CHAPTER 10

Sleep Slow Oscillations and Cortical Maturation

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SLOW WAVES AND SLEEP HOMEOSTASIS

Waves of high amplitude (>75 μV) and low frequency (<4.5 Hz) are a dominant characteristic of the non-rapid-eye-movement (NREM) sleep electroencephalogram (EEG). Such slow waves are most prevalent during deep sleep. Already in the 1930s slow waves were shown to parallel sleep depth (Blake & Gerard, 1937). Today, it is commonly accepted that sleep depth/pressure is homeostatically regulated—it increases in proportion to the time spent awake and decreases during sleep (Borbély & Achermann, 2005). Slow wave activity (SWA, EEG spectral power between 1 and 4.5 Hz) represents a well-established marker for the homeostatic decline of sleep depth during sleep. Recent evidence suggests that slow waves are closely related to synaptic changes (Cirelli, 2009; Diekelmann & Born, 2010; Tononi & Cirelli, 2006). This possible functional relationship of slow waves might be of particular relevance in brain development during childhood and adolescence, when brain structures experience major transformations (Giedd et al., 1999; Huttenlocher, 1979). Thus, it will be fundamental to understand whether slow waves even actively impact synaptic changes during development.

Sleep Slow Oscillations

At the single neuron level, intracellular recordings show that during deep sleep, membrane potentials of cortical neurons alternate between a depolarized up-state and a hyperpolarized down-state with a frequency of about 1 Hz (Steriade, Contreras, Curro Dossi, & Nunez, 1993; Timofeev, Grenier, & Steriade, 2001). Thus, during such slow oscillations, cortical neurons are bistable, oscillating between two distinct states, each lasting a few hundred milliseconds. When large networks of neurons undergo such oscillations in high synchrony, the scalp surface EEG measures high-amplitude voltage changes (Vyazovskiy et al., 2011; Vyazovskiy et al., 2009). Only a

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few human studies have investigated slow oscillation on the surface EEG (Achermann & Borbely, 1997; Bersagliere & Achermann, 2010). The authors found such slow oscillations among slow waves (<4.5 Hz). The question of the origin of slow waves with higher frequencies (1–4.5 Hz) is unresolved. However, since slow oscillations seem to travel across the cortex with a distinct origin and propagation path (Massimini, Huber, Ferrarelli, Hill, & Tononi, 2004), it might be possible that such waves originate from the collision of slow oscillations starting at a similar time, however with different origin. Such collisions of traveling slow oscillations may produce the higher frequency waves (Riedner et al., 2007). Traditionally, on the surface EEG, sleep slow waves are quantified by slow wave activity during NREM sleep (Borbély & Achermann, 2005).

Regulation of Sleep

We have a good understanding of the regulation of sleep. The *Two-Process Model* of sleep regulation describes two main processes involved in the regulation of sleep in humans and in a variety of other species (Borbély & Achermann, 2005; Tobler, 2000). The model proposes that sleep pressure is determined by the interaction of a circadian process C and a homeostatic process S. Process C represents the circadian component that maintains an approximate 24-hour rhythm. The homeostatic process S increases during waking and decreases during sleep. The immediate history of sleep and waking thus determines the level of process S. The probability to fall asleep is explained by the interplay of processes S and C. Understanding the physiological mechanisms of both processes and examining the dynamic response of the model to challenge (e.g., sleep deprivation) has been a major focus of sleep research during the past 30 years (Borbély & Achermann, 2005). It is known that the circadian rhythm (process C) is generated by an intrinsic pacemaker located in the suprachiasmatic nucleus (SCN). During the last decade the molecular machinery responsible for the clock-like output of SCN cells has been uncovered in great detail (Aston-Jones, 2005; Mistlberger, 2005; Saper, Lu, Chou, & Gooley, 2005; Zee & Manthena, 2007). In contrast, the knowledge about the mechanisms underlying process S is limited. Fortunately, SWA was uncovered as a well-established electrophysiological marker of process S. Numerous studies have confirmed that SWA during NREM sleep is homeostatically regulated—it increases as a function of time awake and decreases during sleep (Borbély & Achermann, 2005). One assumption of the *Two-Process Model* is that the loss of NREM sleep can be recovered by an intensification of

NREM sleep, measured as a SWA increase, and not necessarily by an increase in sleep duration. This assumption strengthens the important role of SWA in sleep regulation. A second important concept of the *Two-Process Model* is that the homeostatic and the circadian processes operate independently. This has been confirmed by sleep deprivation studies in SCN-lesioned rats. These animals no longer exhibit circadian modulation of sleep and wakefulness. Nevertheless sleep deprivation still results in an increase of SWA (Mistlberger, Bergmann, Waldenar, & Rechtschaffen, 1983; Tobler, Borbely, & Groos, 1983; Trachsel, Edgar, Seidel, Heller, & Dement, 1992).

Local Use-Dependent Sleep

In recent years it has become more and more evident that sleep is regulated locally. Unihemispheric sleep is known in birds and cetaceans (Siegel, 2009; Tobler, 2000), whereby selective deprivation gives rise to a unihemispheric slow-wave sleep rebound (Oleksenko, Mukhametov, Polyakova, Supin, & Kovalzon, 1992). Although not in a unihemispherical fashion, an increasing number of studies provide evidence for local and use-dependent sleep in humans (e.g., Huber et al., 2006; Huber, Ghilardi, Massimini, & Tononi, 2004; Kattler, Dijk, & Borbely, 1994; Landsness et al., 2009; Maatta et al., 2010). For example, in young adults extensive sensory stimulation of the hand lead to an increase of EEG power in the SWA frequency range during subsequent sleep (Kattler et al., 1994). The question was raised whether local sleep is adaptive or maladaptive (Vyazovskiy et al., 2011). In rats, it was shown that restricted sleep over days reveals sleep EEG characteristics during the behavioral state of waking (Leemburg et al., 2010). During subsequent sleep, the frontal regions exhibited the largest SWA rebound. Another study identified sleep-like features in the local waking EEG, associated with worsened performance, after a long period of waking (Vyazovskiy et al., 2011). Rats sleep approximately 12–14 hours per day with sleep cycles of approximately 10–20 minutes (Cirelli & Tononi, 2008). When these cycles are interrupted, rats are able to quickly adapt to shorter sleep periods and to maintain their overall daily time of NREM sleep (Tartar et al., 2006). These two examples describe an adaptive role of local sleep. In the animal kingdom, other forms of adaptive inactivity are also observed: hibernation, torpor, periods of migration in birds, mating season (Siegel, 2009). Therefore, while unihemispheric sleep seems to be adaptive, behaviorally dissociated states as sleep walking, REM sleep behavior disorder, and other parasominas are clearly maladaptive as Vyazovskiy et al. pointed out (Mahowald & Schenck, 2005; Terzaghi et al., 2009; Vyazovskiy et al., 2011).

Topographical assessments of the sleep EEG support a region-specific need for sleep (Huber et al., 2004; Landsness et al., 2009; Maatta et al., 2010). This region specific sleep SWA is possibly use-dependent, and could represent neuronal tiredness such as synaptic overload as introduced in Tononi & Cirelli (2006). This might be particularly important for the developing brain undergoing a period of major synaptic change.

At the cellular level two recent studies provide evidence for local differences in sleep measures: Nir and coauthors showed by means of intracerebral EEG in humans that sleep slow waves appear as both global or local waves (Nir et al., 2011). They showed that slow waves became more local in late sleep as compared to early sleep. In addition, local waves were predominantly of low amplitude, and low amplitude waves typically occur in late sleep, when sleep pressure has largely dissipated (Nir et al., 2011; Riedner et al., 2007). The largest discrepancy of activity states within the brain is found when some brain regions are asleep, while others are awake. Long periods of waking in rats were associated with EEG and behavior clearly recognized as waking, however, individual local neuronal populations exhibited aspects of sleep at the same time. In addition, this state was associated with impaired performance (Vyazovskiy et al., 2011). In adult epileptic patients, a similar dissociation of vigilance states was observed (Nobili et al., 2011). Nobili et al. found coexisting wake-like and sleep-like patterns simultaneously in different cortical areas. This regional occurrence of sleep corroborates the local regulation of sleep slow waves.

