# Chapter 8
# The Need of Slow Wave Activity and Cognitive Functions

**Abstract** According to the synaptic homeostasis hypothesis of Tononi and Cirelli (Sleep Med Rev 10(1):49–62, 2006), the homeostatic regulation of sleep slow wave activity is related to the amount of the synaptic potentiation that has accumulated during the preceding waking state. The homeostatic increase of slow wave activity is shown to be valid for regional involvement in special localization related tasks, especially true for the frontal lobe.

High synaptic potentiation characterizes the early childhood's abundant plastic changes when sleep contains high amounts of delta activity, while the decrease of potentiation in the elderly is associated with important decrease of sleep slow waves, nicely supporting the hypothesis.

According to this hypothesis, slow waves promote a generalized depression or downscaling of synaptic strength reached during wakefulness. Very much in congruence with the hypothesis, it was found that the cerebral blood flow is low in the morning after a night sleep compared to the end of a waking day, as measured by $H_2{}^{15}O$ PET studies. Furthermore, the blood flow values proved to be less and less parallel with the decrease of slow wave activity along the sleep cycles.

Sleep deprivation results in well-known negative cognitive symptoms. That also fits into the hypothesis because of the synaptic overload without the possibilities of downscaling because of the lack of sleep.

A close relationship between the amount of sleep slow wave activity and the cognitive performances in different human pathological conditions also supports the hypothesis.

Sleep deprivation mimics the prefrontal symptoms of mental deterioration in the elderly, where the rebound in frontal delta activity after sleep deprivation is missing. Another aspect of the relationship between human cognitive functions and sleep slow wave activity is that disorders like sleep apnea, Alzheimer disease, or insomnia, all associated with different degree of cognitive decline, show impairment of both NREM sleep and frontal slow wave activity.

The evidences about the importance of NREM slow wave activity in cognitive functions explains the interest about the role of CAP $A_1$ phenomenon in cognition. We present here studies pointing to relationship between cognitive employment and

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CAP $A_1$ type amount during the next night sleep. These preliminary results again connect input-dependent slow wave regulation with the use of dependent long-term homeostatic regulation.

**Keywords** Synaptic homeostasis hypothesis • Slow waves • Delta activity Cognitive functions • Sleep deprivation • Synaptic potentiation

The wisdom of "sleep on it" is confirmed.

## 8.1 The Need of Slow Wave Sleep

Slow waves were the protagonists of the previous chapters. Why and for which function are they so important? The most coherent and well-established hypothesis of sleep function is presently the so-called synaptic homeostasis hypothesis (Tononi and Cirelli 2006), which places just the slow wave homeostasis in the center of the concept. The hypothesis starts with the well-evidenced assumption that due to the production of a large amount of LTP owing to waking activity, synaptic potentiation increases in many cortical circuits. A necessary requisite for LTP production is the presence of a neuromodulatory milieu, where the firing of presynaptic neurons is followed by the depolarization and firing of postsynaptic neurons. This condition is fulfilled during wakefulness when continuous streaming of impulses impinges on cortical neurons innervated by the ascending arousal systems missing during NREM sleep.

The next statement of the hypothesis is that the homeostatic regulation of sleep slow wave activity is tied to the amount of the synaptic potentiation of the preceding waking state. The higher the amount of potentiation in cortical circuits during wakefulness, the higher is the increase of slow wave activity during subsequent sleep. Several studies have proved that not only the duration of wakefulness but the induction of synaptic potentiation by use-dependent tasks – as it was shown previously – that is responsible for the homeostatic drive increasing slow wave activity (Kattler et al. 1994; Huber et al. 2004; Vyazovskiy et al. 2000). The homeostatic increase of slow activity is shown to be valid for regional involvement in special localization related tasks, and especially the frontal lobe proved to be sensitive for this homeostatic drive (Cajochen et al. 1999; Finelli et al. 2001). The association of synaptic potentiation with developmental periods of early childhood when plastic changes are the most abundant, and high amount of sleep delta activity while decay of potentiation in the elderly associated with important decrease of sleep deltas, fits very well into the hypothesis.

