neurophysiological and cellular processes underlying the need for sleep.

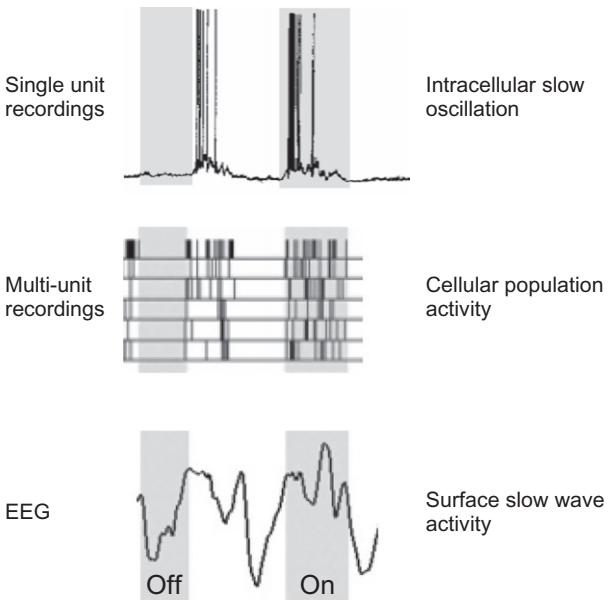

Fig. 1. Neuronal activity measured at three different levels. *Top row:* Intracellular slow (~0.3–0.4 Hz) depolarizing oscillation measured by single unit recordings (adapted from Steriade et al., 1993). *Middle row:* Raster plots of neuronal activity in one representative rat showing highly synchronized cellular population activity in early NREM sleep and the corresponding surface EEG showing slow-wave activity (*bottom row*; adapted from Vyazovskiy et al., 2009a). Single unit recordings reveal intracellular slow oscillations (<1 Hz) with the characteristic alternation of depolarized up- and hyperpolarized down states (Steriade et al. 1993). This activity is highly synchronized across cellular populations during early sleep, as multiunit recordings show (Vyazovskiy et al., 2009a). Periods of neuronal silence correlate with the negative peak of surface slow-wave activity, as measured with EEG, and high population activity is correlated to the positive deflection of SWA. Grey squares indicate simultaneous occurrence of activity on all three levels.

In this chapter, we will highlight the changes in slow waves during development, linking cortical maturation, sleep, and behavior. Also we propose a hypothesis for the mechanisms possibly driving the inverted U-shaped time course of slow waves.

Characteristics of slow waves

Definition, generation, and behavior of slow waves

During NREM sleep, the transition from the low-voltage, fast activity EEG observed during wakefulness to the characteristic EEG of NREM sleep is due to the occurrence of depolarized *up states*, episodes of sustained firing, and brief periods of

hyperpolarization with neuronal silence, also called *down states*, in thalamocortical and cortical neurons. Down states are due to reduced activating input from ascending cholinergic and other neuromodulatory pathways (for reviews, see Llinas and Steriade, 2006; McCormick and Pape, 1990; Steriade et al., 1993), which is primarily due to an increase in leakage potassium conductances (McCormick and Pape, 1990).

Intracellular recordings have shown that during NREM sleep compared to REM sleep or wakefulness, virtually every cortical neuron engages in the slow oscillation that consists of alternating periods of sustained firing or neuronal silence, respectively (Amzica and Steriade, 1998; Steriade et al., 1993, 2001; Fig. 1). The repeated occurrence of down states characterized by synaptic silence is probably the reason why brain metabolism and blood flow are diffusely reduced during NREM sleep as compared to wakefulness, as shown by imaging studies (Braun et al., 1997). Moreover, a close temporal relationship between these cellular phenomena and simultaneously recorded slow waves on the surface was shown (e.g., down states correspond to the negative part of the surface slow waves; Amzica and Steriade, 1998; Vyazovskiy et al., 2009a; Fig. 1).

Human EEG recordings using 256 channels have revealed that, in adults, the slow oscillation behaves as a traveling wave that sweeps across a large portion of the cerebral cortex (Massimini et al., 2004). Slow oscillations seem to originate from nearly any region of the scalp and propagate in any direction. Yet, most frequently, slow oscillations started in frontal areas and propagated in an anteroposterior direction.

Slow waves and sleep homeostasis

It was discovered early on that arousal thresholds—measured, for example, as the duration of an acoustic stimulus required to awaken a sleeping subject—are positively correlated with the amount of slow waves in the EEG of NREM sleep. It was also noticed that high-amplitude slow waves predominate in the first 2 h of sleep and decrease thereafter (Blake and Gerard, 1937). It was later shown that the amount of slow-wave sleep is positively correlated with the duration of prior waking (Webb and Agnew, 1971), suggesting that this aspect of sleep is homeostatically regulated.

In 1982, Alexander Borbély proposed the *two-process model of sleep regulation* which postulates that sleep propensity is determined by the interaction of a homeostatic process S and a circadian process C (Borbély, 1982). Process S increases during waking and decreases during sleep. Therefore, the positive relationship between slow waves and the duration of wakefulness is best seen under the influence of sleep deprivation. If we are not allowed to sleep and are forced to stay awake longer than usual, sleep pressure mounts and soon becomes overwhelming. The more we stay awake, the longer and more intensely we sleep afterward: arousal thresholds increase, there are fewer awakenings. Thus, sleep is homeostatically regulated. An important advance has been the demonstration that process S is reflected accurately by the amount of SWA (electroencephalographic power in the low frequency range between 0.5 and 4 Hz) during NREM sleep (Borbély, 1982; Borbély and Achermann, 2000). As repeatedly shown in both humans and mammals, SWA increases exponentially with the duration of prior wakefulness and decreases exponentially during sleep, thus reflecting the accumulation of sleep pressure during wakefulness and its release during sleep. Therefore, the immediate history of sleep and waking determines the level of process S.

