CHAPTER 2

# Electrophysiological correlates of sleep homeostasis in freely behaving rats

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**Abstract:** The electrical activity of the brain does not only reflect the current level of arousal, ongoing behavior, or involvement in a specific task but is also influenced by what kind of activity, and how much sleep and waking occurred before. The best marker of sleep–wake history is the electroencephalogram (EEG) spectral power in slow frequencies (slow-wave activity, 0.5–4 Hz, SWA) during sleep, which is high after extended wakefulness and low after consolidated sleep. While sleep homeostasis has been well characterized in various species and experimental paradigms, the specific mechanisms underlying homeostatic changes in brain activity or their functional significance remain poorly understood. However, several recent studies in humans, rats, and computer simulations shed light on the cortical mechanisms underlying sleep regulation. First, it was found that the homeostatic changes in SWA can be fully accounted for by the variations in amplitude and slope of EEG slow waves, which are in turn determined by the efficacy of corticocortical connectivity. Specifically, the slopes of sleep slow waves were steeper in early sleep compared to late sleep. Second, the slope of cortical evoked potentials, which is an established marker of synaptic strength, was steeper after waking, and decreased after sleep. Further, cortical long-term potentiation (LTP) was partially occluded if it was induced after a period of waking, but it could again be fully expressed after sleep. Finally, multiunit activity recordings during sleep revealed that cortical neurons fired more synchronously after waking, and less so after a period of consolidated sleep. The decline of all these electrophysiological measures—the slopes of slow waves and evoked potentials and neuronal synchrony—during sleep correlated with the decline of the traditional marker of sleep homeostasis, EEG SWA. Taken together, these data suggest that homeostatic changes in sleep EEG are the result of altered neuronal firing and synchrony, which in turn arise from changes in functional neuronal connectivity.

**Keywords:** sleep homeostasis; synaptic homeostasis; multiunit activity; neurons; cortex.

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### Behavior and brain activity in waking and sleep

In all species carefully studied so far, waking and sleep alternate on a regular basis and neither wake nor sleep last spontaneously for more than several hours (individual rat: Fig. 1a; Cirelli and Tononi, 2008; Tobler, 2005). This observation led to the notion that wake and sleep should be associated with opposite processes, as manifested in increased sleep drive during wake and its dissipation during sleep (Borbely, 1982). A fundamental difference between wakefulness and sleep is the extent to which the brain is engaged in the acquisition and processing of information. During wakefulness, animals face environmental challenges that require an adequate behavioral response, and continuous behavioral adjustments necessarily involve learning, associated with neuronal plasticity (Whitlock et al., 2006). The cortical activity in awake animals is generated not only by ascending influences from specific wake-promoting areas (Jones, 2005; Villablanca, 2004) and intracortical and cortico-subcortical interactions (Boutrel and Koob, 2004; Miller and O'Callaghan, 2006) but also by behavior (Gentet et al., 2010; Petersen et al., 2003; Vyazovskiy et al., 2006) and processing of incoming external stimuli (Sporns et al., 2000). In contrast, in non-rapid eye movement (NREM) sleep, neocortical activity is spontaneous and organized largely "from inside" (Steriade and Amzica, 1998b; Steriade et al., 1993c, 2001).
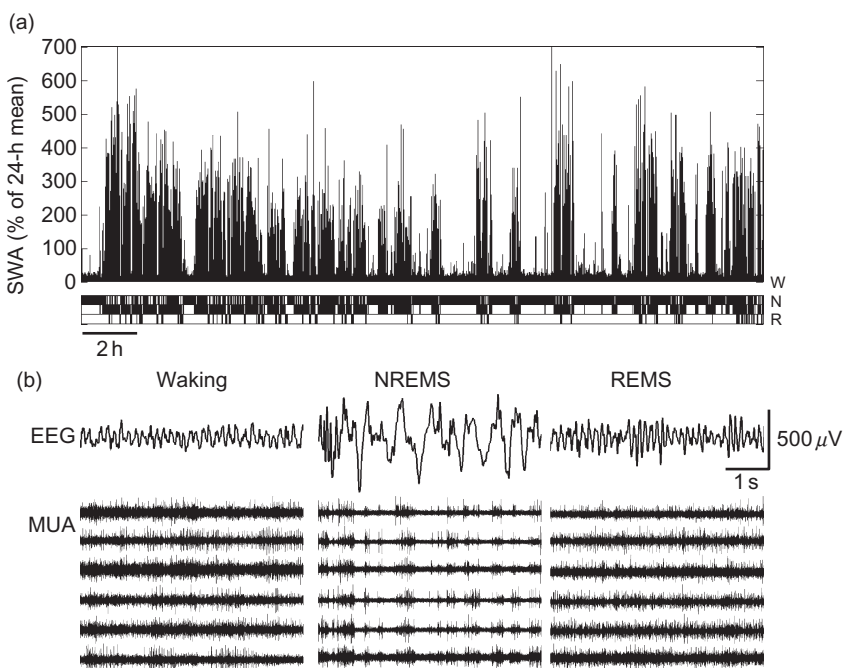


Fig. 1. Sleep architecture and vigilance-specific cortical activity. (a) EEG slow-wave activity (SWA, EEG power between 0.5 and 4 Hz) and corresponding hypnogram during an undisturbed 24-h baseline in one individual rat. Vertical bars depict consecutive 4-s values of SWA. Note that SWA decreases during the 12-h light period and increases after long consolidated waking episodes. (b) From top to bottom: Surface electroencephalogram (EEG) traces from the right barrel cortex during waking, NREM sleep, and REM sleep in a representative rat. Raw multiunit activity (MUA) recorded simultaneously in the same rat from a microwire array placed in the left barrel cortex (six individual channels are shown). Note high-frequency tonic firing in waking and REM sleep, and the periods of population neuronal activity and silence in NREM sleep.

Not surprisingly, cortical neuronal firing patterns in wakefulness and another activated state, REM sleep, are profoundly and characteristically different from those in NREM sleep (Burns et al., 1979; Desiraju, 1972; Hobson and McCarley, 1971; Murata and Kameda, 1963; Noda and Adey, 1970, 1973; Steriade et al., 2001; Verzeano and Negishi, 1960; Fig. 1b). At the EEG level, wake in rodents is traditionally distinguished from NREM sleep by the virtual absence of large-amplitude slow waves, and by the presence of pronounced ∼7–9 Hz activity presumably arising as a result of physical spread of theta activity from the hippocampus (Green and Arduini, 1954; Leung and Borst, 1987; Petsche and Stumpf, 1960; Robinson, 1980; Sirota et al., 2008; Whishaw and Vanderwolf, 1973). Hippocampal theta activity has been related to voluntary activity, arousal, attention, the representation of spatial position, learning, and other behaviors or functions (Buzsaki, 2002; Feder and Ranck, 1973; Green and Arduini, 1954; Kemp and Kaada, 1975; O'Keefe and Recce, 1993; Vanderwolf, 1969). Based on phase analysis and pharmacological studies, it has been postulated that there is more than one generator and more than one type of theta activity in the hippocampus (Kramis et al., 1975; Robinson, 1980). The functional significance of hippocampal theta activity is still unclear, but it can be highly relevant for various aspects of behavior and cognition, given the complex interactions between the cortex and hippocampus during sleep and waking (Born et al., 2006; Buzsaki, 1998; Clemens et al., 2007; Hahn et al., 2007; Isomura et al., 2006; Ji and Wilson, 2007; Molle et al., 2006; Sirota and Buzsaki, 2005; Sirota et al., 2003, 2008; Tierney et al., 2004; Tononi et al., 2006; Wierzynski et al., 2009). Apart from the EEG, the activated pattern of brain activity during waking is also apparent at the level of firing of cortical neurons. Overall, neuronal discharge in waking is largely fast and irregular (Fig. 1b), although it is determined strongly by behavior and involvement in specific tasks.