Learning and Slow Wave Activity

Numerous studies propose a close relationship between waking activity and subsequent EEG activity during sleep (Diekelmann & Born, 2010). For example, visuomotor learning was associated with a region-specific local increase of sleep SWA (Huber et al., 2004). In contrast, a local reduction of SWA was found as a consequence of reduced activity in sensorimotor areas as a result of arm immobilization (Huber et al., 2006). Several studies show a direct link between changes in SWA and sleep-dependent performance improvements. For example, the local increase of SWA after visuomotor learning was positively correlated with the performance improvement the next morning (Huber et al., 2004). A causal relationship between sleep SWA and performance improvements was shown in protocols artificially manipulating the level of SWA. Slow wave deprivation by acoustic stimuli hindered sleep-dependent performance gains of visuomotor learning (Landsness et al., 2009). In contrast, artificial boosting

of slow waves, by means of transcranially applied oscillating currents, was associated with performance improvement in the declarative memory system (Marshall, Helgadottir, Molle, & Born, 2006).

The above findings provide good evidence for an involvement of sleep slow waves in plastic processes related to learning. Long-term potentiation is the cellular basis of learning and involves activity-induced molecular changes at the synapse (Bliss & Lomo, 1973; Kandel, 2001; Whitlock, Heynen, Shuler, & Bear, 2006). How sleep SWA and such plastic processes may be related is illustrated in the hypothesis about a function of sleep below.

SLOW WAVE SLEEP IS THE PRICE PAID FOR PLASTICITY IN A COMPLEX NEURAL SYSTEM

The Synaptic Homeostasis Hypothesis

The *Synaptic Homeostasis Hypothesis* proposed by Tononi and Cirelli provides an interesting explanation for the close relationship between neuronal activity during waking and sleep (Tononi & Cirelli, 2006). The hypothesis links the homeostatic regulation of sleep to the homeostatic regulation of synaptic strength. Changes in synaptic strength by means of long term potentiation processes are thought to be the underlying mechanism of learning and memory (Bliss & Lomo, 1973; Whitlock et al., 2006). We learn throughout our life. To prevent a saturation of overall synaptic strength due to such learning and to ensure a rather stable learning capacity across decades during adulthood synaptic strength needs to be balanced. Thus, recent work proposes the idea that average synaptic strength is homeostatically regulated to promote stability of the system (Turrigiano, 1999). The Synaptic Homeostasis Hypothesis now proposes that the rebalancing of synaptic strength takes place during sleep. More specifically, according to the hypothesis the homeostatic SWA decrease during sleep reflects the decrease of synaptic strength. The hypothesis further proposes that SWA is not only reflecting synaptic strength but is also responsible for its reduction. Thus, according to the Synaptic Homeostasis Hypothesis SWA actively triggers synaptic downscaling, i.e., renormalizes synaptic strength to a baseline level. The hypothesis assumes that such global "downscaling" of cortical connections does not happen in a selective manner, but depends on the strength of synapses in cortical regions: strong synaptic connections are downscaled into weaker connections but maintained, whereas weak connections may be entirely deleted.

Recent *in vitro* and *in vivo* animal experiments have found evidence for a net prevalence of synaptic potentiation mechanisms during wakefulness

and a net reduction of synaptic strength during sleep. Thus, prolonged wakefulness was found to increase the frequency and amplitude of miniature excitatory postsynaptic currents (EPSCs) in cortical slices—a key *in vitro* measure of synaptic strength (Liu, Faraguna, Cirelli, Tononi, & Gao, 2010). In *Drosophila melanogaster* prolonged wakefulness was associated with an increase in the protein levels of key components of central synapses (Gilestro, Tononi, & Cirelli, 2009), as well as an increase in the number and size of synapses (Bushey, Tononi, & Cirelli, 2011). In rats, wakefulness increased the rate and synchrony of firing of cortical neurons (Vyazovskiy et al., 2009) and the slope of the local field potentials (LFPs) evoked by electrical cortical stimulation (Vyazovskiy, Cirelli, Pfister-Genskow, Faraguna, & Tononi, 2008), a classic measure of synaptic strength *in vivo*. As SWA decreases in the course of sleep these measures of synaptic strength decrease as well, i.e., the responsiveness of cortical neurons and the protein levels of key components, as well as the size and number of synapses and the frequency and amplitude of miniature EPSCs (Bushey et al., 2011; Gilestro et al., 2009; Liu et al., 2010;Vyazovskiy et al., 2008). These observations suggest that the homeostatic regulation of sleep, as reflected by SWA, parallels the regulation of measures of synaptic strength. Using a combination of transcranial magnetic stimulation (TMS) and high-density EEG (hdEEG), a recent study observed that human cortical excitability, measured as the immediate EEG reaction to TMS, also progressively increases with time awake, from morning to evening and after one night of total sleep deprivation, and that it decreases after recovery sleep (Huber et al., 2012).

Synchronization of Neural Activity during Sleep

The strength of population excitatory postsynaptic currents is best reflected by the slope of LFPs evoked by electrical stimuli (Rall, 1967). Vyazovskiy et al. used this technique in the rat to show that the slope of LFPs increases as a function of the time spent awake and decreases during sleep (Vyazovskiy et al., 2008). Furthermore, the slope of LFPs was positively correlated with SWA during the first hour of NREM sleep (Vyazovskiy et al., 2008). Multiunit recordings in the rat allow a simultaneous assessment of the firing patterns across numerous neurons. Thus, at the beginning of the night, when synaptic strength is high, most individual neurons start and stop firing in near synchrony with the rest of the population (Vyazovskiy et al., 2009). Moreover, 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. This observation

proposes the slope of slow waves as a direct measure of synaptic strength. In humans (Riedner et al., 2007), rats (Vyazovskiy, Riedner, Cirelli, & Tononi, 2007), and *in computo* (Esser, Hill, & Tononi, 2007) the slope of slow waves was shown to decrease from the beginning to the end of a sleep period. This slope decrease of slow waves during sleep was explained as homeostatic reduction of synaptic strength.

These observations show that changes in synaptic strength affect the characteristics of sleep slow waves via the changes in synchronization. Several cortical network properties affect neuronal synchronization and therefore are directly linked to the generation of sleep slow waves. For example, the capacity of white matter fiber tracts impacts the speed of signal propagation, and gray matter volume/thickness, which is proportional to synapse number/density, in turn impacts the efficiency of signal proliferation from the pre- to the postsynapse. In neuronal systems with reduced connectivity, a lower synchronization between the elements (e.g., neurons or neuronal populations) is expected. The occurrence of a down-state in a neuron is always maintained by its input, i.e., the number of and connectivity to neighbored neurons: the greater the degree of presynaptic activity (number of neurons/synapses) impinging onto a target neuron, the higher the probability that an action potential is elicited in this neuron. Network modeling, *in vivo*, and *in vitro* recordings agree that the role of short-range connections is important in maintaining and synchronizing the slow oscillation (Hill & Tononi, 2005; Sanchez-Vives & McCormick, 2000; Timofeev, Grenier, Bazhenov, Sejnowski, & Steriade, 2000). Computer simulations of the activity of the thalamocortical system reveal that synchronization and amplitude of the slow oscillation are dependent on the strength of both intra- and interareal corticocortical connections (Hill & Tononi, 2005), again consistent with *in vivo* (Amzica & Steriade, 1995) and *in vitro* (Sanchez-Vives & McCormick, 2000) results.