Homeostatic sleep regulation at the cellular level

The accumulation of sleep pressure during wakefulness and its decline during sleep are not only reflected by EEG SWA but can also be observed at the cellular level. It is well known that at the cellular level, cortical neuronal firing patterns are

characteristically different in NREM sleep compared to both REM sleep and wakefulness (e.g., Steriade et al., 2001). However, recently, it was shown that cortical neuronal firing patterns not only depend on the behavioral state but also depend on how long a rat has been awake or asleep (Vyazovskiy et al., 2009a). Unit activity recordings in the rat showed that firing rates change as a function of sleep pressure, showing that higher sleep pressure is related to higher firing rates, which progressively decrease across sleep episodes. The same study found that also synchrony of firing activity is higher under high sleep pressure during early sleep compared to low sleep pressure during late sleep. In summary, this study yields evidence for a homeostatic regulation of sleep at the cellular level, by modulating firing rates. Thus, changes in firing patterns are expressed in the typical homeostatic behavior of the cortical SWA measured in the surface EEG (Fig. 1).

Sleep homeostasis during development

At birth, sleep homeostasis is not yet present in both animal and humans but develops in the first months of life (Bes et al., 1991; Jenni et al., 2004). For example, when very young rats (P12) are sleep deprived, they mainly compensate the sleep dept by increasing sleep duration (Frank et al., 1998). However, only 12 days later (P24), sleep deprivation results in an increase in sleep SWA, as is the case in adult animals, whereas sleep duration remains constant. Similarly, in humans: selective or total sleep deprivation in human neonates leads to compensatory increases in NREM sleep duration only (Anders and Roffwarg, 1973; Thomas et al., 1996). Moreover, it seems that the dynamics of sleep homeostasis according to the two-process model of sleep undergoes developmental changes. It was shown that the buildup of homeostatic sleep pressure during wakefulness is faster in both prepubertal children and rats compared with young adolescents or postpubertal rats, respectively (Alfoldi et al., 1990; Jenni et al., 2005a). In contrast, the decline of the homeostatic process is similar in both groups. The following sections all refer to a maturational stage where sleep homeostasis is developed.

However, as the example of sleep homeostasis shows, sleep is not a uniform phenomenon across the life span. Specifically, slow waves undergo significant changes during development, which the next section will focus on.

Development of slow waves—disparities in infants, children and adolescents

It is noteworthy that some properties of slow waves, such as the duration of slow-wave sleep (Tucker et al., 2007) or the topography of SWA (Finelli et al., 2001), vary impressively between subjects but intraindividually remain stable over time. However, this intraindividual stability is only true after reaching adulthood. During development, the characteristics of slow waves undergo prominent changes until they reach a mature stage.

Slow-wave amplitude follows an inverted U-shaped time course

Development is a phase of substantial changes in brain morphology and function (Johnson, 2001). Since slow waves originate from synchronized activity of cortical neurons (Steriade et al., 1993; Vyazovskiy et al., 2009a), it is expected that brain maturation, which results in remarkable cortical reorganization, should be reflected in the sleep EEG. In fact, longitudinal and cross-sectional studies point to major age-dependent changes in the slow-wave frequency band (Feinberg et al., 2006; Jenni and Carskadon, 2004; Jenni et al., 2004; Kurth et al., 2010b).

Cross-sectional and longitudinal studies show that SWA follows the time course of an inverted U-shaped curve (Campbell and Feinberg, 2009; Feinberg, 1982; Gaudreau et al., 2001; Jenni

et al., 2004; Kurth et al., 2010b). The amplitude of slow waves increases during childhood and is highest shortly before puberty. Then, in the course of adolescence, slow-wave amplitude or SWA declines by over 60% between 11 and 16 years. This decline is slowed down at about 17 years (Campbell and Feinberg, 2009; Feinberg et al., 2006). It is worth mentioning that the decline during puberty even exceeds the decrease of SWA observed over the subsequent 50 years of life (Feinberg and Campbell, 2010).

So far, little is known about the development of slow waves in animals. Recently, SWA was recorded longitudinally in juvenile rats from postnatal day 25 (P25) to P50. Similar to humans, the time course of SWA followed the course of an inverted U-shape with a peak around the rat's pubertal stage (Olini et al., 2010). Importantly, changes in the amount of wakefulness did not explain the decline of SWA during adolescence.

Slow-wave topography demonstrates regional shifts

While it is well known that in adults, SWA topography typically shows a frontal predominance (Finelli et al., 2001), only few studies have looked at regional differences in the changes of SWA and other frequency bands during development (Jenni et al., 2005b; Tarokh and Carskadon, 2010). Recently, EEG power topography was investigated in a broad sample of children and adolescents between age 2 and 20 years (Kurth et al., 2010b). All-night sleep EEG was recorded using high-density EEG with 128 electrodes. The analysis of the topographical distribution of the most common frequency bands in children showed that SWA topography undergoes large changes from early childhood to adolescence (Fig. 2), while the topography of power in other frequency bands remained largely unchanged. Notably, a striking finding was that SWA exhibited a regional predominance that was characteristic for a certain age range. When the location of maximal SWA was identified across age, the authors found a shift from posterior to anterior regions, reaching frontal derivations during adolescence. The adult frontally predominated pattern of SWA, as found by Finelli et al. (2001), was still not fully present even in late adolescence. In contrast, none of the other frequency ranges exhibited similar age-related alterations in the topographical pattern during development.

These results are in line with imaging studies, showing that cortical maturation follows a posterior–anterior time course, with lower-order primary areas maturing first, followed by higher-order association areas (Gogtay et al., 2004; Sowell et al., 2004).

Developmental aspects and their relation to the function of slow waves

Several studies show that the amplitude of slow waves increases during childhood, reaches its maximum shortly before puberty, and decreases during adolescence (Campbell and Feinberg, 2009; Feinberg et al., 2006; Gaudreau et al., 2001; Jenni et al., 2004). A longitudinal study revealed that during childhood and early puberty, SWA correlates with age but not with other developing biological marker such as weight, height, BMI, or sexual maturation (Feinberg et al., 2006). This may be a hint that SWA is possibly reflecting the driving mechanism underlying brain maturation rather than just being an epiphenomenon of development.