During NREM sleep, instead, the neocortex is functionally disconnected from the surrounding, and the most distinctive feature of the EEG is the near-synchronous occurrence of slow waves in all or most cortical areas (Massimini et al., 2004; Sejnowski and Destexhe, 2000). The fundamental cellular phenomenon underlying the sleep slow waves is the slow oscillation, which consists of an UP state, characterized by sustained neuronal depolarization and irregular firing, followed by a hyperpolarized DOWN state, during which every cortical cell ceases firing (Amzica and Steriade, 1998; Destexhe et al., 1999; Steriade et al., 1993c, 2001). *In vivo*, *in vitro*, and *in computo* evidence indicates that the DOWN state of the slow oscillation is the result of disfacilitation (i.e., a lack of synaptic input), rather than of active inhibition (Hill and Tononi, 2005; Steriade et al., 1993c; Timofeev et al., 2001). Slow oscillations ($<1$ Hz) have also been observed in the EEG under anesthesia and in naturally sleeping cats and humans (Achermann and Borbely, 1997; Steriade and Amzica, 1998a). As a result, the firing pattern of cortical neurons in NREM sleep is dominated by periods of elevated population activity (ON periods), lasting several hundreds of milliseconds, alternated with shorter periods of generalized silence, corresponding to the negative phase of EEG slow waves (Fig. 1b). It is currently unclear what determines the regularity in the occurrence of prolonged intracellular UP and DOWN states and extracellular synchronous ON and OFF periods that ultimately give rise to the large number of high-amplitude slow waves typical of deep sleep. A bistability between ON and OFF periods can be brought about by potassium leak channels and Ih currents, whose voltage-dependent properties depend on arousal-promoting neuromodulation (McCormick, 1992a; McCormick and Bal, 1997; Steriade, 1993; Steriade et al., 1993a, 2001). The altered pattern of neuronal firing during sleep can in turn lead to reduced responsiveness to sensory stimuli, and can be expected to affect brain metabolism.

Indeed, it is well known that cerebral metabolic rates are largely determined by the levels of neuronal activity (Attwell and Gibb, 2005; Attwell and Laughlin, 2001). For example, barbiturate anesthesia, which is associated with inhibition of catecholamine release (Hirota et al., 2000) and marked suppression of neuronal activity (Antkowiak, 1999), is characterized by lowered cerebral blood flow (Hendrich et al., 2001; Lowry and Fillenz, 2001) and reduced 2-DG utilization (Sokoloff et al., 1977). Given the pronounced differences in cortical firing between sleep and waking, one could expect also vigilance state-specific differences in brain metabolism. Indeed, compared to waking, the uptake of 2-deoxyglucose during NREM sleep is reduced in animals (Kennedy et al., 1982; Ramm and Frost, 1983, 1986), while a global deactivation of the neocortex and thalamus has been demonstrated with PET studies in humans (reviewed in Maquet, 2000). Moreover, there is evidence that mRNA and protein levels of genes involved in cerebral energy metabolism (e.g., mitochondrial enzymes and glucose transporters) are lower during sleep than during waking (Cirelli et al., 2004; Nikonova et al., 2005; Petit et al., 2002), and several key components of the mitochondrial electron transport chain are upregulated after prolonged waking (Nikonova et al., 2010). During NREM sleep, metabolic activity is inversely correlated with slow EEG activity (Czisch et al., 2004; Dang-Vu et al., 2005; Hofle et al., 1997), presumably because larger and more frequent slow waves are associated with longer and more frequent periods of neuronal silence (Calvet et al., 1973; Esser et al., 2007; Vyazovskiy et al., 2009b).

Thus, behavior, cortical, and subcortical neuronal activity and brain metabolism differ significantly between vigilance states. This notion suggests that in physiological conditions, brain state can be maintained and regulated at different levels of activity. However, the question arises whether brain activity is not only different depending on whether the animal is awake or asleep but also depending on for how long it has been awake or asleep before, within the same vigilance state.

## Global and local regulation of sleep

It is well known that sleep is homeostatically regulated (Borbely, 1982; Daan et al., 1984). In most species, sleep pressure increases as a function of time spent awake and decreases in the course of sleep. There are several markers of sleep pressure (Borbely and Achermann, 2000; Cirelli and Tononi, 2008). For example, after sleep deprivation, sleep time increases, sleep episodes become longer, and the number of brief awakenings decreases (Franken et al., 1991; Huber et al., 2000b; Tobler, 2005; Vyazovskiy et al., 2002, 2007b). However, the best characterized physiological indicator of the sleep–wake history is the level of EEG SWA (SWA, EEG power between 0.5 and 4.0 Hz) during NREMS (Borbely, 1982; Daan et al., 1984; reviewed in Borbely and Achermann, 2000; Figs. 1a and 2a). In mammals, sleep SWA is high in early sleep, when sleep pressure is increased physiologically, and decreases progressively to reach low levels in late sleep (Franken et al., 1991; Rosenberg et al., 1976; Tobler and Borbely, 1986; Vyazovskiy et al., 2007b). Moreover, sleep SWA increases further with sleep deprivation and is reduced by naps (Borbely and Achermann, 2000; Tobler, 2005). Sleep pressure builds up especially after extended wake periods (Borbely et al., 1984; Tobler and Borbely, 1986) and even during relatively short spontaneous waking episodes (Huber et al., 2000b; Vyazovskiy et al., 2006; Werth et al., 1996b), and several studies showed that the changes in sleep need unlikely arise from stress or changes in brain temperature incurred during preceding waking (Franken et al., 1991; Tobler et al., 1983).