It is hence conceivable that the maturation of anatomical connectivity impacts the EEG in both wake and sleep. The first two decades of life are the only time where such dramatic changes in our brain's architecture occur under healthy conditions. Accordingly, sleep should also change during development. How sleep changes and how those changes parallel anatomical changes is discussed in the next sections.

Maturation of Sleep Homeostasis

The homeostatic regulation of sleep and its electrophysiological marker SWA are not present right from the start. First signs for a homeostatic regulation

of sleep can be observed in the first months of life (Bes, Schulz, Navelet, & Salzarulo, 1991; Jenni & Carskadon, 2004). Similar results come from animal studies, which also allow challenging sleep homeostasis. They show that while sleep deprivation does not impact SWA in 12-day-old rats, a clear increase in SWA follows sleep deprivation in 24-day-old rats (Frank, Morrissette, & Heller, 1998). Instead, the 12-day-old rats compensate for the sleep loss with increased sleep time and continuity. Similar results are found in human neonates, where sleep restriction leads to compensatory increases in NREM sleep duration only (Anders & Roffwarg, 1973; Thomas et al., 1996). In humans, the exact timing of when sleep deprivation starts to produce an increase in SWA is unknown. Yet, a SWA decline in the course of the night is first visible during the second postnatal month (Bes et al., 1991). An early indication for homeostatic regulation of sleep in infants might be seen in the decline of theta power in the course of a sleep episode that occurs between 6 and 9 months of age (Jenni, Borbely, & Achermann, 2004). Later in life, the homeostatic process continues to show maturational changes: a slowing in the buildup of homeostatic sleep pressure during wakefulness was proposed to occur from childhood to adolescence (Jenni, Achermann, & Carskadon, 2005). In contrast, the homeostatic decline during sleep remains stable (Rusterholz & Achermann, 2011; Jenni, et al., 2005).

Clear maturational changes of the homeostatic regulation of sleep are present during early development. The question arises whether and how these changes in sleep homeostasis are related to structural and functional brain maturation. The first months of human life are characterized by a huge outgrowth of synaptic connections (Huttenlocher, 1979). Also, several neurotransmitter systems are not yet fully developed (Lidow, Goldman-Rakic, & Rakic, 1991). Interestingly, in rats it was shown that the start of the homeostatic regulation of sleep coincides with the occurrence of brain-derived neurotrophic factor (BDNF) (Hairston et al., 2004), a key marker of synaptic plasticity (Alonso et al., 2005; Cancedda et al., 2004; Castillo, Figueroa-Guzman, & Escobar, 2006; Chakravarthy et al., 2006; Genoud, Knott, Sakata, Lu, & Welker, 2004; Kleim et al., 2006). On the one hand, BDNF is well known as a major mediator of synaptic plasticity (Jiang, Akaneya, Hata, & Tsumoto, 2003). On the other hand, in adult rats, BDNF was closely linked to the regulation of SWA: BDNF increases after sleep deprivation (Hairston et al., 2004) and it is more expressed in rats showing more SWA after exploring enriched environments (Huber, Tononi, & Cirelli, 2007). A causal relationship between BDNF and sleep SWA was shown in a more recent study (Faraguna, Vyazovskiy, Nelson, Tononi, & Cirelli, 2008): blockage of

BDNF by direct infusion of anti-BDNF resulted in a subsequent reduction of SWA. In contrast, local infusion of BDNF resulted in a corresponding increase of SWA. Taken together it seems that the evolvement of synaptic plasticity is closely linked to the homeostatic regulation of sleep during development. Interestingly, in humans, the increase of BDNF mRNA levels in the dorsolateral prefrontal cortex during adolescence coincides with the time when the frontal cortex matures both structurally and functionally (Webster, Weickert, Herman, & Kleinman, 2002).

Even after the homeostatic regulation of sleep is fully functional the developmental changes of this system continue.

THE DEVELOPMENT OF SLOW WAVES PARALLELS CORTICAL MATURATION

Slow Waves and the Maturation of Gray Matter

A major developmental change during the first two decades of life concerns the number/density of synapses (Huttenlocher, 1979). It is clear that the formation and elimination of synapses is intensified during the developmental period (Goldman & Nauta, 1977; Huttenlocher, 1979; Majewska & Sur, 2003; Rakic, Bourgeois, Eckenhoff, Zecevic, & Goldman-Rakic, 1986). In early childhood, neurons explore much wider areas than their final targets (Gao, Yue, Cerretti, Dreyfus, & Zhou, 1999) and the number of synapses exceeds adult levels by far (Huttenlocher, 1979). Then, in the course of adolescence, more connections are eliminated than formed (Zuo, Lin, Chang, & Gan, 2005). Postmortem studies in the macaque reveal that most pronounced synaptic overproduction occurs in supragranular layers, suggesting that synaptic pruning and stabilization are more important for the maturation of corticocortical circuits (Petanjek, Judas, Kostovic, & Uylings, 2008; Woo, Pucak, Kye, Matus, & Lewis, 1997). The elimination processes occur in an activity-dependent fashion (Hua & Smith, 2004). Evidence is increasing that in a system of concurrent synapse formation and elimination, activity modulates development, by controlling the formation of new and the maintenance of existing connections (Hua & Smith, 2004). Synaptic plasticity in adult neural circuits may involve the strengthening or weakening of existing synapses as well as structural plasticity, including synapse formation and elimination (Holtmaat & Svoboda, 2009).

The pattern of an initial overproduction followed by elimination and refinement associated with increased specificity is also found in other biological systems. This mechanism of refinement is in the neuronal context

termed pruning (Huttenlocher, 1990), and seems to follow the principle of *Trial and Error* (Holmes, 1907; Jennings, 1904). In terms of neuronal plasticity, the synaptic activity can be considered as stimulus (trial), while inactivity leads to elimination of connections (error). The advantage of systems with higher complexity is the ability to flexibly respond. But flexibility carries also costs: although synaptic plasticity enables high-capacity learning, it also introduces increased energy consumption and a reduction in efficiency. Interestingly, across development, brain energy consumption follows a similar time course as synapse density (brain oxygen consumption (Kety, 1956; Kety & Schmidt, 1948) or glucose utilization (Chugani, 1998)). The maintenance of synapses is one of the most energy-demanding processes (see Tononi & Cirelli, 2006). A system with high synaptic connectivity may also be less efficient, compared to a system with lower synaptic connectivity but instead more long-range fibers. In the high synaptic density system, signals need to be transmitted via numerous synaptic connections, which is time consuming (millisecond range (Borst & Sakmann, 1996)). The transmission speed of the action potential across the synaptic cleft is estimated to be about 0.2 mm/s, i.e. >1000 times slower than when the electrical impulse travels down the nerve axon (>25 m/s) (Wheatley, 1998). Of course, myelination, which significantly changes during development (see Deoni et al. (2011) for quantitative analyses or Paus et al. (2001) for a review of magnetic resonance imaging (MRI) studies), also plays an important role in signal transduction. Oligodendrocytes wrap the axon with myelin, consisting of multiple layers of closely opposed glial membranes. Myelin acts as insulator of the axonal membrane, improving the passive flow of electrical current. Myelin speeds up action potential conduction, e.g., from 0.5–10 m/s in unmyelinated axons, to 150 m/s in myelinated axons.

In summary, we have seen that synapse density and energy consumption follow a similar time course across development. Interestingly, Feinberg already in the 1980s found that SWA parallels both the time course of synapse density and energy consumption (Feinberg, 1982), suggesting a possible relationship (Fig. 10.1). At the age when synaptic growth is maximal the amplitude of slow waves also reaches a peak. Thus SWA reaches a ceiling level at the time of maximal synaptic density during childhood. Adolescence is then accompanied by a sharp decrease in the amount of deep sleep (Feinberg, 1982), synaptic density (Huttenlocher, 1979) and in the rate of brain metabolism (Chugani, 1998).