Already in 1982, Feinberg alluded to the similarity of the time course of slow-wave amplitude and synaptic density, proposing that the decrease of SWA during adolescence reflects the decrease of synapses through pruning (a process eliminating overproduced synapses which results in an increase of the specification of synaptic connectivity; Campbell and Feinberg, 2009; Feinberg, 1982; Feinberg and Campbell, 2010). This

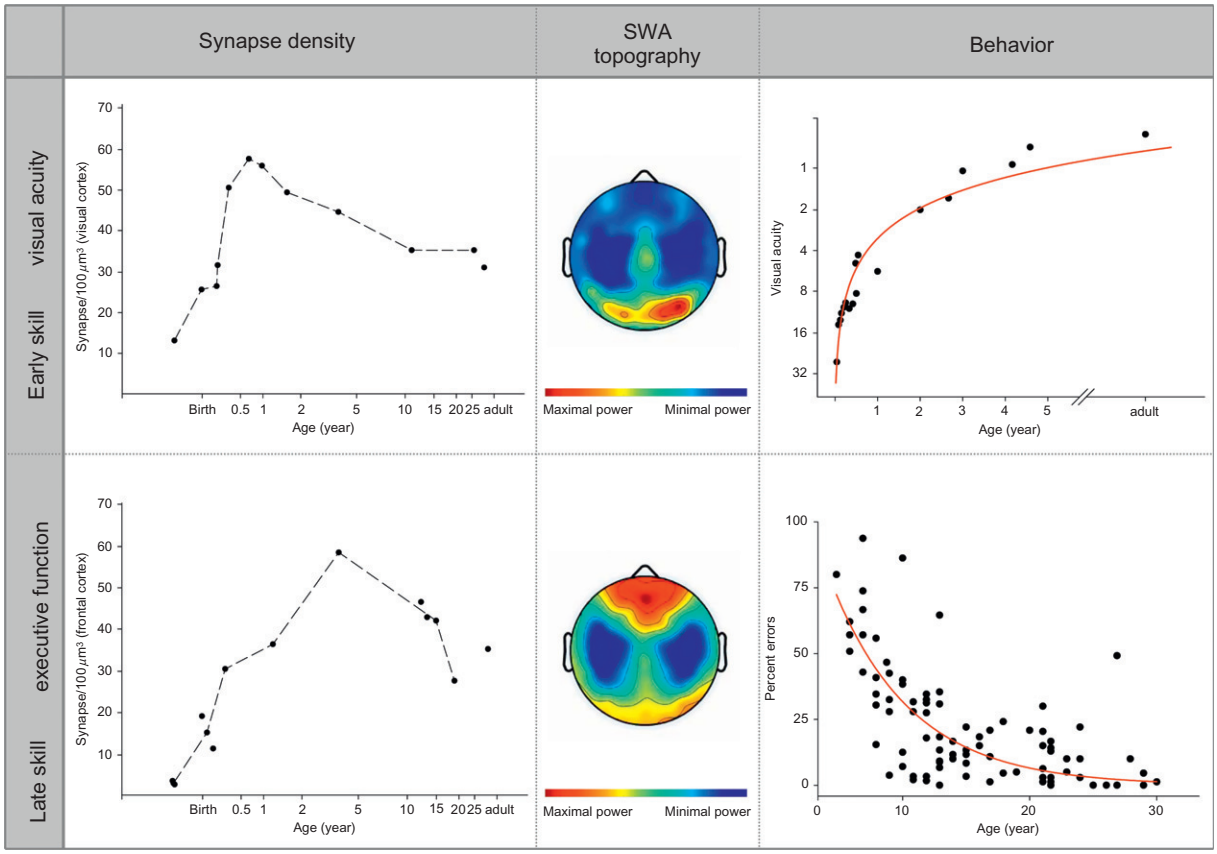

Fig. 2. Linking brain maturation, SWA topography, and behavior at an early and a late state of development. *Left column:* Mean synaptic density (synapses/100 µm^3) in visual cortex (area 17; top) and prefrontal cortex (bottom) at various ages (adapted from Huttenlocher and Dabholkar, 1997). *Middle column:* Maps of EEG power during NREM sleep (adapted from Kurth et al., 2010b). Topographical distribution of NREM sleep SWA for age groups 2–5 years (top) and 17–20 years (bottom). Maps are based on 109 derivations from the first 60 min of NREM sleep stages 2 and 3. Maps were normalized for each individual and then averaged for each age group. Values are color coded (maxima in red, minima in blue) and plotted on the planar projection of the hemispheric scalp model. To optimize contrast, each map was proportionally scaled, and values between the electrodes were interpolated. *Right column:* Development of visual acuity in human infants plotted against age (top; adapted from Teller 1981). Both axes are logarithmically scaled. *y*-axis shows the number of minutes subtended by each black or white stripe of the acuity (smaller number indicating advanced maturation) grating and *x*-axis age in years. Bottom: Direction error in percentage versus age in the antisaccade task with the target located on the right side and the correct saccades generated to the left side. The red line represents exponential decline in percent error across age (adapted from Munoz et al. 1998). *Top row:* Synaptic density in the visual cortex is highest at around 8 month after birth and decreases thereafter as a matter of maturation, reaching adult levels shortly before puberty (left). Also SWA is highest over the occipital cortex during the first years of life (middle), reflecting gray matter maturation. Brain maturation is accompanied by the specification of skills and behavioral changes. Visual acuity, a function located in the occipital cortex, is developed during the first years of life, reaching adult levels at around 3 years (right; smaller digits indicate better acuity). *Bottom row:* An example for a skill maturing at a later state is given at the right. "Executive functions" is a general term to which a set of cognitive abilities is subsumed. In Munoz et al. (1998), executive functions are tested using the antisaccade task, where subjects are asked to look in the opposite direction of an appearing stimulus. While prepubertal children look at the cue reflexively (which is rated as error), reaction control (suppression of reflexive saccades) is reached during puberty and error rate decreases near 20 years. During the same time, synaptic density in the frontal cortex, where executive functions are located, is starting to decrease, as a sign of brain maturation (left). Paralleling this process, SWA is highest over frontal derivations (middle).

proposition became more conceptional in light of a recently formulated, comprehensive hypothesis, the *synaptic homeostasis hypothesis* (Tononi and Cirelli, 2003, 2006).