While the homeostatic regulation of SWA is a precise, ubiquitous, and basic feature of sleep in mammals and birds (Cirelli and Tononi, 2008; Tobler, 2005), its underlying mechanisms remain unknown. However, an important insight came from the observation that sleep is not only a global process but has a local use-dependent component manifested in regional differences in SWA
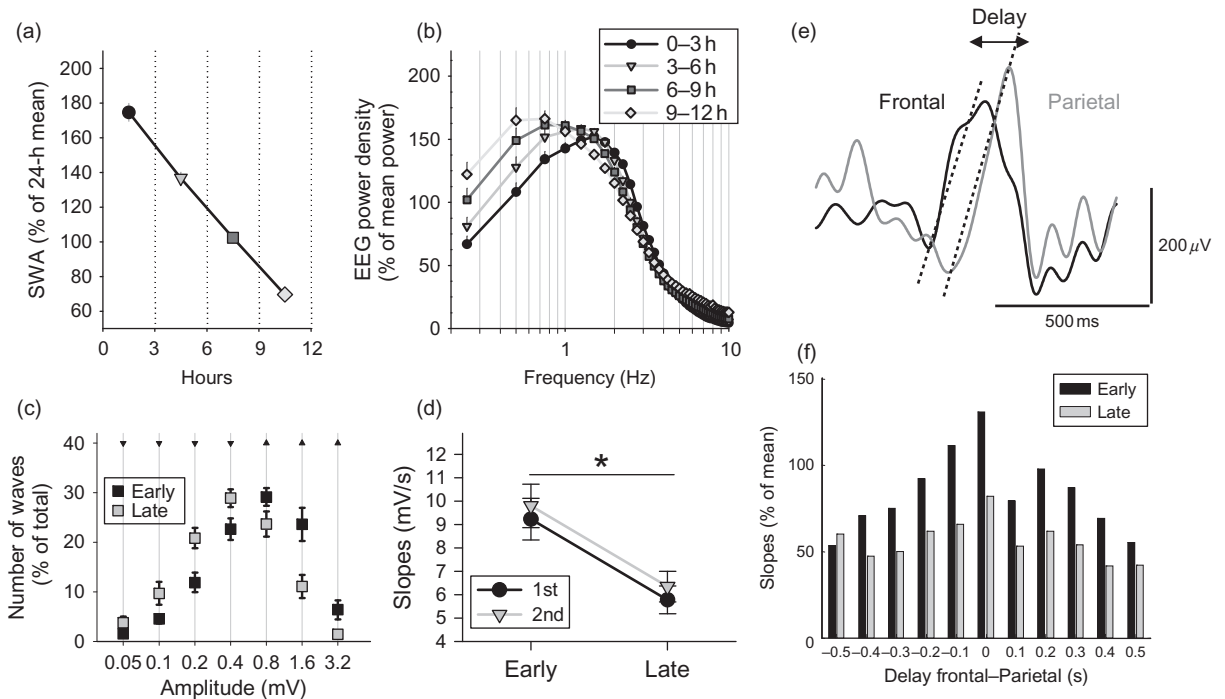
Fig. 2. Homeostatic regulation of SWA and slow wave parameters. (a) Time course of SWA in NREM sleep during the light period. Mean values ($n=15$ rats, SEM) are plotted for consecutive 3-h intervals. (b) Time course of EEG power spectra in NREM sleep during the light period (same data as in (a)). Mean spectra are plotted for consecutive 3-h intervals. Note a progressive shift of the spectral peak toward slower frequencies in the course of the light period. (c) Distribution of the amplitude of slow waves during early and late sleep. Mean values (SEM, $n=15$ rats) are plotted as percentage of the total number of waves. Triangles: amplitude ranges where slow wave incidence was higher during early sleep (triangles up) or higher during late sleep (triangles down, $p<0.05$, Sidak test). (d) Slopes of the 1st and 2nd segment of EEG slow waves in early sleep and late sleep. Mean values, $n=15$ rats. Asterisk: $p<0.05$, paired $t$-test. (e) Near-simultaneously occurring LFP slow waves recorded from layer V of the frontal and parietal cortical areas. Note that the parietal slow wave is delayed relative to the frontal wave. Dotted lines depict slopes of the slow waves. (f) Relationship between the delay between slow waves occurring in the frontal and in the parietal derivation and the corresponding slow wave slopes. One individual rat is shown. Note that slow waves have steepest slopes when they occur synchronously in the two derivations, especially in early sleep.

(Kattler et al., 1994; Krueger and Obal, 1993; Krueger et al., 2008). Over the past two decades, multiple studies showed that during spontaneous sleep, SWA is not uniform across the cortical surface, but topographically organized. In both humans and animals, SWA is more intense in the frontal derivations, especially in early sleep or after sleep deprivation (Cajochen et al., 1999; Finelli et al., 2001; Huber et al., 2000a; Vyazovskiy et al., 2002; Werth et al., 1996a; Zavada et al., 2009). Frontal predominance of sleep SWA may arise from corticocortical connectivity (Vyazovskiy and Tobler, 2005), cognitive load (Anderson and Horne, 2003a,b), topographic differences in cortical metabolism (Drummond and Brown, 2001; Vyazovskiy et al., 2004b), or preceding motor activity (Leemburg et al., 2010; Vyazovskiy et al., 2006, 2007a; Vyazovskiy et al). An intriguing possibility is that the anterior–posterior gradient in SWA is related

to a "preferred origin" of sleep slow waves in frontal regions, from where slow waves would propagate across cortical areas. Such a possibility is suggested in various species and preparations, for example, *in vitro*, in anesthetized animals, and in sleeping rats and humans (Leemburg et al., 2010; MacLean et al., 2005; Massimini et al., 2007; Murphy et al., 2009; Richardson et al., 2005; Rigas and Castro-Alamancos, 2007; Sanchez-Vives and McCormick, 2000; Timofeev et al., 2000; Vyazovskiy et al., 2009a), and may have a functional role.

For example, more recently, a number of studies addressed the question of whether regional differences in SWA are activity- or use-dependent. It was found that peripheral experimentally induced stimulation or the spontaneous use of circumscribed cortical areas leads to more intense local slow waves (Kattler et al., 1994; Vyazovskiy et al., 2000, 2004b). Moreover, local, topographically distinct enhancement of slow waves was associated with learning of a motor task (Hanlon et al., 2009; Huber et al., 2004; Vyazovskiy and Tobler, 2008), while unilateral arm immobilization led to a local decrease in slow waves (Huber et al., 2006). Such observations suggested that waking activities could in a selective manner affect intensity of subsequent sleep. Indeed, it is well known that staying awake inevitably leads to decreased neurobehavioral performance (Czeisler, 2009; Dijk et al., 1992) and altered brain metabolism (Everson et al., 1994; Wu et al., 2006), suggesting that being awake leads to changes in cortical networks, which are manifested in enhanced SWA during subsequent sleep. It has recently been proposed that waking, which is associated with a variety of plastic processes, is associated with net synaptic potentiation, whereas sleep results in synaptic downscaling (Tononi and Cirelli, 2003, 2006). The experimental evidence for this hypothesis has been provided by several studies in humans, rodents, and flies (Bellina et al., 2008; Cirelli et al., 2004; De Gennaro et al., 2008; Gilestro et al., 2009; Hanlon et al., 2009; Huber et al.,

2004, 2006, 2007a,b; Vyazovskiy et al., 2000, 2008), as well as in rats and mice *in vitro* (Liu et al., 2010). Most importantly, such regulation of cortical plasticity would ensure the restoration of the brain's ability to learn by preventing synaptic saturation, and would maintain an overall balance of space and energy resources.