A possible explanation for the close relationship between SWA and synaptic density is provided by the observation that the amplitude of slow

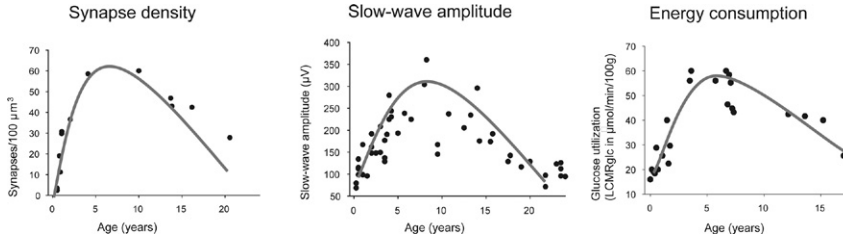

Figure 10.1 Development of synapse density (left, postmortem data, reconstructed from Huttenlocher & Dabholkar (1997)), slow wave amplitude (middle, reconstructed from Feinberg (1982)), and energy consumption (right, glucose utilization (reconstructed from Chugani, (1998)). The three measures follow a similar time course across the first two decades of life.

waves, the major contributing factor to spectral power in the slow wave frequency range, depends on the ability of a cortical network to synchronize its activity (Vyazovskiy et al., 2009). How fast a cortical network can synchronize its activity depends on the strength and density of its connections (Esser et al., 2007; Vyazovskiy et al., 2009). Thus, maximal synaptic density reached during childhood results in maximal synchronization of cortical activity during sleep, which in turn gives rise to maximal amplitude slow waves. If this mechanism holds true it would also explain why the maturational changes of the EEG are not restricted to sleep, but also seen in waking (Gasser, Verleger, Bacher, & Sroka, 1988).

In the sleep EEG, the analysis of the slope of slow waves provides a useful tool to study the level of synchronization and associated change in synaptic strength (Kurth, Jenni et al., 2010; Riedner et al., 2007; Vyazovskiy et al., 2007). A computer model of the thalamocortical system reproduced in detail the cortical slow oscillations underlying EEG slow waves during sleep (Esser et al., 2007). The model showed that the slope of sleep slow waves is the best indicator for changes in synaptic strength (Esser et al., 2007). Moreover, local field potential recordings in the rat also showed a decline of the slope of slow waves across a sleep period, again indicating that the slow-wave slope may reflect the level of synchronization (Vyazovskiy et al., 2007), This finding was also observed in adult humans, where the slope of slow waves decreased across the night (Riedner et al., 2007). We used this measure to compare cortical synchronization in prepubertal children and mature adolescents (Kurth, Jenni et al., 2010). We found that the slow-wave slope was steeper in prepubertal children compared to mature adolescents, even when controlling for amplitude. The steeper slope in premature children may indicate greater synaptic strength in prepubertal children compared to mature adolescents.

Gray matter, however, is not the only part maturing during childhood and adolescence. Thus, the next section illustrates the major maturational changes of white matter and how these changes may be related to slow waves.

Slow Waves and the Maturation of White Matter

Myelination

In general, and in contrast to gray matter maturation, white matter maturation follows a linear increase. The efficiency of long-range cortical connections in the vertebrate cerebral cortex is influenced by myelin sheets surrounding axons (Deoni et al., 2011; Paus, Keshavan, & Giedd, 2008). Myelination of axons accelerates the propagation of action potentials, through a mechanism that does not require large amounts of additional space or energy (Frankenhaeuser, 1952; Halter & Clark, 1991; Huxley & Stampfli, 1949). During development myelination increases (Lebel & Beaulieu, 2011; Paus et al., 2001), which results in increased efficiency of action potential propagation. Well-established MRI measures offer insights into structural maturation, via white matter volumetry or diffusion tensor imaging (DTI) (Gogtay et al., 2004; Paus et al., 2008). During cortical maturation, the relaxation times, upon which such analyses are based, are influenced by different facets of development, such as changes in axonal density, size, membrane structure, and the content of lipids, macromolecules, and proteins, as well as water compartmentalization (Deoni et al., 2011). State-of-the-art imaging technologies can provide a quantification of myelination processes (Deoni et al., 2011). Also, electrophysiological measures offer the possibility to assess white matter efficiency. For example, coherence measures assess the connectivity between distant cortical regions (Achermann & Borbely, 1998). Interestingly, the increasing myelination across the developmental period is accompanied by an increase in EEG coherence (Tarokh, Carskadon, & Achermann, 2010). In a dataset of 59 subjects, we confirm these findings for the age range 2–26 years (Fig. 10.2). This linear increase in coherence, as exemplified for a left central region in the SWA frequency band, is in line with the increase of white matter until the 30s (Lebel & Beaulieu, 2011; Paus et al., 2001).

Another measure used in sleep EEG recordings that might be related to white matter maturation is the characteristics of sleep slow waves to behave as traveling waves. In the NREM sleep EEG, Massimini et al. showed that slow oscillations sweep across the cortex as waves (Massimini et al., 2004). Thereby, each wave maintains a definite site of onset, spatial propagation, and speed of traveling. Source localization of spontaneous and evoked slow

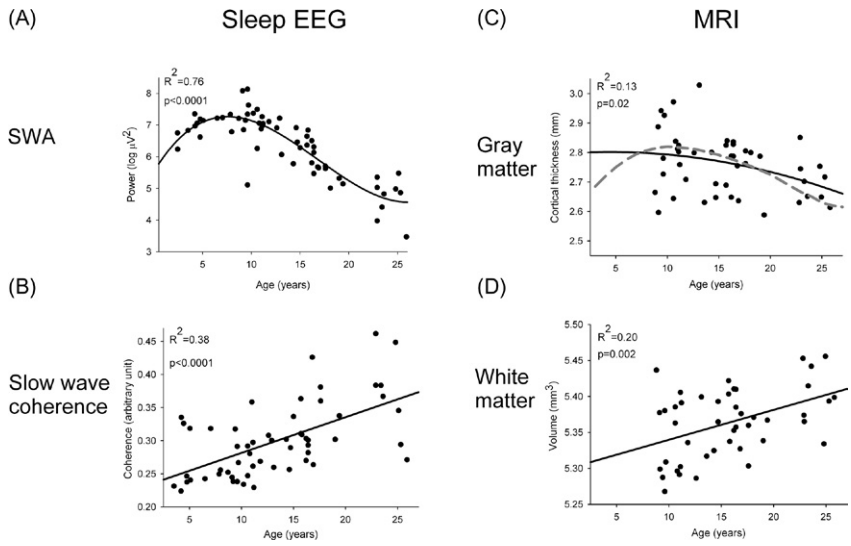

Figure 10.2 ***Comparison of the maturation of the sleep EEG and MRI-derived anatomical markers of cortical maturation.*** (**A**) Slow wave activity (SWA) across age for the derivation C4A1 (n = 62, 2.4–25.9y, $R^2 = 0.76$, $p < 0.0001$). (**B**) EEG coherence in the slow-wave frequency range (1–4.5 Hz) for the derivations F3C3-C3P3 (n = 59, 2.4–25.9y, $R^2 = 0.38$, $p < 0.0001$). Coherence was calculated using Welch's averaged periodogram method (see Achermann & Borbely, 1998) and represents a measure for the similarity of the EEG activity at different derivations. (**C**) MRI-derived gray matter thickness across age, shown for the left hemisphere (n = 45, 8.8–25.8y, $R^2 = 0.13$, $p = 0.02$). The dotted gray line indicates the expected developmental time course during childhood, as known from previous studies (Giedd et al., 1999; Shaw et al., 2008). (**D**) MRI-derived white matter volume of the left hemisphere is shown across age (n = 45, 8.8–25.8y, $R^2 = 0.20$, $p = 0.002$). For a detailed description of the MR data analysis see Buchmann et al. (2011) and Buchmann et al. (2010).

waves in adults identified frequent traveling activity in the anteroposterior direction (Murphy et al. 2009), possibly associated with the superior longitudinal fascicle. Thus, traveling waves might serve as an indicator for fiber maturation during brain development.

