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REVIEW
Sleep function: current questions and new approaches

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Abstract

The mammalian brain oscillates through three distinct global activity states: wakefulness, non-rapid eye movement (NREM) sleep and REM sleep. The regulation and function of these 'vigilance' or 'behavioural' states can be investigated over a broad range of temporal and spatial scales and at different levels of functional organization, i.e. from gene expression to memory, in single neurons, cortical columns or the whole brain and organism. We summarize some basic questions that have arisen from recent approaches in the quest for the functions of sleep. Whereas traditionally sleep was viewed to be regulated through top-down control mechanisms, recent approaches have emphasized that sleep is emerging locally and regulated in a use-dependent (homeostatic) manner. Traditional markers of sleep homeostasis, such as the electroencephalogram slow-wave activity, have been linked to changes in connectivity and plasticity in local neuronal networks. Thus waking experience-induced local network changes may be sensed by the sleep homeostatic process and used to mediate sleep-dependent events, benefiting network stabilization and memory consolidation. Although many questions remain unanswered, the available data suggest that sleep function will best be understood by an analysis which integrates sleep's many functional levels with its local homeostatic regulation.

Introduction

Sleep's contributions to mental and physical health have been established through large-scale epidemiological studies of normal sleep and clinical studies documenting the adverse health consequences of disordered sleep (Drake *et al.*, 2003; Reid *et al.*, 2006; Bliwise & Young, 2007). Understanding the mechanisms which mediate these associations holds great promise for improving both physical and mental health. This, however, will require a better insight into the basic functions of sleep for the body and the brain.

A shared interest in sleep's contribution to brain function and the underlying neuronal and molecular mechanisms brought together about 140 sleep scientists and clinicians, including 18 speakers, in Lausanne (see Editorial). The focus of this meeting was on research into the neural functions of sleep with an emphasis on the putative role of sleep in neuronal plasticity. The researchers agreed that sleep serves important functions for the brain but, when asked what these functions are, the simple consensus that it was 'all for plasticity' did not emerge and lively discussions broke out instead. For the purpose of this review we discuss broad questions of sleep regulation and function in the context of questions that arose during our discussion, during the presentations of new research findings at the meeting, and in selected recent publications relevant to the role of sleep in neuronal plasticity.

Background and traditional questions about sleep function

Sleep can be defined on the basis of behavioural criteria (Table 1) and on the basis of electrophysiological criteria (Table 2). Traditionally, questions about sleep and sleep's function are asked at the level of the whole organism:

1. Do all animals sleep and is sleep function invariable across species? Where in the phylogenetic tree does sleep emerge?
2. Should sleep be viewed as a recovery process, i.e. does sleep contribute to brain function by reversing some of the consequences of wakefulness? Alternatively, is sleep a distinct state, just as hibernation is a different state, not thought to directly contribute to waking brain function?
3. Irrespective of the nature of its function, is sleep an indispensable state, endowed with unique properties that directly mediate functions which could not be executed during wakefulness? Alternatively, is sleep merely a permissive state, during which for example recovery events optimally occur because of reduced interference by the sensory and processing activities of wakefulness?

Many of these traditional sleep questions have not yet been answered definitely, but this should not be taken as evidence for lack of progress in the quest for sleep's functions (Siegel, 2005; Allada & Siegel, 2008). The easiest way to tackle sleep is from its less elusive end: sleep need. Indeed, the study of sleep's function has relied heavily on the use of the sleep deprivation paradigm. This paradigm has established that wakefulness is accompanied by an increase in sleep propensity (Table 2) and sleep loss is compensated for by a subsequent increase in sleep intensity and/or duration. The term 'sleep propensity' refers to the likelihood of sleep, at any level of organization, global or local. At the behavioural level, the latency to fall asleep can be measured and human subjects can report on their level of subjective sleepiness, and both measures can be used as indicators of sleep propensity. At the neuronal and circuitry levels, bioelectrical events associated with sleep can be measured. Thus, both

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Table 1. Behavioural criteria of sleep

Species-specific posture
Behavioural quiescence
Reversible upon stimulation
Elevated arousal threshold
Rebound after deprivation

global and local correlates of sleep propensity can be studied and will be discussed in this review.