It is reasonable to assume that an increase in cortical synaptic strength, engendered by prolonged waking, would lead to specific changes in spontaneous and evoked cortical activity, both at the level of the EEG and cortical neurons. In the next section, we will discuss the changes in EEG waves during sleep incurred as a function of preceding sleep/wake history and their functional significance.

## Homeostatic sleep pressure is reflected in the amplitude and slopes of sleep slow waves

Traditionally, sleep homeostasis is measured with EEG power spectral analysis, which shows larger SWA at sleep onset after sleep deprivation relative to baseline. However, we reasoned that if sleep is associated with a generalized decrease in cortical synaptic strength, the latter should be most apparent in the temporal domain of the EEG. Therefore, in a recent series of studies *in vivo*, complemented by computer simulations (Esser et al., 2007; Riedner et al., 2007; Vyazovskiy et al., 2007c), we set out to investigate how changes in the EEG signal *per se* account for the homeostatic changes in the corresponding power spectra.

First, apart from the well-known overall decline of spectral power in the SWA range with decreasing sleep pressure, we observed a redistribution of power toward lower frequencies, resulting in a shift of the spectral peak (Fig. 2b). The mechanisms underlying this shift had not been investigated before, although several previous studies had reported a dissociation between the homeostatic behavior of frequencies <1 Hz and the remaining SWA frequencies (Achermann and Borbely, 1997, 1998; Campbell et al., 2006; Dijk et al., 1987).

To disentangle the mechanisms underlying the decrease of SWA from the shift of the spectral peak, we first quantified individual slow wave events and compared the relationship between their amplitude and incidence between early and late sleep. Invariably, in both rats and humans, we found that, while the total number of slow waves during sleep remained roughly constant, the proportion of high-amplitude slow waves decreased from early to late sleep (Riedner et al., 2007; Vyazovskiy et al., 2007c; Fig. 2c). Computer simulations revealed that such decrease in slow wave incidence could fully account for an overall decline of SWA (Vyazovskiy et al., 2007c). Thus, we concluded that the overall homeostatic decline of spectral power in SWA range occurs largely due to lower incidence of high-amplitude slow waves.

Next, we reasoned that slowing of the peak of the spectrum could arise from the change in the shape of slow waves, as suggested by previous studies employing period–amplitude analysis, which showed an increase in slow wave period with decreasing sleep pressure (Bergmann et al., 1987; Feinberg et al., 1978; Mistlberger et al., 1987). Indeed, when we performed additional simulations where slow wave amplitude and incidence were kept constant, but the slope of slow waves was varied, a shift of the spectral power was observed, as we found *in vivo* (Vyazovskiy et al., 2007c). Consistently, in both animals and humans, we found a clear-cut decrease in the slope of slow waves with decreasing homeostatic sleep pressure (Bersagliere and Achermann, 2009; Riedner et al., 2007; Vyazovskiy et al., 2007c; Fig. 2d). Thus, while decreased incidence of slow waves may account for the overall lower SWA values, the changes in the slopes may lead to the slowing of the spectral peak.

In order to address the mechanisms underlying the decrease in slow wave slopes, we performed further computer simulations (Esser et al., 2007), which revealed that changes in slow wave slope can be accounted for by the speed of recruitment/decruitment of neurons in the population slow oscillation (the steeper the slope, the quicker the recruitment), which was determined by the efficacy of cortical connections. Additional experiments performed *in vivo* also suggested that the slopes of cortical sleep slow waves reflect the level of synchrony between cortical regions, especially in early sleep (Fig. 2e and f). Thus, these results suggested that stronger cross talk between neuronal populations after increased sleep pressure is reflected in steeper slopes of slow waves. A similar link between sleep homeostasis and cortical synchrony was also reported in mice, in which interhemispheric coherence of slow EEG frequencies increased after sleep deprivation and declined during recovery (Vyazovskiy et al., 2004a).

Thus, altogether, these data suggested that high levels of EEG SWA in early sleep are brought about by (i) more frequent occurrence of high-amplitude slow waves and (ii) more synchronous cortical activity, as measured by slow wave slopes. We suggest that slow wave slope may be an even more sensitive marker of sleep homeostasis than SWA, since their slope was steeper in early sleep compared to late sleep even after the two conditions were matched for amplitude and SWA (Riedner et al., 2007; Vyazovskiy et al., 2007c). As traveling slow waves in the developing neocortex may be important for maturation of cortical circuits (Conhaim et al., 2010), spatial neuronal synchrony during sleep may be important for some aspects of plasticity and ultimately to the function of sleep. However, such increased sensitivity would be expected if the slope of the slow waves reflects some basic cellular and network phenomena, for example, the efficacy of corticocortical connectivity. Therefore, next, we asked whether cortical net synaptic strength indeed increases during wake and decreases during sleep.

## Homeostatic sleep pressure is reflected in slopes of the early and late components of electrically evoked cortical responses

If wake and sleep are associated with a net increase and decrease of synaptic strength, respectively, then sleep–wake history should be

reflected in the parameters of cortical evoked potentials. This hypothesis is based on the notion that the amplitude or the slope of excitatory postsynaptic potential (EPSP) or field potentials increased as a result of high-frequency tetanization of afferent pathways in hippocampal slices (Alger and Teyler, 1976), cortical slices (Aizenman et al., 1996; Artola et al., 1996; Lee et al., 1991; Rioult-Pedotti et al., 1998), in the hippocampus *in vivo* (Abraham et al., 1985; Bliss and Collingridge, 1993; Bliss and Lomo, 1973), and in the cortex *in vivo* (Beiko and Cain, 1998; Glazewski et al., 1998; Iriki et al., 1991). Empirical data and computational experiments show that the time derivative, that is, the slope, of EPSP is proportional to the amplitude of transmembrane currents (Araki and Terzuolo, 1962; Rall, 1967). It has been postulated that neuronal plasticity is manifested in long-term potentiation (LTP) and long-term depression (LTD) of synaptic transmission, which involve rapid adjustments in the strengths of individual synapses in response to specific patterns of correlated synaptic activity (Stellwagen and Malenka, 2006), or *in vivo* experience (Rioult-Pedotti et al., 2000; Whitlock et al., 2006). Since active wake is likely associated with learning, and most learning occurs through potentiation, it can be expected that wake would lead to potentiation of cortical circuits (Tononi and Cirelli, 2003, 2006). The hypothesis that waking, which is characterized by increased norepinephrine modulation (Armstrong-James and Fox, 1983; Berridge and Waterhouse, 2003; Jones, 1991; McCormick et al., 1991), is associated with synaptic potentiation (Tononi and Cirelli, 2006) was supported by the observation that cortical catecholaminergic depletion disrupts plasticity (Bear and Singer, 1986), and affects waking-related gene expression (Cirelli et al., 1996, 2004), and subsequent increase in sleep SWA (Cirelli et al., 2005). Consistently, it has recently been shown that a wake-dependent increase in another well-known arousal-related neuromodulator histamine (Jones, 2005; McCormick,

1992a) promoted hippocampal LTP in freely moving rats (Luo and Leung, 2010).