The synaptic homeostasis hypothesis

The synaptic homeostasis hypothesis is based on a large number of observations at many different levels, from molecular and cellular biology to systems neurophysiology and neuroimaging (for more details, see Tononi and Cirelli, 2003, 2006).

The main points of the hypothesis are as follows. During wakefulness, we interact with the environment and acquire information about it. The neuromodulatory milieu (e.g., a high level of noradrenaline, NA; Cirelli and Tononi, 2004) favors the storage of information, which occurs largely through synaptic potentiation (Trachtenberg et al., 2002). A key functional corollary of the hypothesis is that, due to the net increase in synaptic strength, such plastic changes during wakefulness have a cost in terms of energy requirements, space requirements, supplies of key cellular constituents, and progressively saturates our capacity to learn. When we go to sleep, we become virtually disconnected from the environment (Steriade et al., 1993). Changes in neuromodulatory milieu when falling asleep trigger slow oscillations (Steriade and Timofeev, 2003). The changed neuromodulatory milieu (e.g., low NA; Cirelli and Tononi, 2004) also ensures that synaptic activity is not followed by synaptic potentiation, which makes adaptive sense given that synaptic activity during sleep is not driven by interactions with the environment. Since the average strength of synaptic connections at the end of the wake period has increased, neurons synchronize their firing better and the resulting slow oscillations of early sleep are of high amplitude (Esser et al., 2007; Vyazovskiy et al., 2009a). In the sleep EEG, these high-amplitude slow oscillations are reflected by increased SWA. The slow oscillations, however, are not just an epiphenomenon of increased synaptic strength, but according to the hypothesis have a role to play. Specifically, the repeated sequences of depolarization–hyperpolarization of slow oscillations would lead to the proportional downscaling of all synapses impinging on each neuron (Turrigiano and Nelson, 2000, 2004). In other words, the downscaling of synapses leads to an overall decrease of synaptic strength. The reduced synaptic strength reduces the amplitude and synchronization of the slow oscillations, which is reflected in a decrease of SWA in the sleep EEG. Because of the dampening of the slow oscillation, the downscaling process is progressively reduced, making the process self-limiting when synaptic strength reaches a baseline level (Olcese et al., 2010). By returning total synaptic weight to an appropriate baseline level, sleep enforces synaptic homeostasis. Again, the key functional corollary is that synaptic homeostasis has benefits in terms of energy and space requirements and of the supply of key cellular constituents, and due to increased signal-to-noise ratios in terms of learning and memory (Olcese et al., 2010). Thus, when we wake up, neural circuits do preserve a trace of previous experiences but are kept efficient at a recalibrated level of synaptic strength, and the cycle can begin again.

In the past years, important progress was made in unraveling the originally hypothesized mechanisms. Molecular studies support the idea of a reduction of synaptic strength during the night, by confirming that markers of synaptic potentiation are high after wakefulness and low after sleep, in both rodent cortex/hippocampus and fly brains (Cirelli and Tononi, 2004; Gilestro et al., 2009; Vyazovskiy et al., 2008). Further, in slices obtained from frontal cortex of rats and mice, it was found that both the frequency and the amplitude of miniature postsynaptic potentials, the most direct reflection of synaptic strength, increase after wakefulness and decreased after sleep (Liu et al., 2010). On the electrophysiological level, early findings of single-neuron recordings were extended (Steriade et al., 1993) in that also neuron populations change

their firing rate across the night which was closely related to the changes of SWA (Vyazovskiy et al., 2009a). High synchrony firing and higher firing rates were found during early sleep and declined across the night. States of hyperpolarization, corresponding to the negative peak slow waves on the surface (Fig. 1), were longer and more frequent at the beginning of the night and showed a decrease in incidence and duration in the course of sleep. Alterations in the firing behavior were highly correlated to the changes in SWA (Vyazovskiy et al., 2009a). Recently, recordings from cortical slices provided evidence for alterations of plasticity during sleep. Induction of repetitive burst pairings in layer V pyramidal cells of the rat was followed by long-term depression, which was inversely related to excitatory postsynaptic potentials, thus suggesting a mechanism by which synaptic inputs are proportionally downsized during NREM sleep (Czarnecki et al., 2007). Further, in a computer model, the interplay of activity and changes in plasticity was proposed as a regulating mechanism that modulates the renormalization of synaptic strength during NREM sleep (Olcese et al., 2010). The model suggests that the strength of a connection is downregulated by a self-limiting control loop: for example, a strong connection leads to high firing rates and synchrony. This will also lead to stronger synaptic depression, which brings the system down to baseline connectivity values. When connections are renormalized, activity levels are too low to induce significant plastic changes and the system will reach an equilibrium point.

Synaptic strength is reflected in the slope of sleep slow waves

Wakefulness is associated with a net increase in synaptic strength which is renormalized during sleep (Olcese et al., 2010). The strength of population excitatory postsynaptic currents is reflected by the slope of local field potentials (LFPs) evoked by electrical stimuli (Rall, 1967). Slope and amplitude of LFPs increase as a function of the time spent awake and decrease during sleep (Vyazovskiy et al., 2008). Furthermore, the slope of LFPs is positively correlated with the mean and peak SWA of first hour of NREM sleep (Vyazovskiy et al., 2008). Synaptic strength is high at the beginning of the night and most individual neurons start and stop firing in near synchrony with the rest of the population (Vyazovskiy et al., 2009a). Synchronous transitions at the unit level were associated with steep slopes of slow waves during early sleep and less synchronous transitions with reduced slopes at the end of the night. Slow-wave slope decreased from the beginning to the end of the night as was shown in humans (Riedner et al., 2007), in rats (Vyazovskiy et al., 2007), and *in computo* (Esser et al., 2007). The decrease of slope over night was explained as homeostatic reduction of synaptic strength.

This homeostatic regulation, that is, the reduction of steepness overnight is already present during development, as was found by investigating the slope of slow waves in prepubertal children and mature adolescents (Kurth et al., 2010a). Furthermore, the comparison of the two groups showed that the slope of children exceeded that of adolescents and remained steeper across the night, in both conditions, during baseline as well as after sleep deprivation. In light of a recently proposed thalamocortical computer model (Esser et al., 2007), these findings might indicate greater synaptic strength of neurons involved in the generation of sleep slow waves in prepubertal children, compared to mature adolescents. Such increased synaptic strength may be due to greater density or greater efficacy of cortical synapses or both.