Interaction of Gray and White Matter Maturation

Local Progression of the Cortical Developmental Changes

Already the studies by Huttenlocher have shown that the time course of synapse density is not uniform across the cortex (Huttenlocher, 1979; Huttenlocher & Dabholkar, 1997). More specifically, depending on the cortical area peak synaptic density was reached at different ages: occipital cortex reached peak synaptic density first and frontal cortex last. MRI-derived gray

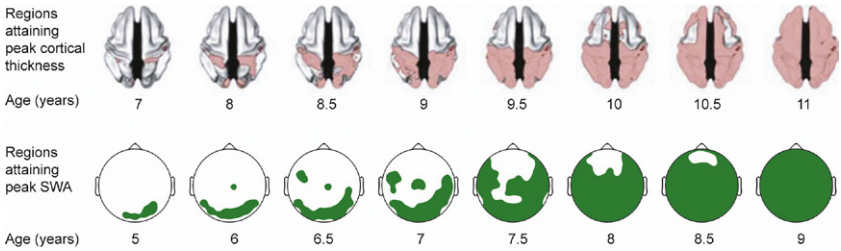

Figure 10.3 ***Posterior-to-anterior maturation of the cortex.*** *Upper panel*: Age of attaining peak cortical thickness across the cerebral cortex (adapted after Shaw et al., 2008). *Lower panel*: Topographical distribution of sleep slow wave activity (SWA) maturation. Electrodes that have reached peak SWA at the age given at the bottom are shaded. SWA was normalized for common regional differences across age (e.g., minimal SWA over temporal regions) by normalizing SWA power for each electrode and individual to the average power across all ages.

matter volume or thickness show a very similar spatial trajectory (Giedd, 2004; Shaw et al., 2008; Sowell et al., 2004). In general, these studies show a posterior-to-anterior maturational pattern, where occipital regions exhibit an early peak, and frontal regions do so late (Shaw et al., 2008). Interestingly, the close relationship between gray matter maturation and changes in sleep SWA across development (see Fig. 10.2) can be extended to the topography. hdEEG recordings in children and adolescents showed that maximal SWA is located over posterior regions in childhood, and shifts over parietal/central regions during adolescence (Fig. 10.3), resulting in the well-known frontal maximum in adults (Finelli, Borbely, & Achermann, 2001; Kurth, Ringli et al., 2010). In analogy to the analysis of cortical thickness by Shaw et al. (2008), we identified the age of peak of SWA for every electrode. For each age range (see Fig. 10.3) electrodes were colored when peak SWA had been reached. Our main observation of this analysis was the posterior-to-anterior maturation of SWA. Other sleep EEG studies across development support this finding of a posterior-to-anterior maturation of power in the low-frequency range (Campbell & Feinberg, 2009). A central feature of this comparison is the close temporal relationship of the electrophysiological and anatomical development (Fig. 10.3). It appears that the maturation of SWA precedes the maturation of gray matter thickness by approximately 2 years, e.g., at the age of 11 years the entire cerebral cortex has attained peak thickness, whereas SWA peaks are entirely attained with the age of 9 years.

The pattern of posterior-to-anterior maturation can also be observed when looking at the maturation of brain functions. Thus, the visual cortex, located in posterior areas, is known to undergo early maturation that

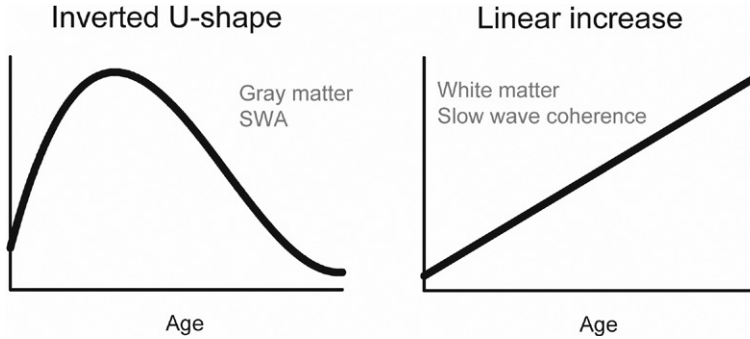

Figure 10.4 The two patterns of cortical maturation during the first two decades of life.

can be assessed for example by visual acuity (Teller, 1981). Motor abilities, for example assessed by the Zurich Neuromotor Assessment (ZNA; Gasser, Rousson, Caflisch, & Jenni, 2010; Largo et al., 2001), mature in adolescence, and cognitive abilities, for example needed for executive functions, continue to mature into young adulthood (Luna & Sweeney, 2004). Although these observations on EEG, MRI, and behavior describe the maturation of the brain from a different perspective, they show the same posterior-to-anterior spatial trajectory along the cortex. We have explored the relationship between the maturation of brain functions and changes in SWA topography in a cross-sectional sample of developing subjects (Kurth et al., 2012). In our analyses, SWA topography preceded the maturation of behavioral skills by approximately 3 years. Moreover, when gray matter thinning was included, it was the last to reach maturity.

It is clear though that the maturation of brain functions not only relies on the maturation of gray matter but is also dependent on white matter maturation. In particular, higher cognitive skills (like executive functions) located in the prefrontal cortex (PFC) profit from the white matter connectivity changes, because such functions depend on the interplay of different brain regions. Only efficient long range connections allow the timely integration of complex information originating from different modalities. Thus, the PFC receives projections from virtually all cortical sensory systems, motor systems, and many subcortical structures allowing it to coordinate a wide range of neuronal processes (Miller & Cohen, 2001).

In summary, there exist two particular maturational patterns (Fig. 10.4): (1) the inverted U-shape time course of synaptic density/gray matter, which shows an approximate posterior-to-anterior propagation, and (2) the maturation of white matter/myelin, which increases linearly until the third decade,

also following a particular spatial trajectory (Paus, 2005; Tarokh et al., 2010). We have shown that sleep SWA very closely parallels gray matter maturation and EEG coherence parallels white matter maturation. Since these processes (white and gray matter maturation) take place at the same time, it is clear that the development of brain functions reflects both of these processes.

Gray and white matter maturation may also depend on each other.

A Competition within the Brain?

One limitation occurring while the number of synapses grows is the restriction of space. It is well known that the largest growth of the human brain volume takes place before adolescence (Courchesne et al., 2000). During this time, MRI reveals a growth of gray matter together with an increase of white matter. At the peak of this process, before puberty, also slow waves are most pronounced. Sleep staging such EEG recordings is impressive, since slow waves during deep sleep can easily reach 1000 microvolts in amplitude and continue to occur for minutes. Then, during adolescence things change. Now gray matter volume decreases while the volume of white matter keeps increasing. As pointed out before, during adolescence, SWA decreases dramatically, while at the same time EEG coherence keeps increasing. The decrease in gray matter volume most likely reflects the documented decrease of synapse density (Huttenlocher, 1979; Huttenlocher & Dabholkar, 1997). Thus, the huge decrease in synapse density during adolescence is accompanied by continuous growing of long range fibers (Lebel & Beaulieu, 2011). Particularly, the myelination of long-range fibers accounts for the linear white matter volume increase during the first two decades (Lebel & Beaulieu, 2011; Paus et al., 2001). Recent DTI analyses delineate the microstructural maturation of brain white matter tracts and reveal a regional succession of fibers: commissural and projection fibers mature earliest, while association fibers and frontal-temporal connections demonstrate the most prolonged development (Lebel & Beaulieu, 2011; Lebel, Walker, Leemans, Phillips, & Beaulieu, 2008). Space needs, together with the demand for efficient functioning, thus requires a reduction in energy consumption while the brain system is growing.