To evaluate changes in synaptic efficacy as a function of preceding wake and sleep, we implanted two groups of rats with bipolar concentric electrodes for electrical stimulation and chronic intracortical local field potential (LFP) recordings (Vyazovskiy et al., 2008). We recorded LFPs from the frontal cortex on one side of the brain after electrical stimulation of the opposite side in quietly awake rats (Vyazovskiy et al., 2008), and measured the slope of the first negative component of this transcallosal evoked response after several hours of continuous waking and sleep. We hypothesized that, in analogy with LTP induction, increased slopes of the evoked responses after wake would reflect stronger corticocortical synapses. Indeed, we found that the slope of the first LFP component increased on average by 22% from the beginning to the end of the continuous waking period (Vyazovskiy et al., 2008)—an increase of magnitude similar to that recently found in the hippocampus *in vivo* after physiological learning (Whitlock et al., 2006). By contrast, in rats that had been almost continuously asleep during the first 4 h of the light phase, the slope of the first LFP component decreased by almost 20% between the two recording sessions. Thus, an electrophysiological indicator of synaptic efficacy—the slope of the early component of cortical evoked potentials—was high after spontaneous wakefulness and low after spontaneous sleep. Moreover, the increase in slope correlated positively with preceding waking duration, whereas the magnitude of its decline was determined by the duration of preceding NREM sleep (Vyazovskiy et al., 2008). Crucially, the increase in the slope of the LFP response after a period of waking positively correlated with SWA at the beginning of the subsequent sleep period, while the decrease in the slope correlated positively with the decrease in SWA and slow wave slopes during sleep (Vyazovskiy et al., 2008). Thus, the changes in synaptic efficacy could be revealed both with electrically evoked and spontaneously generated volleys (Vyazovskiy et al., 2008).

We noticed that if the intensity of electrical stimuli is sufficiently high, the early, presumably monosynaptic, negative potentials are followed by a large, ∼150 ms-long depth-positive waves (Fig. 3a), similar to previously described late potentials evoked by electrical stimulation in slices or under anesthesia (Chang, 1953; Contreras and Steriade, 1995; McCormick, 1992b). The late cortical potential is known to be strongly attenuated in active waking, is related to the suppression of multiunit activity (Vanderwolf et al., 1987; Fig. 3b), and is considered a population inhibitory postsynaptic potential, occurring as a result of polysynaptic activation of cortical interneurons (McCormick, 1992b). A similar cortical potential was also recorded after thalamic stimulation that evokes hyperpolarization of neurons in the deep cortical layers (Ohsaki and Iwama, 1961). Intriguingly, we found that the slope of the late potential was consistently steeper after a period of wakefulness and decreased after sleep (Fig. 3c and d), just like the slope of sleep slow waves (Vyazovskiy et al., 2007c) or the slope of early monosynaptic potentials (Vyazovskiy et al., 2008).

While specific cellular and network mechanisms underlying the slopes of the early and late
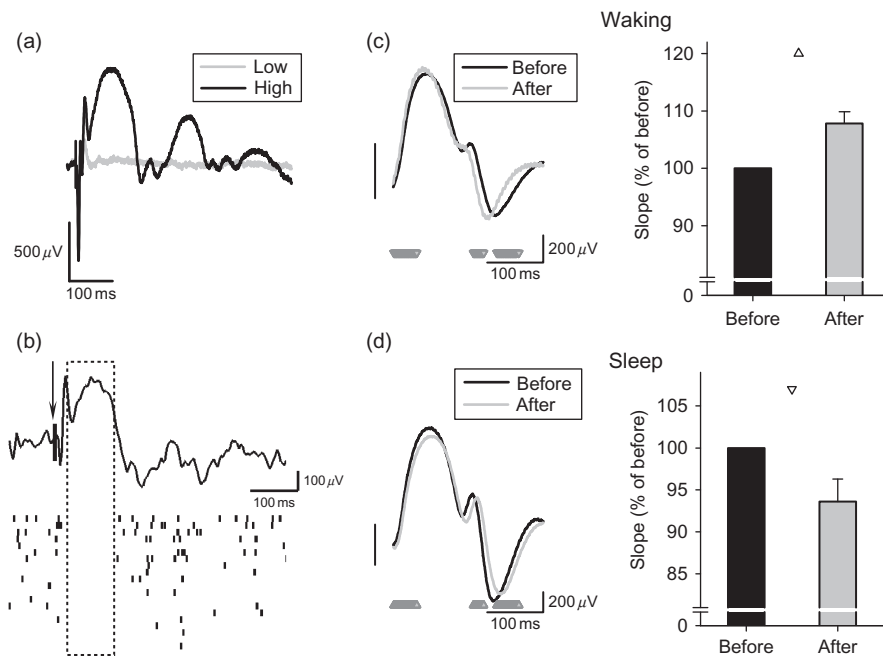


Fig. 3. Sleep–wake history affects the late component of transcallosal evoked response. (a) Individual representative evoked responses after stimulation at low and high intensity. (b) Representative individual transcallosal evoked LFP response and the corresponding neuronal activity (raster below the LFP trace, each bar is a spike). Note that all neurons remain silent for about 100 ms after the stimulus (arrow), during the positive LFP wave (boxed). (c) Left: Average late component of the evoked response before and after a 4-h period of waking. Mean values ($n=15$ rats). Triangle depicts significant difference (paired $t$-test). Right: Slopes of the late component before and after 4 h of waking. Values are mean+SEM ($n=15$) expressed as percentage of the "before" condition ($=100\%$). (d) Left: Average late component of the evoked response before and after a 4-h period of consolidated sleep. Mean values ($n=24$ rats). Triangles depict significant differences (paired $t$-test). Right: Slopes of the late component before and after 4 h of sleep. Values are mean+SEM ($n=24$) expressed as percentage of the "before" condition ($=100\%$).

component in waking and the slope of slow waves during sleep are presumably different, their consistent changes in relation to the sleep/wake history unequivocally indicate that the state of cortical networks is altered following waking and sleep in an opposite manner. Intracortical stimulation appears a promising tool to investigate dynamic changes in the responsiveness of cortical networks as well as the mechanisms of synaptic interactions after sleep and waking. The question then arises: what are the consequences of increased synaptic strength after waking on brain functioning?

## Increased homeostatic sleep pressure affects cortical plasticity

An important property of the potentiation of cortical synapses is saturation, which is manifested in a relative inability to further enhance the amplitude of synaptic currents in the response to the stimulus of increasing intensity or frequency (Heynen and Bear, 2001). Saturation of both LTP and LTD after repeated electrical or pharmacological stimulation was found in different species and preparations (Doyere et al., 1997; Frey et al., 1995; Heynen and Bear, 2001; Lante et al., 2006; Moser et al., 1998). We hypothesized therefore that if wake is associated with a physiological increase in synaptic strength, then the experimentally induced LTP should be, at least partially, blocked after waking and, on the contrary, facilitated again after sleep.