The past decade saw an impressive expansion of the spatial and temporal domains within which sleep and the effects of sleep deprivation are analyzed. Sleep and sleep loss have correlates and consequences over a wide temporal range, e.g. seconds (Destexhe *et al.*, 2007), days (Belenky *et al.*, 2003) and months (Gais *et al.*, 2007). Furthermore, sleep and sleep loss are accompanied by changes at many levels of functional organization, from gene expression to network connectivity, from memory consolidation to emotions. Within a given level of organization, sleep and sleep loss have correlates in many different variables, e.g. alterations in cytokine production and in the dynamics of electric field potentials in neuronal networks.

We will focus on some of the local aspects of sleep regulation that have recently emerged. These local aspects have consequences for our view on what constitutes the minimal unit in which sleep can be observed and studied. Local aspects of sleep regulation also have implications for the discussion on whether sleep is regulated in a 'top-down' or 'bottom-up' manner. One of the most robust markers of change in sleep propensity is a change in the slow or delta

Table 2. Definitions of terminology and concepts used in sleep research

Electrophysiologically defined sleep phenomena	
Electroencephalogram (EEG)	Measure of electrical potentials at the surface of the head
Vigilance (or behavioural) state	Corresponds to a set or constellation of behavioural and physiological variables. Experimentally assessed by the coordinated recording and analysis of the EEG and the electromyogram (EMG) of a face or neck muscle, as well as by the recording of eye movement, i.e. the electrooculogram. Three vigilance states are distinguished in mammals and birds: wakefulness, non-rapid eye movement (NREM) sleep and REM sleep
Wakefulness	Vigilance state characterized by a low amplitude, high frequency, mixed EEG pattern
NREM sleep	Vigilance state characterized by high amplitude, low frequency oscillations, dominated by the slow/delta and spindle oscillations (see below) and a relaxed muscle tone. In animal studies that use the term paradoxical sleep (see below), NREM sleep is referred to as slow wave sleep
REM sleep	Vigilance state characterized by an EEG resembling wake or stage-1 sleep in humans, in association with muscle atonia. In rodents, REM sleep is dominated by theta oscillations (see below). In some animal studies REM sleep is referred to as paradoxical sleep
Slow wave sleep (SWS)	The deepest stages of NREM sleep (stages 3 and 4 in humans) during which slow/delta waves are especially prevalent and arousal thresholds highest
Slow waves (or delta oscillations) (in this review referred to as 'slow/delta waves')	EEG oscillations within the 0.75–4.5 Hz frequency range. High amplitude slow/delta waves are a defining feature of NREM sleep stages-3 and 4, i.e. SWS
Slow wave activity (SWA) (or delta power)	Mathematical variable extracted from the EEG which quantifies the amplitude and prevalence of slow/delta waves. The relative value of SWA at the onset of NREM sleep can be accurately predicted on the basis of prior wake duration. Because of this, SWA is widely acknowledged to reflect sleep need and is thought to reflect a sleep homeostatic process
The slow (< 1 Hz) oscillation	Rhythmic alternation in the activity of cortical neurons during NREM sleep. Intervals of high activity during which bursts of action potential occur ('up states') alternate with intervals of almost complete silence and membrane hyperpolarization ('down states'). The slow (< 1 Hz) oscillation is assessed by intra- or juxtacellular recordings
Sleep spindles	Transient (0.5–2 s), spindle-shaped 10–15 Hz EEG features which prevail during early sleep (stage-2 in humans), and also herald NREM-REM sleep transitions. Sigma activity refers to the prevalence and amplitude of spindle oscillations in the 10–15 Hz range
Theta oscillations	EEG oscillations in the 5–10 Hz range. In rodents coherent theta oscillations are characteristic of REM sleep and exploratory waking behaviour and are thought to be of hippocampal origin. In humans, the origin of the EEG activity in this frequency range is less clear
Definitions of concepts	
Sleep propensity	Probability or tendency to be in or to transition into a sleep state. At the global level sleep propensity can be assessed behaviourally. At the local level, it can be assessed using electrophysiological markers of the sleep state
Synaptic strength (or weight)	Input–output relationship of a synapse
Synaptic plasticity	Ability to change synaptic strength and/or number
Hebbian (experience-dependent) plasticity	Model by which correlated presynaptic and postsynaptic activity strengthens a synapse whereas uncorrelated activity weakens it. Long-term potentiation (LTP) and long-term depression (LTD) are electrophysiological assays thought to measure Hebbian plasticity
Homeostatic plasticity	Non-Hebbian regulatory mechanisms thought to counteract the destabilizing effects of experience-dependent, Hebbian events and maintain postsynaptic excitability within a functional range. This term encompasses a wide variety of processes, including synaptic scaling
Synaptic scaling	Mechanism thought to adjust all of a neuron's synapses up or down in strength proportionally, so that while average synaptic strength is regulated homeostatically, the relative strengths of individual synapses remain constant