Wakefulness-related molecular mechanisms of a net increase in synaptic weights by LTP are related to enhanced noradrenaline release, enhanced brain-derived neurotrophic factor (BDNF) release, and increased the glutamine receptor1 (GluR1) containing α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors in the synaptoneurosomes, as well as to some specific patterns of phosphorylation of GluR1 and calcium-/calmodulin-dependent kinase II (CamKII). Noradrenaline was shown to enhance LTP and to be preferentially released during wakefulness. Accordingly, noradrenaline-depleted rats show a significantly dampened increase of the sleep slow oscillation after prior sleep deprivation (Cirelli et al. 2005). Concerning BDNF, it was repeatedly shown that BDNF is involved in LTP and that the levels of BDNF are higher during wakefulness than during sleep (Vyazovskiy et al. 2008). Moreover, BDNF release is increased in association with exploratory behavior and strongly correlates with the sleep deprivation-induced increase in subsequent sleep slow wave activity (Huber et al. 2007). BDNF was shown to have a causal role in sleep homeostasis and to be involved in local sleep regulation, as local microinjections induced hemisphere-specific increases in sleep slow wave activity. Effects were specific to NREM sleep and did not occur in REM sleep or wakefulness (Faraguna et al. 2008). Functional polymorphisms of the gene encoding the BDNF receptor tyrosine kinase B affect the time spent in slow wave sleep, slow wave EEG activity during NREM sleep (Bachmann et al. 2012), as well as the performance in some neuropsychological tests also impaired by sleep deprivation (Egan et al. 2003; Pezawas et al. 2004). Last, but not least, the changes in the GluR1 containing AMPA receptors and CamKII are the core elements of LTP induction in vivo. Their changes were shown to parallel the changes in the homeostatic sleep need assessed by electrophysiological and behavioral methods (Vyazovskiy et al. 2008). A mechanism of use-dependent GluR1 AMPA receptor increase was proposed by Krueger et al. (2008). Authors are arguing that presynaptic neuronal firing is associated with ATP-release, which binds in part to the P2R purine receptors on the glial cells. In turn glial cells release somnogenic cytokines, like TNFα and IL1β. These cytokines activate postsynaptic enzymatic activities in relation with the NF-κB enzyme. The outcome of this activation is the increase in GluR1 AMPA receptors and adenosine $A_1$ receptors on the postsynaptic membrane. This cascade of events provides a plausible explanation for the use-dependent sleep regulation process. Although Krueger et al. (2008) argue that sleep homeostasis per se is an emergent property of a large set of neuronal groups (columns), the question of a central sleep-inducing system is still an open one. (We refer to the earlier presented results of the McCarley group showing that local increases in adenosine near the basal forebrain arousal centers can lead to global sleep processes. A similar argument for the possible existence of a global sleep-inducing center and sleep homeostasis is related to the specific involvement of the VLPO region in inducing sleep as well as to the experimental evidence suggesting that local adenosine injection to the VLPO region can induce global sleep.)

The next question is about the function of the sleep slow wave activity. According to the synaptic homeostasis hypothesis, slow waves promote a generalized depression or downscaling of synaptic strength reached during wakefulness.

The exponential decrease of slow wave activity across the sleep cycles described by the Borbély group represents strong electrophysiological fingerprint of this downscaling process. Downscaling probably represents a certain cleaning and refreshing synaptic capacities for new learning. Extended wakefulness or sleep deprivation does not only lead to a net increase in synaptic weights but also to a concomitant occlusion of the LTP process. This is probably due to the saturation of the neural networks (Vyazovskiy et al. 2008). The partial loss of consciousness during sleep is advantageous excluding any interference with the downscaling process.

Very much in congruence with the hypothesis, the cerebral blood flow measured by $H_2{}^{15}O$ PET studies showed a decrease in the flow in the morning after a night sleep compared with the values of the end of a waking day (Braun et al. 1997). Furthermore, the blood flow values proved to be less and less parallel with the decrease of slow wave activity along the sleep cycles.

Sleep deprivation results in the well-known negative cognitive symptoms which also fit into the expectation of the hypothesis because of the synaptic overload without downscaling possibilities. Insomnia associated with hyperarousal also impairs synaptic homeostasis and, consequently, results in fatigue, concentration difficulties, cognitive impairment, and irritability. Depression which is epidemiologically related to insomnia and associated with memory disturbances is also related to the so-called hypofrontality, witnessed by neuroimaging studies, and disrupted sleep pattern (Mobascher et al. 2009). Sleep deprivation which accumulates slow wave activity brings transitory benefit for these symptoms. The ever enigmatic effect of electroshock therapy may get an explanation by the synaptic homeostasis hypothesis as well since the therapeutic effect might be due to artificially induced synaptic up- and downscaling.

The neurophysiologic mechanism of synaptic downscaling and its relationship with slow waves is poorly understood. It is evident that long-term depression (LTD) is an important process taking place during sleep and taking part in the synaptic homeostasis by downscaling. Molecular signs of LTD were revealed to be higher during sleep than during wakefulness, which is the reverse of what we see during wakefulness. The glutamatergic AMPA receptors containing the GluR1 subunit were shown to be removed from the synaptoneurosomes during LTD. Indeed, these receptors are downregulated during sleep compared to periods of wakefulness. A specific pattern of phosphorylation of the receptor suggests that it is not only the low LTP, but indeed the presence of LTD during sleep that is involved in these differences. Thus, LTD seems to be the mechanism of synaptic downscaling taking place during sleep (Vyazovskiy et al. 2008).