While mechanisms underlying satiability of LTP are not yet clear, it appears to be a crucial property for establishing a functional link between LTP-like processes and learning. It was predicted that an experimental treatment that results in LTP saturation should produce deficits in learning of a task that requires an involvement of the corresponding neuronal circuit (Moser and Moser, 1999). Indeed, there is compelling evidence that by triggering LTP-like mechanisms, learning can strengthen synapses to near the maximum of their modification range, impairing the

further induction of LTP (Foster et al., 1996; Rioult-Pedotti et al., 2000; Sacchetti et al., 2002). Several studies have shown conclusively that LTP or LTD is strongly affected by learning and vice versa (Barnes et al., 1994; Castro et al., 1989; Makhracheva-Stepochkina et al., 2008; Moser and Moser, 1999; Moser et al., 1998; Rioult-Pedotti et al., 1998, 2000; Stefan et al., 2006; Whitlock et al., 2006; Ziemann, 2004). There is also indirect evidence suggesting that LTP-like plasticity may be partially saturated after wakefulness. For example, several *in vitro* studies in the hippocampus showed that insufficient or fragmented sleep impairs the induction of LTP but favors the induction of LTD (e.g., Campbell et al., 2002; Kopp et al., 2006; McDermott et al., 2003; Tartar et al., 2006).

The occlusion of electrically induced LTP after wake is therefore a key test to prove that staying awake shares the same mechanisms underlying LTP. To address this possibility, we used an LTP induction paradigm as in Racine et al. (1995) and Vyazovskiy et al. (2008). First, we found that after a period of waking, the magnitude of LTP induction was smaller compared to that seen after the period of sleep (Fig. 4a and b). Next, to prove that this effect was indeed sleep related, we correlated the magnitude of the slope decline after sleep with the magnitude of its subsequent increase after LTP and found that they were positively correlated (Fig. 4c and d). In other words, the more synaptic strength declined during sleep, the larger was the capacity for its subsequent increase after LTP. This result suggested that sleep might restore the ability to undergo further cortical potentiation. Finally, we observed that NREM SWA was also increased after LTP by $\sim 12\%$ as compared to pre-LTP levels ($p < 0.05$), suggesting that local strengthening of synapses as a consequence of the LTP induction could have resulted in a more intense local sleep.

Caution is warranted, however, in interpreting changes of cortical evoked field potentials, as they might be affected by behavior, brain temperature,
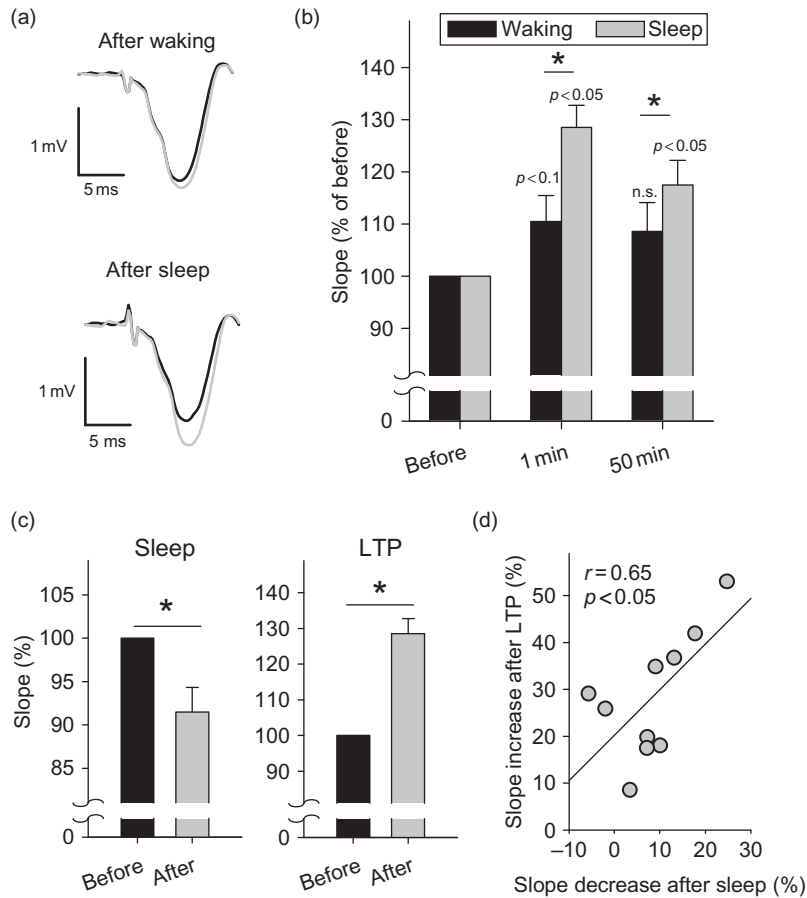
Fig. 4. LTP is partially occluded after waking. (a) Representative average evoked LFPs from the right frontal cortex induced by transcallosal stimulation of the left frontal cortex in a quietly awake rat before (black) and after (gray) LTP induction. Note a minor change in the response when LTP induction was attempted after waking (top), and a substantial increase when LTP was induced after a period of sleep (bottom). (b) Slopes of evoked potentials immediately before and after LTP induction (1 min, 50 min) attempted following a period of waking or sleep. Values are mean ± SEM ($n = 10$) expressed as percentage** of the corresponding "before" condition ($= 100\%$). (c) Left: Slopes of evoked LFPs before and after a consolidated 4-h period of sleep. Right: Slopes of evoked LFPs before and after LTP induction (mean values, SEM, $n = 10$). Asterisks: $p < 0.05$; two-tailed paired $t$-test. (d) Relationship between the decrease in LFP slope after sleep and the following increase after LTP, shown in (c). Each circle is an individual rat ($n = 10$).

and background activity. Moreover, they reflect the summed activity of a relatively large heterogeneous population of neurons and may be confounded by antidromic or polysynaptic components. Thus, a recent study (Liu et al., 2010) used a direct measure of synaptic efficacy, that is, measured the effects of sleep/wake on miniature excitatory postsynaptic currents (mEPSCs). This is because the analysis of mEPSCs amplitude and frequency is one of the best established methods to directly measure synaptic strength: changes in mEPSCs frequency are thought to result from modification of the presynaptic component of synaptic transmission, while

amplitude changes indicate alterations in the postsynaptic component. The study used coronal cortical slices from the frontal cortex of rats, and compared mEPSCs after wake (at night) versus sleep (during the day), after sleep versus sleep deprivation (both during the day), and after sleep deprivation versus recovery sleep (both during the day). In all cases, it was found that frequency and amplitude of mEPSCs recorded from layer II/III cortical neurons increased after wake and sleep deprivation as compared to sleep, and another experiment confirmed these results in sleep-deprived mice compared to sleeping mice (Liu et al., 2010).