(slow/delta) waves measured by electroencephalographic (EEG) recordings (see Table 2 for definitions). We will discuss the proposed relationships between sleep slow/delta waves and changes in neuronal network connectivity. From considerations about sleep-dependent synaptic strength regulation and the role of sleep-regulatory substances, we will move on to models of the role of sleep in memory consolidation. In this context, the two types of sleep, rapid eye movement (REM) and non-REM (NREM) sleep, must be distinguished. Throughout, we will continue to discuss the functional significance of the markers of sleep and sleep homeostasis we have been using.

It has been established that sleep–wake regulation is closely linked to circadian rhythmicity and some of the molecular mechanisms underlying circadian processes have been elucidated (Takahashi *et al.*, 2008). This, together with the recognition that circadian rhythmicity is also about temporal organization of processes that contribute to higher brain functions such as memory and cognition (Barnard & Nolan, 2008), and the recognition that some of the proteins involved in circadian rhythm generation also play a role in the homeostatic regulation of sleep (Franken & Dijk, this issue), has led to a renewed cross-fertilization between these two research areas. This review, however, will not discuss the mechanisms of circadian rhythmicity in any detail. Furthermore, following early work by Tobler (1983) and Kaiser & Steiner-Kaiser (1983), recent years have witnessed the introduction of simple model organisms such as *Drosophila melanogaster* (Shaw *et al.*, 2000) and *Caenorhabditis elegans* (Zimmerman *et al.*, 2008) to study the genetic and molecular aspects of sleep regulation as well as sleep's contribution to central nervous system function and development. Recently, birds have appeared as major players in the sleep and memory consolidation field (Jackson *et al.*, 2008; Shank & Margoliash, 2009). In this meeting, however, the emphasis was on new approaches in the study of sleep in mammals. Finally, the role of sleep in glucose homeostasis, metabolism and other physiological processes is being increasingly studied (e.g. Dijk, 2008; Tasali *et al.*, 2008), but this review will focus on the brain.

We hope that an overview of the current approaches and concepts may be useful at a time when scientists from many disciplines enter the sleep field and new models, new methods and new reduced preparations for the study of sleep function are introduced at a high rate.

New approaches to the study of sleep function: is sleep a global or local phenomenon?

The traditional definitions of sleep are based on observed behavioural and physiological phenomena in the whole organism. Vigilance states (Table 2) are defined as constellations of variables associated with these phenomena, and in mammals and birds three vigilance states are distinguished: wakefulness, NREM sleep and REM sleep (Table 2). The animal is in one, and only one, of these vigilance states at a time. In other words, vigilance states have been considered temporally discrete and spatially global states, but recent observations indicate that these concepts may require some refinement.

The discrete nature of sleep and wake states is challenged by the following observations:

1. In the diseased brain elements of different vigilance states can occur simultaneously. For example, in Parkinson's disease, and in general in REM sleep behaviour disorder, motor actions occur while the patient is in REM sleep (Arnulf *et al.*, 2008). Clinical recognition of mixed states in sleep disorder patients led to the term 'status dissociatus' as early as 1991 (Mahowald & Schenck, 1991).
2. Below the surface of observable behaviour, when analyzed with a temporal resolution in the minutes to hour range, vigilance states are not invariable. A defining feature of NREM sleep is the occurrence of high-amplitude slow/delta waves. Within each NREM sleep episode, slow-wave activity (SWA), also called delta power, an EEG measure of power in the 0.75–4.5 Hz frequency range (Table 2), gradually rises and abruptly declines prior to the onset of REM sleep (Fig. 1). Furthermore, in the course of the resting period (e.g. a night for humans) SWA declines over consecutive NREM–REM sleep cycles. In contrast, wakefulness is characterized by a low-amplitude, high-frequency EEG pattern but the contribution of slow/delta and theta oscillations (5–10 Hz, Table 2) increases as the duration of wakefulness increases. Thus, as wakefulness progresses the EEG becomes more 'sleep-like' (Franken *et al.*, 1991; Cajochen *et al.*, 2002) and as NREM sleep progresses, the EEG becomes more 'wake-like' (Dijk *et al.*, 1997).
3. When analyzed with a higher temporal resolution, of the order of seconds and less, the behaviour of cortical neurons during NREM sleep is highly dynamic, yielding bouts of widespread high-amplitude synchronized fluctuations in activity. These fluctuations, known as the 'slow (< 1 Hz) oscillation' (Table 2) with a period of ~2 s (Steriade *et al.*, 1993), consist of intervals with high activity during which bursts of action potential occur ('up states') alternating with intervals of almost complete silence and membrane hyperpolarization ('down states'). These synchronized alternations of up and down states appear in the EEG as slow waves and spread coherently throughout the cortex as a travelling wave (Massimini *et al.*, 2004). It has been suggested that the 'up states' of slow-wave sleep (SWS; Table 2) are dynamically similar to wakefulness and provide a context for the 'replay' of firing sequences that occurred in the waking animal, for example during execution of a specific task. These 'fragments of wakefulness' may contribute to memory consolidation (Destexhe *et al.*, 2007). According to this interpretation, and at this temporal resolution, we are partly awake when we are asleep but are not aware of this!

The global nature of sleep and wake states has also been challenged:

1. Local activation of specific brain regions during wakefulness, through unilateral vibrations of hands (Kattler *et al.*, 1994) or twitching of whiskers (Vyazovskiy *et al.*, 2000), leads to local increases in EEG SWA during sleep in those brain areas that were more active during wakefulness. One brain area can be more asleep than another.
2. In dolphins and other aquatic mammals, EEG-assessed NREM sleep can occur in one hemisphere while the other is awake (Mukhametov *et al.*, 1977; Lyamin *et al.*, 2008). This unequivocally demonstrates that vigilance states are not necessarily invariable in 'brain space'.
3. Sensory stimulation by whisker twitches and auditory clicks evokes local field potentials in the cortex with amplitudes which fluctuate between high and low values, be the animal awake or asleep. It has been hypothesized that these fluctuations reflect local functional state differences within individual groups of highly connected neurons called cortical columns (Rector *et al.*, 2005; Rector *et al.*, 2009, this issue). The high-amplitude responses are most prevalent during NREM sleep and, it is hypothesized, represent a sleep-like state, whereas the low-amplitude responses would indicate a wake-like state. The amplitude of these potentials fluctuates to some extent independently of overall vigilance state and can be different in the two hemispheres and even in adjacent cortical columns. This suggests that some cortical columns may be 'awake' while others are 'asleep', and this during either sleep or wakefulness.