Since higher synaptic density is related to higher activation during wakefulness, an equivalent proportion of downscaling is needed to return to base levels. This observation would explain the parallel time course of synaptic density and slow-wave amplitude during development.

In the following part, the relationship between cortical maturation and SWA is discussed in more detail.

SWA and cortical maturation

During early childhood, neurons grow bushier and establish more numerous connections to other cells (DeFelipe, 1997). Moreover, axons initially explore areas much wider than their final targets (Gao et al., 1999). Then, in the course of adolescence, more synapses are eliminated than formed (Zuo et al., 2005), in part through activity-dependent processes (Hua and Smith, 2004). Synaptic pruning during adolescence is accompanied by a reorganization of neuronal connections, whereby mistargeted axons and unused synapses are eliminated, and connectivity becomes more specific. The decrease of synaptic density during adolescence, which is reflected in changes in gray matter, proceeds asynchronously in different brain areas (Paus, 2005), in line with the maturation of specific cognitive functions (Shaw et al., 2006a).

Changes in synaptic density are paralleled by changes in slow-wave amplitude (Feinberg, 1982; Huttenlocher, 1979; Huttenlocher and Dabholkar, 1997) and brain metabolism, presumably due to the increased energy requirements associated with increased synaptic activity (Chugani, 1998). This observation has been confirmed both in humans and in rats (Glantz et al., 2007; Nakamura et al., 1999). As suggested by the synaptic homeostasis hypothesis (Tononi and Cirelli, 2006), and confirmed by computer simulations and experimental studies in both humans and rats, changes in synaptic efficacy can account for the observed changes in sleep slow waves (Esser et al., 2007; Olcese et al., 2010; Riedner et al., 2007; Vyazovskiy et al., 2007, 2009a,b). Thus, sleep SWA could be taken as a reliable indicator of net changes in average synaptic density/strength, both in the course of the night (sleep homeostasis) and in the course of development.

Investigation of sleep SWA topography during childhood and adolescence confirmed this assumption, by showing that the location on the scalp exhibiting maximal SWA changed during development by following a posterior to anterior time course (Kurth et al., 2010b; Fig. 2). This posterior to anterior shift is well known from MRI studies, reporting a similar time course for gray matter volume change during development (Giedd, 2004, 2008; Shaw et al., 2008; Sowell et al., 2004). Thus, the changes in SWA topography probably reflect synaptic changes accompanying the pruning process during cortical maturation (Fig. 2). Another link between cortical maturation and slow waves arises from a study that compared the SWA decrease during adolescence with alterations in gray matter volume (Buchmann et al., 2011). Both factors were positively correlated. Further, this relationship was most pronounced in cortical areas maturing during adolescence. An interesting aspect concerns sex differences: It has been reported that average delta power was significantly lower in girls than in boys at the age of 12–14 years, while at the age of 9–11 years, no sex differences were observed (Feinberg et al., 2006). This has been explained by the earlier pruning of frontal gray matter in girls (Giedd et al., 1999).

Plasticity-dependent changes of SWA

Evidence for a link between SWA and plastic changes arises not only from maturational studies but also from settings in which synaptic changes are triggered experimentally. High-density EEG recordings in adults show that reduced motor activity due to arm immobilization during the day is followed by a local decrease of SWA over the corresponding motor region compared to a normal night (Huber et al., 2006), while potentiation of synapses in the motor cortex with transcranial magnetic stimulation leads to a local increase of SWA (Huber et al., 2007), indicating a direct relationship between synaptic strength and SWA. In another study of the same author, high-density

EEG recordings showed that also learning a visuomotor task, compared to a control non-learning task, produces an increase in SWA which is localized to the brain region (right parietal cortex) that is known to be involved in learning the task (Ghilardi et al., 2000; Huber et al., 2004). The subjects were trained on a rotation adaptation task where they had to reach for visual targets using a handheld cursor, while unconsciously adapting to an imposed rotation. Performance, measured as the degree of deviation to the straightest movement (directional error), improved not only during the training phase before sleep but also at retest after sleep. Remarkably, when performance after sleep was related to SWA, the size of the local SWA increase during the first 30 min of NREM sleep predicted the decrease in directional error at retest after sleep. In another study, which also investigated the relationship between sleep SWA and task performance, participants were trained on the same learning task (Landsness et al., 2009). However, during subsequent sleep, they were deprived of slow waves by means of acoustic stimulation. In this case, no increase of SWA over the corresponding region was observable and also no learning improvement took place (Landsness et al., 2009). From these studies, it can be concluded that changes in SWA not only reflect changes in synaptic plasticity but also affect performance. Likewise, the causal relationship between SWA and test performance is not limited to the visuomotor modality but was also found in a texture discrimination task (Aeschbach et al., 2008).

Recently, it was shown that the beneficial effect of sleep on visuomotor performance is independent of the time of day the task is being trained (Maatta et al., 2010). Subjects were trained in the morning instead of right before sleep and allowed to pursue their normal daily activities. Similar to previous studies, SWA was locally increased over the trained region during the subsequent night and improved performance was found during retest the following morning. However, independency of timing might be task specific as several other memory tasks only demonstrate sleep-dependent performance improvement, when sleep follows training closely (Gais et al., 2006; Talamini et al., 2008; Van Der Werf et al., 2009).

There is increasing evidence that sleep-dependent performance improvement can not only be experimentally inhibited by the suppression of slow waves but also be boosted by the stimulation of slow oscillations. Stimulation of oscillating potential fields by transcranial application of oscillating potentials (0.75 Hz) during the first NREM sleep leads to enhanced improvement in a declarative memory task compared to sham stimulation (Marshall et al., 2006). These findings further support the hypothesis that SWA plays an active role in the regulation of cortical synaptic strength.

Recently, a simplified version of the learning task as was used in Huber et al. (2004) was applied in a sample of children and adolescents, ranging from 8 to 20 years. The results showed that the beneficial effects of sleep on task performance as well as the corresponding local increase in SWA are not only found in adults but already present in children and adolescents (Ringli et al., 2009).