The increase in myelination may result in more efficient signal transfer. The gray matter reduction, on the other hand, is associated with fewer synapses, which results in space gains and a reduction of energy consumption (Chugani, Phelps, & Mazziotta, 1987). It is noteworthy that age-related changes in synaptic strength or density not only should result in changes of the sleep EEG in the SWA frequency range, but might also explain the age-related amplitude changes of oscillations in other frequency ranges and

other vigilance states observed (Feinberg et al., 1990; Gasser et al., 1988; Gaudreau, Carrier, & Montplaisir, 2001).

The question arises whether space constraints are a limiting factor during cortical maturation and are overcome by pruning processes. Thus, do space constraints initiate the "reversal point," where synaptic density stops growing and starts decreasing? It is likely that space restriction is associated with competition over supplies. Regarding neurons it would mean a competition over access to the postsynaptic cells. When a new synapse is formed the presynaptic axon influences the postsynapse to outgrow cell plasma (Yuste & Bonhoeffer, 2004). Moreover, there are indications that used synapses restrain unused synapses in their neighborhood (Balice-Gordon & Lichtman, 1994). An extreme example of maturational synaptic alteration is found in the neural maturation of *Caenorhabditis elegans*, where existing synapses in DD motoneurons are completely eliminated and new synapses are formed without changing cell morphology (Park et al., 2011). The current literature is, however, very limited and does not allow a conclusive understanding of these processes. Important question remain, like, which genes are involved? How does this switch of the changes in synaptic density occur without interference of behavioral output? Clearly these processes need to be studied in more detail. Our data show that the sleep EEG might be a useful tool to explore these processes (even more so due to the following observations).

Quantifying Cortical Maturation during Development

As introduced above, three main methods have been used to quantify developmental changes in the human cerebral cortex: structural MRI, EEG, and postmortem synapse counting using electron microscopy or phosphotungstic acid staining. Although different methods were used, the observed developmental changes were similar: an increase during childhood, a decrease during adolescence, and a stabilization in adulthood. MRI allows for the estimation of cortical thickness. Studies show that cortical thickness is reduced with a rate of about 0.1 mm/year during adolescence with local maxima in reduction of up to 0.3 mm/year (Table 10.1). However, whether these maturational changes in cortical thickness are related to changes in neuropil, neuronal size, or dendritic arborization can only be answered with postmortem or animal studies.

To assess neuronal connectivity, counting and estimating synapse number is restricted to animal studies or the investigation of postmortem human brains. Synaptic densities obtained by phosphotungstic acid staining have been similar to those obtained by conventional electron microscopy

Table 10.1 Cortical changes during Adolescence

	Annual Change	%	Reference	Method
Number of synapses	$5.7 \star 10^7$ synapses/mm^3 of cortical tissue/year (middle frontal gyrus) $4.8 \star 10^{13}$ synapses/year (entire cortex)	55%	(Huttenlocher, 1979); (Good et al., 2001) for cortical volume estimation (young adults: 0.85 liter)	Postmortem, middle frontal gyrus layer 3, phosphotunstic acid method (see Bloom and Aghajanian, 1968), synaptic decrease quantified (slope of decline)
	$3.15 \star 10^{12}$ synapses/year (entire cortex)	50%	(Bourgeois & Rakic, 1993; Rakic, et al., 2009)	Electron microscopy, extrapolation from primary visual cortex (sections of calcarine fissure) in macaque to human cortex, decrease in synapse number quantified during puberty, estimation for entire cortex
Sleep slow waves	155 μV^2/year		(Campbell et al., 2011)	Slow wave activity (SWA) in sleep EEG decrease quantified according to slope of SWA decline in electrode C3 (C4) referenced to mastoid
	215 μV^2/year (Fz) 265 μV^2/year (Cz) 120 μV^2/year (O1)	170% (Fz) 320% (Cz) 340% (O1)	(Feinberg, de Bie, Davis, & Campbell, 2011)	SWA decrease in sleep EEG quantified according to slope of SWA decline in electrodes Fz, Cz, C3, C4, and O1 referenced to mastoid
Cortical thickness	About 0.1 mm cortical thickness reduction per year	40%	(Shaw et al., 2008)	MRI, superior frontal gyri
	Up to 0.3 mm cortical thickness reduction per year		(Sowell et al., 2004)	MRI, topographical annual change (mm), in kids 5–11y; changes that happen after 11y are not considered

Findings from literature are summarized based on three different methods: postmortem synapse number in humans or macaques, slow waves in the sleep EEG, and cortical thickness deriving from MRI. Calculations of annual changes are based on the phase of steepest decline of the particular measure (slope). Percent change was calculated as the difference between maximal values in late childhood and stabilized levels in young adulthood.

(Aghajanian & Bloom, 1967; Armstrong-James & Johnson, 1970). However, the former method might underestimate immature synapses, requires extrapolation from single sections, and synapses close to the synaptic cleft may not be recognized. Bourgeois & Rakic show in the macaque that the mean maximum density of 90 synapses/100 μm^3 of neuropil is reached by the third postnatal month (corresponding to childhood in humans), and decreases during puberty to reach adult levels of 40–50 synapses/100 μm^3 (Bourgeois & Rakic, 1993). This corresponds to a reduction rate of $3.2 \star 10^{12}$ synapses/year for the entire cortex during this period (see Table 10.1, and Bourgeois & Rakic, 1993; Rakic, Arellano, & Breunig, 2009). Huttenlocher's postmortem quantification of the reduction of synapses in humans (Huttenlocher, 1979) reveals a reduction rate of $5.7 \star 10^7$ synapses/mm^3 of cortical tissue per year. This corresponds to an approximate reduction of $4.8 \star 10^{13}$ synapses/year for the entire cortex (Table 10.1). Comparing this human synaptic loss with the extrapolated data from macaque reveals only a small discrepancy of 6.5%.

In electron microscopy analyses, the cortex of old animals is not noticeably thinner than that of adolescent animals, despite a decreasing percentage of neuropil (Bourgeois & Rakic, 1993). This discrepancy might at least in part be due to the continuous process of myelination (Deoni et al., 2011; Paus et al., 2008). In addition, the magnitude of pruning in the basal dendritic trees of pyramidal cells differs dramatically between cortical regions and layers (Elston, Oga, & Fujita, 2009; Rabinowicz, Petetot, Khoury, & de Courten-Myers, 2009). Thus, such region- and layer-specific changes of cortical structure might also impact the subdivision into gray and white matter in MRI analyses. Estimation of cortical thickness and volume may be affected by these difficulties.

The sleep slow waves of the scalp EEG preferentially originate from extragranular layers of the cortex (Rappelsberger, Pockberger, & Petsche, 1982), which are sites of increased plasticity not only in the adult but also in the developing brain (Heynen & Bear, 2001; Trachtenberg, Trepel, & Stryker, 2000). Local field potential recordings in rats show that the rhythmic polarization changes of the membrane potential during deep sleep (i.e., slow oscillation) is highly synchronized between neighbored neuronal units (Vyazovskiy et al., 2009). A firing burst (ON state) occurs simultaneously with the positive deflection of the surface EEG signal, whereas neuronal silence during the oscillation (OFF state) corresponds to the negative deflection of the slow wave in the surface EEG (Vyazovskiy et al., 2009). These studies show that neuronal activity is directly reflected in the SWA EEG signal. On this background, maturational changes of cortical connectivity might specifically be reflected in the EEG. Thereby, the sleep

EEG represents a tool with minimized external disturbance. In the past, the major restriction of the EEG has been its spatial resolution. Today, electrode nets containing up to 256 electrodes enable higher spatial resolution.