Thus, this collective evidence, encompassing spontaneous and evoked cortical activity at the level of sleep slow waves, the early and late components of LFPs as well as of spontaneously occurring mEPSCs, suggests that physiological waking is associated with net synaptic potentiation of cortical synapses. It is well known that EEG and LFP slow waves as well as evoked field potentials are large-scale phenomena, which reflect concerted, mainly postsynaptic activity of relatively large populations of cortical neurons. The question remains, how does the spiking activity of individual cortical neurons change in relation to the sleep–wake history?

## Homeostatic sleep pressure is reflected in synchronization of cortical neurons

It is well known that cortical activity consists of ongoing changes of membrane potentials and spiking of individual neurons that are tightly linked to vigilance state, movement, behavior, and the presence or absence of sensory stimuli (MacLean et al., 2005; Petersen et al., 2003; Sakata and Harris, 2009; Steriade et al., 2001; Vyazovskiy et al., 2009b). The fluctuations in neuronal activity are not only caused by external sensory stimuli that reach the neocortex via thalamocortical projections (Crunelli and Hughes, 2009; Sakata and Harris, 2009; Steriade et al., 1993b) but can arise also

spontaneously from local intracortical networks (Petersen et al., 2003). What are the factors that determine spontaneous firing patterns of cortical neurons? This question is relevant since changes of the internal brain state affect markedly cortical responsiveness (Hasenstaub et al., 2007; Petersen et al., 2003; Vyazovskiy et al., 2009a; Watson et al., 2008). Moreover, periodic synchronous increases of neuronal activity can recruit large distributed cortical areas (Diesmann et al., 1999; Ikegaya et al., 2004; Thiagarajan et al., 2010), while decreases in firing can contribute significantly to energy savings (Attwell and Laughlin, 2001; Sokoloff et al., 1977).

During NREM sleep large populations of neurons transition quasi-synchronously between periods of elevated activity (ON periods) and neuronal silence (OFF periods; Ji and Wilson, 2007; Sirota and Buzsaki, 2005; Vyazovskiy et al., 2009b). There is a close temporal relationship between ON and OFF periods, the underlying cortical slow oscillation, and simultaneously recorded slow waves (Amzica and Steriade, 1998; Contreras and Steriade, 1995). Specifically, the surface negativity in the EEG signal (or depth positivity in the LFP) corresponds to the DOWN state of cortical neurons as recorded intracellularly, and to the suppression of spiking activity as recorded extracellularly, suggesting that EEG or LFP slow waves are a reflection of near-synchronous transitions between UP and DOWN states in large populations of cortical neurons (Burns et al., 1979; Calvet et al., 1973; Contreras and Steriade, 1995; Ji and Wilson, 2007; Luczak et al., 2007; Molle et al., 2006; Mukovski et al., 2006; Murata and Kameda, 1963; Noda and Adey, 1973; Steriade et al., 1993b, 2001). However, until recently, it was unknown whether cortical neurons fire differently depending on how long the brain has been awake or asleep.

In order to address this question, we implanted chronic microwire arrays in the frontal and parietal cortex and recorded cortical unit activity along with the EEG and LFPs during spontaneous sleep and wake in freely behaving rats (Vyazovskiy

et al., 2009b). In NREM sleep, a striking difference was apparent between early and late sleep: during early sleep, when large slow waves predominate, short ON periods alternated frequently with relatively long OFF periods, whereas in late sleep, when large slow waves are rare, ON periods were longer and only occasionally interrupted by short OFF periods (Fig. 5a). Quantitative analysis revealed that both the duration of population ON and OFF periods changed as a function of preceding sleep and waking. During early sleep, when most neurons were active or silent synchronously, ON periods were short and frequent. During late sleep, the periods of activity

and inactivity of individual neurons became progressively less synchronized (Fig. 5b). Notably, the changes in the number and duration of ON and OFF periods were correlated with the decrease in SWA in the course of sleep (Vyazovskiy et al., 2009b), suggesting that homeostatic changes in sleep SWA arise from an altered pattern of cortical neuronal activity.

It was apparent that in early sleep, following prolonged bouts of wakefulness, individual neurons stopped or resumed firing in near synchrony with the rest of the population. By contrast, during late sleep, following prolonged bouts of NREM sleep, the time of entry into
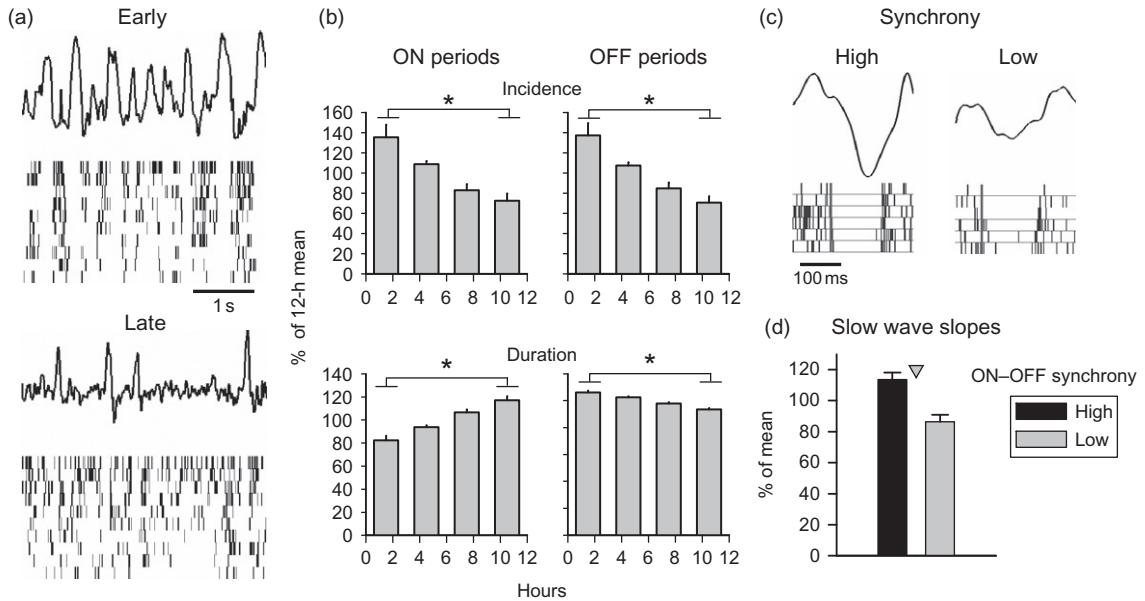


Fig. 5. Sleep–wake history affects cortical neuronal firing patterns. (a) 4-s frontal LFP records in early and late NREM sleep. Corresponding raster plots of spike activity (10 units are shown, each vertical line is a spike) are shown below the LFP traces. Note the close temporal relationship between silent (OFF) periods and the positive phases of LFP slow waves in NREM sleep. (b) Mean values ($n=6$ rats) of incidence and duration of the ON and OFF periods shown for consecutive 3-h intervals during the light period expressed as percentage of the corresponding mean 12-h value. (c) Representative examples of a high-amplitude slow EEG wave with steep slopes typical of early sleep (left) and low-amplitude slow wave typical of late sleep (right), and the corresponding OFF periods (raster plots, each bar is a spike). Note that neurons are more synchronous at the ON–OFF and OFF–ON transitions during the high-amplitude slow wave. (d) Mean slopes of slow waves corresponding to synchronous ON–OFF transition (high: top 50%) and asynchronous ON–OFF transitions (low: bottom 50%). Neuronal synchrony was computed as the average latency between the last spikes of individual neurons to the onset of the population OFF period. Note that high neuronal synchrony is associated with steeper slow wave slopes (triangle, $p < 0.01$). Mean values, $n=6$ rats.