In summary, there is good evidence that sleep SWA is a reliable indicator of net changes of synaptic strength in the course of a night (sleep homeostasis), which seems directly related to the observed postsleep performance improvements. In the next section, we will discuss how age-dependent changes in SWA may be related to behavior and cortical maturation during development.

Slow waves and their relation to behavior

Cognitive skills

There is a large body of evidence showing that full sleep deprivation as well as part-time or chronic sleep restriction causes impairment in cognitive functioning (e.g., Banks and Dinges,

2007). Also it is well known that the consequences of restricted sleep duration are mainly reflected in an increase of SWA during the recovery night (Borbély and Achermann, 2000), implying a relationship between SWA and cognitive impairment.

If sleep and especially slow-wave sleep do play a critical role in brain development and learning, then sleep disorders, sleep restriction, and sleep loss early in life may impair cognitive functioning. Some evidence in favor of such a relationship is becoming available. For example, a positive correlation between increased sleep/earlier bedtimes and higher school grades was found in a representative population of high school students (Wolfson and Carskadon, 1998). Moreover, actigraphy, an objective measure for evaluating sleep patterns, revealed that sleep fragmentation correlates significantly with daytime sleepiness, attentional deficits, and learning impairments (Sadeh et al., 2000). Such effects seem to be more evident in younger children (Sadeh et al., 2002), possibly suggesting that sleep is even more important for neurobehavioral functioning at a younger age.

As introduced in Section "SWA and cortical maturation," the predominance of SWA on the scalp parallels cortical brain maturation, originating over posterior areas during childhood and shifting forward to frontal sites during puberty (Giedd, 2004; Kurth et al., 2010b; Shaw et al., 2008; Sowell et al., 2004). Interestingly, many cognitive and behavioral functions related to the frontal cortex do not mature until late adolescence (Luna and Sweeney, 2004). Progressive maturational changes in performance of cognitive demanding tasks can be seen from childhood to adulthood. This cognitive development is thought to rely on pruning processes as well as myelination of fiber tracks (Luna and Sweeney, 2004).

In Fig. 2, evidence for a link between maturation, SWA topography, and behavior is illustrated for an early and a late state of development. For example, maturation of the visual cortex occurs early in life as is shown by the decrease in synaptic density, which already starts in the first year after birth and reaches adult levels shortly before puberty (Huttenlocher and Dabholkar, 1997). Consistently, SWA is highest over the occipital cortex during the same time (Kurth et al., 2010b). At the behavioral level, maturation of the visual cortex is accompanied by the specification of visual skills. For example, visual acuity, a function located in the occipital cortex, is developed during the first years of life and reaches adult levels at around 3 years (Teller, 1981). However, a set of cognitive abilities, subsumed under the term executive functions, are known to mature later in life. Executive functions are mainly controlled by the frontal cortex, a brain region maturing at a later stage of development. Synaptic density in the frontal cortex decreases around the age of 4 years and continues to decline until late adolescence (Huttenlocher and Dabholkar, 1997). Again these changes on the synaptic level are reflected in the sleep SWA whose maximal values are located over central to anterior derivations at the beginning of puberty and shift more and more to the frontal cortex during the teenage years (Kurth et al., 2010b). Paralleling brain maturation, executive functions are developed during puberty. Among others, executive functions can be investigated using saccadic task performance (Munoz et al., 1998). Young children exhibit high error rates, when asked to look in the opposite direction of an appearing stimulus, while during puberty, the ability to suppress reflexive saccades is progressively developed and consequently error rates decrease (Munoz et al., 1998).

However, the exact temporal relationship between brain maturation, SWA topography, and behavior still needs to be investigated.

Mental and neurological developmental disorders

Several mental and neurological disorders during development seem to relate to sleep. Thus, there is an increasing number of such

disorders in which sleep was investigated, for example, in patients with Williams syndrome (WS), a neurodevelopmental genetic disorder, characterized by distinctive cognitive impairments and physical abnormalities (Gombos et al., 2011). More than 50% of WS individuals are also diagnosed with attention-deficit hyperactivity disorder (ADHD; Leyfer et al., 2006; Morris and Mervis, 2000). Sleep SWA was investigated in a study with participants between ages 14 and 28 years. When compared with age- and sex-matched healthy controls, WS showed increased SWA in frontal derivations. Based on the finding that absolute SWA decreases in the course of development (Campbell and Feinberg, 2009; Feinberg et al., 2006; Kurth et al., 2010b), this result might reflect delayed brain maturation in WS.

ADHD is defined by difficulties in sustaining attention and/or hyperactivity and is the most common disorder in childhood (Olfson, 1992). Its relationship to sleep is illustrated by the observation that short sleep duration and sleeping difficulties are predictors of the occurrence of ADHD symptoms (Paavonen et al., 2009). Unfortunately, quantitative investigations of the sleep EEG (e.g., SWA) are still missing in children with ADHD. The idea of a maturational lag as the underlying cause of the disorder has been proposed by several researchers (Drechsler et al., 2005; Gustafsson et al., 2010; Kinsbourne, 1973; Shaw et al., 2007) and is supported by behavioral (Drechsler et al., 2005) and imaging studies (Shaw et al., 2006b, 2007). Thus, in the light of the close relationship between cortical maturation and sleep SWA (Kurth et al., 2010b), it might be interesting to investigate the sleep EEG more closely. Specifically, it might be possible that such a developmental delay in ADHD appears in the topographical distribution of SWA, by depicting a pattern typically seen in children of younger age (Kurth et al., 2010b) or alternatively may be expressed by changed levels of absolute SWA.

Schizophrenia often emerges during or shortly after adolescence. A common phenomenon of the illness is a large reduction of amplitude of slow waves, from which it was hypothesized that some kinds of schizophrenia may result from excessive synaptic loss in adolescence (Feinberg, 1982). Confirming this assumption, it was shown that indeed patients with childhood-onset schizophrenia (COS) show an altered pace of neurodevelopmental trajectories with increased velocity in gray matter loss during adolescence (Gogtay, 2008; Rapoport and Gogtay, 2008).