A longitudinal approach to monitor sleep SWA across development revealed a yearly decline of about 155 μV^2 during adolescence (Table 10.1). The reduction of SWA depends on the cortical region, ranging from 120 μV^2 over central regions to 265 μV^2 over occipital regions (Table 10.1). These major regional differences in SWA reduction point out the high sensitivity of this method for developmental changes in cortical activity and connectivity. In addition, comparing the magnitude of change across the different measuring methods, it becomes evident that changes in the sleep EEG are most extreme (up to 340%, Table 10.1). Hence, the EEG provides a powerful tool to identify maturational changes due to its sensitivity and specificity in detecting regional differences (see Kurth, Ringli, et al., 2010).

As noted above, these measures all undergo an inverted U-shape maturational time course across development. However, the maturational peak appears at different time points. Synapse density reaches a maximum at 2.5–5 years (Huttenlocher & Dabholkar, 1997), while gray matter volume and thickness attained maxima at 7–11 years (Giedd, 2008; Shaw et al., 2008). SWA reached a maximum at 5–9 years (Figs. 10.1 and 10.3). The discrepancy between synapse numbers and gray matter changes might arise from the different methods. However, a similar spatial maturation across the cortex has been found for gray matter cortical thickness and SWA. In a recent analysis we have measured the maturation of SWA topography, gray matter thickness, and behavioral skills in the same subjects (Kurth et al., 2012). Exemplified for the motor cortex, we found that SWA matured first, then motor skills, and finally gray matter thinning. Again, this shows that SWA closely reflects cortical maturation. Moreover, SWA labels the early processes of cortical functional maturation, and might thus even be involved in the functional refinement of cortical connectivity

ACTIVE ROLE OF SLOW WAVES?

The Synaptic Homeostasis Hypothesis provides a possible mechanism to describe how sleep slow waves may actively contribute to cortical maturation (Tononi & Cirelli, 2006). According to the hypothesis sleep slow waves are responsible for the renormalization of overall synaptic strength. This process is believed to be fundamental for optimal learning throughout life. Several studies have shown that the manipulation of slow waves causally

impacts sleep-dependent performance improvements (Aeschbach, Cutler, & Ronda, 2008; Landsness et al., 2009; Marshall et al., 2006). Both the "wiring" (connecting) and "reshaping" (pruning) of cortical neurons during childhood and adolescence depend on use (Chklovskii, Mel, & Svoboda, 2004; Hensch, 2004, 2005; Knudsen, 2004; Mataga, Mizuguchi, & Hensch, 2004; Sur & Rubenstein, 2005), i.e., through learning processes. Such learning processes, according to the Synaptic Homeostasis Hypothesis, are shaped by synaptic renormalization during sleep.

Childhood and adolescence is characterized by massive learning. Moreover, it might not be by chance that sleep also plays a more central role during that time; for example, sleep takes up to 50% of the time during early childhood and sleep depth, assessed by sleep SWA (see Fig. 10.2), peaks in late childhood. As introduced above, one of the most prominent changes in sleep is the previously introduced change in SWA. This inverted U-shape time course of SWA led already early on to the proposal that sleep slow waves may be important for cortical maturation. Before going into a model explaining how the Synaptic Homeostasis Hypothesis may interact and shape maturational processes, the next paragraph highlights existing experimental evidence supporting an active role of sleep during cortical maturation.

Sleep Slow Waves Seem to Be Important for the Developing Cortex

Evidence for an important role of sleep in maturational processes stems from experiments investigating one of the best studied developmental processes, the ocular dominance plasticity (White & Fitzpatrick, 2007). Using this model Frank et al. showed that sleep enhanced the synaptic changes induced by a preceding period of monocular deprivation, while wakefulness in complete darkness did not (Frank, Issa, & Stryker, 2001). In contrast, the reversible silencing of visual cortices during sleep led to reduced ocular dominance plasticity (Jha et al., 2005). Thus, plastic changes not only require specific cortical stimulation (activity) during waking, but also activity during sleep. The close relationship between cortical stimulation and sleep SWA is illustrated by the following experiment: cats and mice reared in darkness showed a reduction of sleep SWA, which was restricted to visual cortex and reversible (Miyamoto, Katagiri, & Hensch, 2003). This effect was impaired by a reduction of NMDA receptor function, revealing that both ocular dominance plasticity as well as SWA are sensitive to NMDA receptor function (Miyamoto et al., 2003).

These experiments show that indeed sleep, specifically slow waves during sleep, may be related to cortical maturation. Still the question remains as to how cortical activity during sleep may interact with maturational processes. In the framework of the Synaptic Homeostasis Hypothesis we propose a working hypothesis providing a possible mechanism how sleep impacts on cortical maturation.

A Model for Sleep-Dependent Synaptic Changes during Maturation

Analyzing regional SWA distribution across age uncovered that the topographical distribution of SWA underwent maturational changes (Kurth, Ringli, et al., 2010) that closely resembled the spatial maturation of changes in cortical thickness (Shaw, et al., 2008) (see also Fig. 10.3), and the maturation of functions attributable to the underlying cortical regions (Luna & Sweeney, 2004). Our current analyses show that the maturation of EEG SWA topography correlates with the maturation of skills, as measured with behavioral tasks (Kurth et al., 2012). Moreover, in this cross-sectional sample, the maturation of SWA preceded the maturation of skills by ~3 years. Thus SWA may actively impact cortical structure during this sensitive period.

One possible mechanism for how slow waves may actively contribute to cortical maturation is proposed in a model by Ringli and Huber (2011), which is based on the Synaptic Homeostasis Hypothesis by Tononi and Cirelli (2006). The *Synaptic Homeostasis Hypothesis* assumes that synapses are potentiated during waking and downscaled during slow wave sleep ensuring an overall balance of synaptic strength across 24 hours (Tononi & Cirelli, 2006). Numerous studies show that synaptic potentiation may also lead to growth of synapses, whereas a reduction of synaptic strength causes synapses and spines to retract or shrink (Holtmaat & Svoboda, 2009). Hence, the balancing an overall synaptic strength may be closely related to the balancing of synaptic density. Thus, according to the model by Ringli and Huber, in adults, the sum of synapse formation is in equilibrium with the sum of synapse elimination. However, during development, this balance might be tilted (Fig. 10.5). Ringli and Huber suggest that synapse formation excels synapse elimination during childhood, leading to a net increase in synaptic strength/synapse number (Ringli & Huber, 2011). This is exemplified in Figure 10.5 (first phase), where synaptic potentiation during wakefulness is greater than synaptic downscaling during sleep, which results in a net increase of synaptic strength by 20 arbitrary units. This increase might be very small, hardly measurable on a daily basis, but persisting over several years leading to a

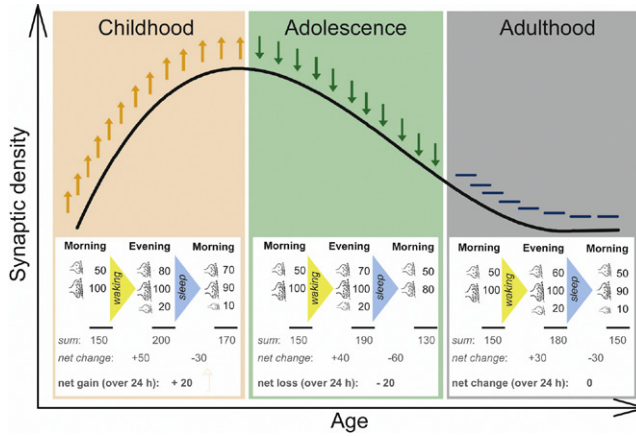

Figure 10.5 ***Model explaining a possible active role of sleep in cortical maturation.*** This model is based on the assumption that synaptic strength increases during waking (synaptic potentiation) and decreases during sleep (synaptic downscaling, Tononi & Cirelli, 2006). Three distinct phases are delineated: childhood, adolescence, and adulthood. The model by Ringli & Huber suggests alterations in the balance of synaptic strength/density during the three phases (Ringli & Huber, 2011). Synapse potentiation/formation (taking place during waking) exceeds synapse elimination and attenuation (taking place during sleep) during childhood, leading to a net increase in synapses. The change in synaptic strength across 24 hours (from the morning to the next morning) for a few exemplary synapses is illustrated as arbitrary values. In addition, the synaptic strength is summed up for each time point (sum), the resulting net changes of synaptic strength across waking and sleep are presented (net change), and finally the change across 24 hours is calculated. Elimination exceeds formation during adolescence, associated with a net decrease in synaptic strength. An equilibrium between synapse elimination and formation is found in adolescence, with no net change in synaptic strength. As presented in the model, these three phases account for the inverted U-shape time course of synaptic density across development.

pronounced overall increase of synaptic strength/density. In the model, the contrary is assumed during adolescence, during which synapse elimination excels synapse formation. Finally, synapse formation and elimination levels off in an equilibrium during adulthood. These three phases together account for the inverted U-shape time course of synaptic density across development, as known from human studies in postmortem or macaques (Bourgeois & Rakic, 1993; Huttenlocher, 1979).