Increasing synaptic weights during wakefulness impinge on neurons to fire in synchrony. This results in increased amplitudes and steeper slopes of the slow waves at the beginning of sleep. Experimental evidence shows that induction of repetitive burst pairings in layer V pyramidal cells of the rat is followed by LTD, suggesting a mechanism by which synaptic inputs are proportionally downsized during periods of slow wave sleep (Czarnecki et al. 2007). The process is self-limiting, as LTD reduces synaptic strengths, thus reducing synchronous firing and synchronous slow waves.

## 8.2 Physiological and Pathological Human Evidences for the Relationship Between Frontal Slow Waves and Frontal Cognitive Functions

There are accumulated human physiological and clinical evidences of interrelationship between slow wave activity of sleep and evolution versus decay of cognitive functions during the human life span. In childhood, delta activity has a higher proportion in sleep and it decreases in parallel with the end of developmental milestones (Darchia et al. 2007). We summarized in the Sect. 7.6 how the delta and/or slow EEG activity during sleep is related to the ontogeny of neuronal systems during childhood and adolescence. Within slow wave activity, the reactive delta portion in the form of CAP A phases follows also significantly the age development as it was described in Sect. 3.6.

In the senium sleep duration (Klerman and Dijk 2008), the amount of sleep delta decreases, especially during the first cycles (Landolt et al. 1996; Landolt and Borbély 2001). Sleep deprivation mimics the prefrontal symptoms of mental deterioration in the elderly (Harrison et al. 2000), and there is diminished frontal delta rebound after sleep deprivation in this age group (Münch et al. 2004).

Chronic insomnia has a negative effect on working memory (Hauri 1997; Boufidis et al. 2004), especially in the elderly (Haimov et al. 2008). Obstructive sleep apnea is harmful for frontal cognitive functions (Mathieu et al. 2008), and SPECT studies in this disorder have shown frontal hypoperfusion (Köves et al. 2003; Puertas et al. 2004). In dementia due to alcoholism and Alzheimer disease, the amplitude of K-complexes and their elicitibility decreases (Colrain et al. 2009).

## 8.3 CAP and Cognitive Functions

CAP has been introduced as a buffer mechanism counterbalancing the perturbation of NREM sleep, reflecting a sleep-promoting effect within the frameworks of the reciprocal inhibitory dynamics of sleep- and wake-promoting structures. At the same time, however, CAP A phase and especially $A_1$ considerably contributes to sleep delta activity. We have learned that sleep delta activity is under use-dependent homeostatic regulation. A further development is that the homeostatic increase of slow waves is related to improvement of cognitive functions (Tononi and Cirelli 2006; Huber et al. 2008; Massimini et al. 2009). In this context, the reactive slow wave activity within the frame of CAP sequences became especially interesting. We hypothesized previously that CAP reactive slow wave elements represent an instant homeostatic regulation by which the slow wave equilibrium is balanced during the same night sleep. The existence of something like “slow wave need” during a night sleep is supported by the study of Dijk et al. (1987). He deprived sleep during the first 3 h of the night in young healthy subjects and observed an increase in power densities in the frequency range from 1 to 7 Hz during the subsequent hours of sleep, compared to the same period of the baseline night. In the situation when the

rate of CAP increases during a disturbed night sleep, the disturbing intervention does not lead to sleep loss; it only "threats" the evolution of slow wave sleep. It is an interesting question, whether this instant homeostatic regulation also results in cognitive improvement of the next day, as seen in experiments where the increase of delta sleep has that effect.

Whether the homeostatic role of CAP in cognitive functioning has detectable traces immediately during the same night sleep of the disturbance is unanswered. However, Ferri et al. (2008) have found that when persons were exposed to cognitive tasks, the number of CAP $A_1$ subtypes/h of NREM sleep on the following night was increased, and this increase correlated positively with post-sleep performance. In another study on young human subjects, the same working group (Aricò et al. 2010) published that CAP $A_1$ subtypes correlated positively with the next-day performance in different neuropsychological tasks, while CAP $A_2$ and $A_3$ subtypes correlated negatively with performance. These results mean that the reactive delta compartment of CAP took part in the specific (cognitive) task-related homeostatic regulation and had a simultaneous role in sleep-related cognitive processes.

CAP $A_1$ phase seems to be an obvious link between responsively of sleep and sleep homeostasis driven by metabolic needs of the brain-fuelling cognitive functions. CAP $A_1$ phase is a tool by which the sleeper "using up" external influences in the building up of slow wave sleep paves the way for synaptic decay and plastic changes.

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