Although nearly all mood disorders express co-occurring abnormalities of sleep, the relationship between sleep and emotion during development is only sparsely investigated. Sleep disturbances in adults suffering from major depression disorder (MDD) are very frequent. Findings in adult patients reported disturbed slow-wave sleep in men, whereas no impairments were found in depressed women (Reynolds et al., 1990). Moreover, sleep deprivation has the potential to temporally reduce depressive symptoms in patients with major depression (Giedke and Schwarzler, 2002). Interestingly, a gender difference was also found in a study with children and adolescents, showing that during puberty, depressed adolescent boys exhibit much larger reduction of slow-wave sleep than female patients or healthy controls (Robert et al., 2006).

Slow waves are also of interest in the context of epilepsy, since the generation of slow waves and the spike wave complexes, which are a typical feature of electrical status epilepticus (ESES) during slow-wave sleep, share common mechanisms. It was shown that the degree of synchrony of cortical neurons progressively increases from a pre-seizure sleep pattern to spike wave seizures (Steriade and Amzica, 1994). Onset of ESES typically occur around 4–5 years and last for several month or years but resolve before adulthood without treatment. Usually, there is a striking activation of spike waves when falling asleep, occurring during more than 85% of NREM sleep (Tassinari et al., 2005). Children suffering of continuous spikes and waves during slow-wave sleep

(CSWS), a kind of epileptic encephalopathy, go through a progressive deterioration of cerebral functioning (Tassinari et al., 1977). Recently, slow-wave sleep of patients with ESES was studied and compared to age-matched, healthy children (Bölsterli et al., in press). The authors analyzed the slope of the slow waves, a recently introduced marker of the degree of synchronization of the firing of cortical neurons (Riedner et al., 2007; Vyazovskiy et al., 2009a). As expected from findings in adults, in healthy children, the slope of slow waves decreased from the first to the last hour of NREM sleep, while patients showed no significant change in slope across the night. In light of the synaptic homeostasis hypothesis, this finding may indicate a disruption of the downscaling process during sleep, which may be related to the neuropsychological regressions that go along with the disorder.

Discussion of the inverted U-shape time course of SWA

In this chapter, we have highlighted the evidence for a close relationship between sleep SWA and cortical maturation. However, it is not known whether the age-dependent SWA changes precede or follow the cortical changes. Longitudinal studies with MRI and sleep EEG data of the same subject may help to answer this question. Thus, uncovering the temporal relationship between sleep SWA and brain maturation may help to understand the mechanism underlying this relationship. Are slow waves merely reflecting the synaptic changes or are slow waves playing an active role in changing synapse density? If changes in SWA follow the maturational changes chronologically, this would speak for a mirroring role of SWA. However, if cortical changes follow changes in SWA during development, this may speak for an active role of SWA in cortical maturation. In Fig. 3, we propose a model of how slow waves could play an active role in cortical maturation.

In adults, in the long run and under normal circumstances, there is a balance between synaptic strengthening and synaptic downscaling. Thus, during wakefulness, in an experience-dependent manner, synapses are strengthened and during sleep, again in an experience-dependent manner, synapses are weakened.

This regulation of synaptic strength is the key mechanism of synaptic homeostasis: Attaining a sustainable level of synaptic strength, which allows learning processes to occur throughout life. There is indeed increasing evidence that synaptic strength is in balance in adult organisms (Tononi and Cirelli, 2006). This balance of synaptic strength (i.e., physiological plasticity) may also apply for the number of synapses (i.e., structural plasticity) given that also the formation of synapses takes place in an experience-dependent manner (Holtmaat et al., 2006; Knott et al., 2002) and there seems to be a continuum between strengthening and formation of synapses (Knott et al., 2006). Such a balance of structural plasticity fits well to the observation that in adults, the total number of synapses remains stable (Huttenlocher, 1979) even though there is a significant turnover of synapses (Zuo et al., 2005). The time window of interest is an important parameter determining whether physiological (e.g., via phosphorylation/dephosphorylation or AMPA receptor turnover) or structural (e.g., via spine and synapse formation) changes take place. Physiological changes in synaptic strength (e.g., via LTP/LTD mechanisms) are rather fast. However, structural changes like the formation of new synapses may take longer (Trachtenberg et al., 2002). In summary, in adults, both physiological (synaptic strength) and structural (number synapses) plastic changes seem to be carefully balanced.

A different picture emerges during development. On the structural level, dramatic changes in the number/density of synapses take place in the first two decades of human life (Huttenlocher, 1979; Huttenlocher and Dabholkar, 1997). Synapse density increases during childhood, reaches