A recent study using two-photon imaging in mice supports at least part of this model. This study showed that while waking is associated with spinogenesis, sleep seems to facilitate spine elimination during adolescence (Maret, Faraguna, Nelson, Cirelli, & Tononi, 2011). In contrast in adult mice, spine turnover was not affected by sleep and waking. These findings

reveal that sleep is critically involved in synaptic turnover during a sensitive period like adolescence (Maret et al., 2011). How sleep would result in a net decrease in synaptic density/strength remains unknown. However, potential mechanisms favoring synaptic depression/elimination during deep sleep may require the repeated alternation between depolarization (associated with synchronous firing) and hyperpolarization (with complete neuronal silence) of slow oscillations (of about 1 Hz) (Birtoli & Ulrich, 2004; Lante, Toledo-Salas, Ondrejcak, Rowan, & Ulrich, 2011). In addition low levels of neuromodulators such as noradrenaline and of plasticity-related molecules such as BDNF may also favor synaptic depression during sleep (Tononi & Cirelli, 2006).

Indirect evidence for a change in the balance of synaptic strength comes from the observation of changes in the dynamics of the homeostatic regulation of sleep during childhood and adolescence. If indeed our marker of sleep homeostasis—SWA—reflects synaptic homeostasis, then quantifying the dynamics of sleep homeostasis may elude developmental changes in synaptic plasticity. Accordingly, the faster increase in the homeostatic process during childhood (Jenni et al., 2005) might possibly also indicate a faster increase and a sooner saturation of synaptic strength during childhood compared to adolescence. Why would synaptic saturation be reached sooner in children than adolescents and adults?

The highly connected cortical network during childhood results in higher synchronized neuronal network activity on a larger scale as compared to more focused activity in adults. This assumption is in line with functional MRI studies revealing activity patterns of greater magnitude in children compared to adults (Casey, Giedd, & Thomas, 2000). Over time, increased and more widespread (and thus less specific) cortical activation results in a faster saturation of synaptic strength during childhood. As a result sleep pressure saturates faster. Only the pruning of synapses during adolescence and the gain in specificity would bring about a slowing of the buildup of sleep pressure during the day. In contrast to the age-dependent changes in the homeostatic increase of sleep pressure, the dynamics of the homeostatic decrease seems to be stable across age (Jenni et al., 2005; Rusterholz & Achermann, 2011). These studies show that the balance between the buildup and dissipation of sleep pressure changes across development. However, how the dynamics of sleep homeostasis relate to changes in, for example, synaptic strength on the neuronal level needs to be determined in future studies.

Moreover, as mentioned earlier the maturation of short-range connectivity (number and strength of synapses) and the maturation of long-range connectivity (degree of fiber myelination) follow a different time course

(Paus et al., 2001; Shaw et al., 2008). Thus, the changes in white matter may also contribute to the observed changes in the dynamics of sleep homeostasis during childhood and adolescence.

Since adolescence in humans is a period of increasing incidence of psychiatric and mood disorders, schizophrenia, anxiety, substance abuse, and personality disorders, it appears that this period of synapse elimination is possibly sensitive for disturbances (Paus et al., 2008).

TRANSLATION INTO CLINICS

Pruning and Psychiatric Disorders

Pruning during adolescence may unmask preexisting synaptic deficits (Hoffman & McGlashan, 1993). In 1982, based on sleep slow-wave amplitude measures, Feinberg hypothesized a faulty pruning during adolescence in schizophrenia patients (Feinberg, 1982), a phenotype that suffers from disturbances in basic cognitive functions (Lewis & Lieberman, 2000). During adolescence, when schizophrenia symptoms often start (Keshavan, Anderson, & Pettegrew, 1994), "overpruning" could explain the reduced expression of synaptic proteins and the decreased volume of neuropil in prefrontal circuits observed in schizophrenic patients (Woo & Crowell, 2005). Indeed later studies in childhood-onset schizophrenia patients showed an altered time course of cortical development, as measured in grey matter loss during adolescence (Gogtay et al., 2008; Rapoport & Gogtay, 2008).

Changes in Downscaling and Sleep Topography

Two studies further broach the issue that pathological phenotypes are probably reflected in the sleep EEG. First, Bölsterli et al. show that in patients with continuous spike wave epilepsy during slow wave sleep, the slope of slow waves does not decrease across the night (Bolsterli et al., 2011). The authors interpret this finding as a deficient overnight synaptic downscaling process in these patients, resulting in the progressive deterioration of cerebral functioning, as is the case in these patients (Tassinari, Rubboli, Volpi, Billard, & Bureau, 2005). Since spike wave epilepsy predominantly occurs in childhood, the faulty downscaling process, mediated by SWA, might impact particular brain regions while they undergo a sensitive period for development (Bolsterli et al., 2011). This might account for the major cognitive dysfunctions in these patients.

Second, a study in progress investigates the sleep EEG in children and adolescents suffering from attention deficit hyperactivity disorder (ADHD) (Ringli et al., 2011). Sleep EEG topography uncovers local deviations of SWA in these

patients when contrasted with age-matched healthy controls. Interestingly, the topographical pattern of SWA seen in children with ADHD is typical for healthy children of younger age (Ringli et al., 2011). Thus, these data point to a maturational delay in sleep EEG topography of patients with ADHD. Imaging findings confirm this implication of a maturational delay in terms of gray matter thickness (Shaw, Gogtay, & Rapoport, 2010). Such findings highlight the clinical relevance of establishing hdEEG during sleep as diagnostic tool.

The Sleep SWA Topography as a Diagnostic/Prognostic Marker

The use of SWA topography as an imaging tool to diagnostically or even prognostically mark cortical maturation provides several advantages: First, SWA is a direct reflection of underlying spontaneous neuronal activity (Steriade, Timofeev, & Grenier, 2001; Timofeev et al., 2001; Vyazovskiy, et al., 2009). SWA topography accordingly represents the spatial variation in neuronal activity. Such cortical activity may be a more straightforward predictor of functional discrepancies than brain anatomy. Second, during sleep possible confounding factors related to waking activities can be excluded, such as attention, motivation, and distractibility. This might be particularly relevant for studies in children and patients with impairments of cognition or performance. The fact that SWA topography is highly reproducible across nights (Finelli, Achermann, & Borbely, 2001; Huber et al., 2004) illustrates the consistency of this measure. Thus, the measurement is objective, reliable, and robust. These factors are also of interest in study conditions, since many functional neuroimaging studies face similar problems as diagnostic settings. Third, sleep SWA is a tool that is easy to apply and not susceptible to moving artifacts, which is important for the investigation of children and patients. In addition, sleep recordings allow the data collection of hours of brain activity representing a stable assessment. Fourth, it is cost-efficient and can be repeatedly applied without any ethical concerns. Finally, brain activity, as measured by SWA, may be more predictive for functional outcome than is gray matter volume. In sum, sleep may be a rich source of information to gain insight into the healthy and disturbed processes of brain function and maturation.

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