ON and OFF periods was much less synchronous (Vyazovskiy et al., 2009b). The changes in neuronal synchrony at the ON–OFF and OFF–ON transitions appeared to be related to the morphology of slow waves. Specifically, we found that firing with high synchrony was associated with steep slopes of simultaneously occurring EEG slow waves, whereas low synchrony was associated with decreased slopes of the corresponding slow waves (Fig. 5c and d). Finally, we found that the changes in neuronal synchrony during sleep correlated with the changes in both slow wave slopes and SWA (Vyazovskiy et al., 2009b). These observations supported the results of computer simulations (Esser et al., 2007) and provided direct *in vivo* evidence that EEG slow wave slopes, as well as their changes as a function of the sleep/wake history, are determined by the rate of recruitment and decruitment of cortical neurons into the slow oscillation. Thus, the sleep–wake history, that is associated with plastic processes in cortical networks, is reflected also in neuronal synchrony.

## Concluding remarks

Homeostatic sleep regulation is manifested in predictable changes of sleep EEG SWA. A crucial question is how the changes in SWA arise from cortical networks, and why SWA is affected by the sleep–wake history. Recent studies began to elucidate cellular and network mechanisms underlying the changes in EEG slow waves that bring about well-known homeostatic changes of SWA. In this review, we presented and discussed electrophysiological correlates of sleep homeostasis at three levels: sleep EEG/LFP slow waves, evoked cortical activity, and spontaneous neuronal firing patterns. The principal observations presented here can be summarized as follows: physiological or prolonged waking leads to (i) increased incidence and steeper slopes of EEG slow waves, (ii) increased slopes of the early and late components of evoked field potentials, (iii) partial LTP occlusion, and (iv) increased synchrony among cortical neurons. Crucially, all these changes were reversed by sleep and correlated with changes of the traditional marker of sleep homeostasis—SWA. How can all these changes at different levels be integrated in one coherent picture? One possibility is that increased net cortical synaptic strength during waking (Bellina et al., 2008; Cirelli et al., 2004; De Gennaro et al., 2008; Gilestro et al., 2009; Hanlon et al., 2009; Huber et al., 2004, 2006, 2007a,b; Liu et al., 2010; Vyazovskiy et al., 2000, 2008) is the mechanism directly underlying increased neuronal synchrony, which then translates in more frequent incidence of high-amplitude slow waves in subsequent sleep, leading in turn to homeostatically increased sleep SWA (Fig. 6).

The essential steps could be the initiation of the UP state at the level of individual cortical neurons and its subsequent propagation across large cortical assemblies. It has been shown that the onset of the UP state is caused by a gradual membrane depolarization that builds up due to the summation of subthreshold events, which occur as a result of spontaneous release of neurotransmitter (Chauvette et al., 2010; Timofeev et al., 2000). Once a subset of neurons enters an UP state, it might be capable of recruiting other neurons, primarily those that, as suggested before, receive most dense or strongest projections from other neurons (Chauvette et al., 2010; Timofeev et al., 2000). Similarly, in humans and rats, a volley of locally applied electrical or magnetic activity that is sufficiently strong to excite and recruit a large cortical neuronal population is capable of inducing full-fledged EEG slow waves during natural sleep (Massimini et al., 2007; Vyazovskiy et al., 2009a). Subsequently, activation can spread through local cortical networks in a sequential order (Luczak et al., 2007), presumably along the gradient of strongest connections within a network. It can be expected that the more frequent occurrence of higher-amplitude mEPSCs after prolonged waking (Liu et al., 2010) would likely
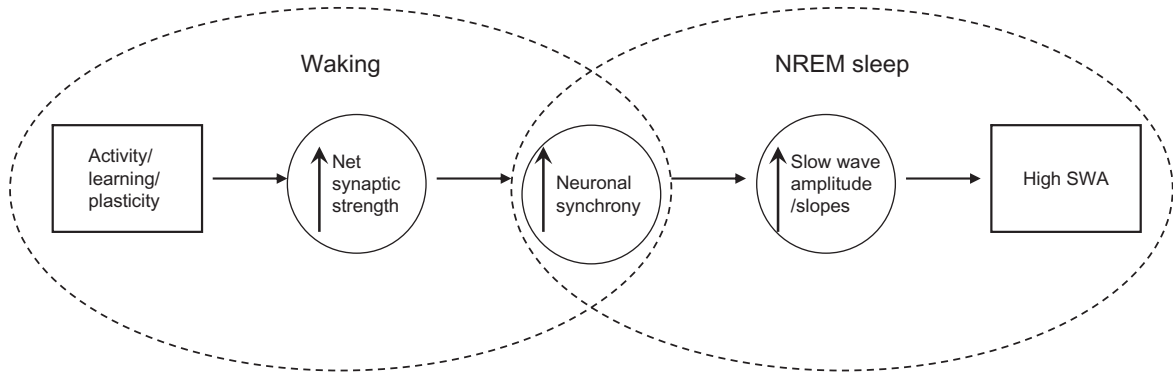
Fig. 6. Waking activities result in a homeostatic increase in NREM sleep SWA. Waking activity is associated with learning/plasticity that lead to increased cortical net synaptic strength. More efficient neuronal connectivity results in more efficient neuronal synchronization, which is manifested in faster rates of decruitment and recruitment of neurons into the slow oscillation in NREM sleep. The occurrence of frequent prolonged periods of neuronal population silence is manifested in the EEG signal as frequent incidence of high-amplitude slow waves with steep slopes. High-amplitude slow waves in turn account for high spectral power in SWA band.

lead to a more frequent occurrence of neuronal UP states, and if the connections between neurons are strong, this would result in faster rates of their recruitment in the population ON periods (Esser et al., 2007; Riedner et al., 2007; Vyazovskiy et al., 2007c, 2009a,b), and in their efficient propagation across large cortical areas (Massimini et al., 2004; Vyazovskiy et al., 2009a). Thus, more frequent EEG slow waves with higher amplitude and steeper slopes would occur in the EEG signals, resulting in higher SWA.

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