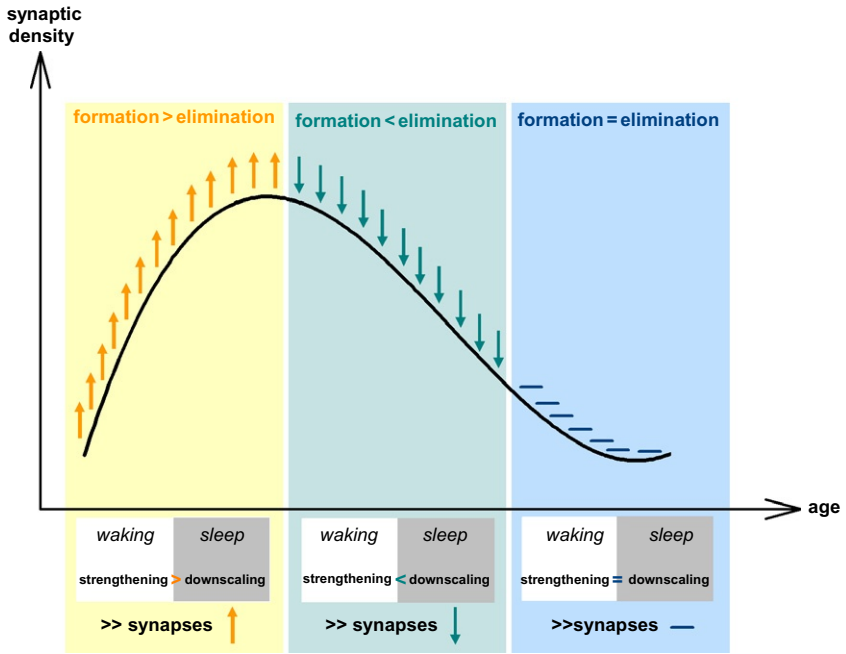

Fig. 3. Illustration of the time course of synaptic density (*y*-axis) at various ages (*x*-axis). Colored areas depict roughly different periods of development: childhood/prepuberty (in yellow), adolescence/postpuberty (in green), and adulthood (in blue). In each period, mechanisms of synaptic plasticity during waking and sleep (indicated at the bottom) favor the strengthening, respectively, weakening of synapses and influence the formation, respectively, elimination of synapses (indicated at the top). In the first two decades of human life, dramatic changes in the number and density of synapses take place. Because more synapses are formed than eliminated, synapse density increases during childhood, reaches a maximum before puberty, and decreases exponentially during adolescence, as more synapses are eliminated than formed (Zuo et al., 2005). Thus, it may be speculated that during development, the balance of strengthening/formation and weakening/elimination is tilted: In the early years, synaptic strengthening prevails over synaptic downscaling leading, in the long run, to a buildup of synapses. However, during adolescence, synaptic downscaling would outweigh synaptic strengthening and, correspondingly leading to a decrease in synapses. In adults, in the long run and under normal circumstances, there is a balance between synaptic strengthening and synaptic downscaling (Tononi and Cirelli, 2006) and the total number of synapses remains stable (Huttenlocher and Dabholkar, 1997).

a maximum before puberty, and decreases exponentially during adolescence. More specifically, during childhood, more synapses are formed than eliminated, which is then reversed during adolescence, during which more synapses are eliminated than formed (i.e., pruned; Zuo et al., 2005). A numerical example illustrates how these age-dependent changes in the formation and elimination of synapses may relate to sleep: during development, when 100 synaptic units are newly formed, presumably during wakefulness, only 99 are downscaled/eliminated during sleep, resulting in an overproduction of 1 unit per day. Although this difference is only small and the dysbalance may be hardly noticeable, this balance shift results in a slow but steady increase in the number/density of synapses over months and years. A consequence of this steady increase in the number of synapses might be increasing network synchronization, which would result in a

corresponding increase in SWA over time. During puberty, the opposite may occur: 100 synaptic units are newly formed during the day but 101 are downscaled/eliminated during the night, therefore, leading to a slow but steady decrease in the number/density of synapses over time. Thus, it may be speculated that during development, the balance of strengthening/formation and weakening/elimination is tilted: In the early years, synaptic strengthening prevails over synaptic downscaling leading, in the long run, to a buildup of synapses. However, during adolescence, synaptic downscaling would outweigh synaptic strengthening and, correspondingly, leading to a decrease in synapses. Which factors would be responsible for such a balance shift is unknown. Uncovering them might be an important scientific achievement, because the structural remodeling during development may be susceptible to interfering factors—whether genetic, epigenetic, environmental, or a combination thereof—leading to an increased risk for the emergence of structural, functional, and ultimately behavioral abnormalities. In fact, a large body of evidence indicates that adolescence is characterized by an increasing incidence of psychiatric disorders. These include schizophrenia as well as mood, anxiety, eating, substance abuse, and personality disorders (Blakemore, 2008; Feinberg, 1982; Keshavan et al., 1994; Lewis and Levitt, 2002; Paus, 2005; Saugstad, 1994).

Although direct experimental evidence for this hypothesis is lacking, it opens new perspective for future research. To validate our hypothesis, an animal model is needed which allows the investigation of alterations at the molecular level, the structural level at the synapse, and the surface EEG at the same time. Moreover, to establish causality direct manipulations of either the slow-wave generation or synapse turnover during development are needed. Such experiments will help answering the critical question of whether sleep only reflects cortical maturation or if it actually triggers maturational processes.

Conclusion and future perspectives

The number of studies investigating sleep in childhood and adolescence is growing. This is important since sleep changes markedly from infancy to adulthood, that is, sleep duration, sleep architecture, sleep slow-wave characteristics, and their topography. The understanding of sleep during childhood is important as it contributes to the understanding of the function of sleep *per se*.

Of special interest is the fact that during development, none of the classical frequency bands change as dramatically as the SWA band (Kurth et al., 2010b). The change of the amplitude of slow waves parallels the number of synapses (Feinberg, 1982; Huttenlocher and Dabholkar, 1997), that is, reduced synaptic density following pruning is reflected by a decline in amplitude. And the location over which maximal SWA can be measured undergoes a shift from posterior to anterior regions across childhood and adolescents, matching the time course of cortical maturation, as known from MRI and behavioral studies (Kurth et al., 2010b; Luna and Sweeney, 2004; Shaw et al., 2008), most likely reflecting cortical plasticity during development.

In the future, examination of SWA topography in patients with neurological or mental disturbance may help to uncover the pathophysiological mechanisms underlying certain developmental disorders. However, to establish a causal relationship between cortical maturation and changes in SWA during development, an animal model is needed.

The use of high-density EEG measures confirmed earlier findings that SWA not only reflects global changes in synaptic density but also mirrors the regional aspects of cortical maturation (Kurth et al., 2010b). This observation is of importance because it shows the potential of high-density EEG as a diagnostic tool. In clinical settings, the assessment of developmental delays or cortical abnormalities is essential. However, to date, the use of imaging techniques in children is limited or problematical due to the application of

radioactive tracers or X-rays. Also newer techniques as MRI, which are free of radiation exposure, are expensive and difficult to apply in children because the needed quiescence often is only reached by sedation. In contrary, EEG offers several advantages as its use is cheap, free from any medical risk, and offers unlimited application. Thus, measurement of sleep SWA could become a powerful tool to investigate cortical maturation in health and disease.

Acknowledgment

Research embodied in this review is supported by Swiss National Science Foundation Grant PP00A-114923.

Abbreviations

ADHD	attention deficit hyperactivity disorder
COS	childhood-onset schizophrenia
CSWS	continuous spikes and waves during slow-wave sleep
EEG	electroencephalography
ESES	electrical status epilepticus
LFPs	local field potentials
NREM	non-rapid eye movement
SWA	slow-wave activity
WS	Williams syndrome

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