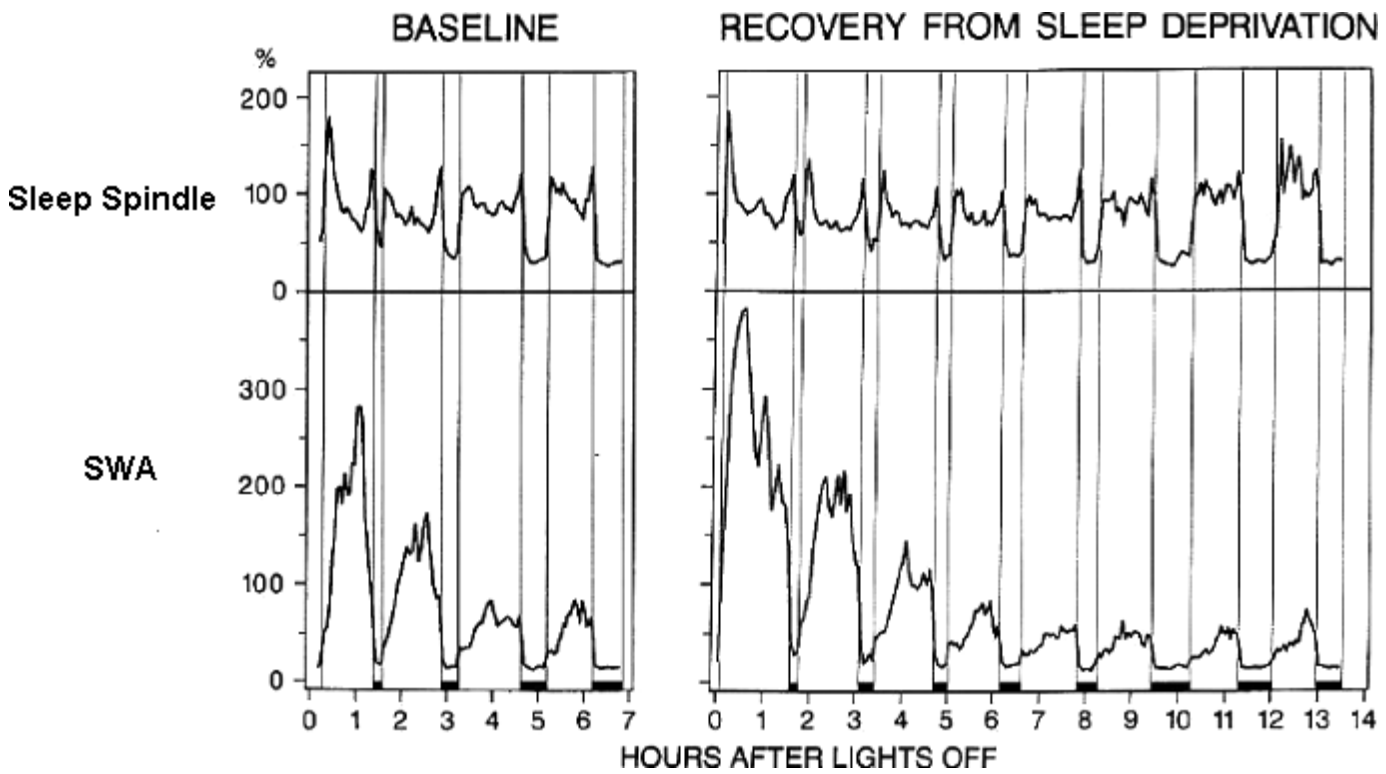

FIG. 1. Time course of SWA (power in the 0.75–4.5 Hz band; lower curves) and activity in the spindle frequency range (13.25–15.0-Hz band; upper curves) recorded under baseline conditions and after sleep deprivation (36 h of wakefulness). NREM sleep episodes were subdivided into 20 equal intervals and REM sleep episodes into five equal intervals. Mean values per interval were calculated prior to averaging across subjects (n = 8, except for cycle 8 of recovery sleep, where n = 6) and are expressed relative to the mean level in baseline NREM sleep (100%). The mean timing of REM sleep episodes is delimited by vertical lines and horizontal bars above the abscissa [Reanalysis by D. Aeschbach of the data from Dijk *et al.* (1990)]. Adapted with permission from Elsevier, © 2009 (Principles and Practice of Sleep Medicine).

These phenomena indicate that, although sleep appears in general to be a global phenomenon in both time and space, at higher temporal and spatial resolution, heterogeneity emerges. This leads to a set of new questions concerning sleep function and the level of organization considered.

Sleep function and the minimal sleep unit

Can we define a sleep unit, a minimal entity that would recapitulate the essence of sleep? Identifying the minimal sleep unit may be useful because this will help to identify protagonists, e.g. neurons, neuronal groups or bioelectrical events, which display causal relationships with sleep functions at the level of the whole organism. Do we need to define this minimal entity in both space and time? Is the minimal sleep unit a whole organism, a brain, a group of closely connected neurons, a single neuron, a synapse? Is the minimal sleep unit a minute, a second, one NREM–REM sleep cycle?

The traditional criteria for defining sleep include a species-specific posture, a reduced but reversible responsiveness to stimulation, i.e. elevated arousal threshold, and homeostatic regulation. There is some consensus that the minimal sleep unit may be smaller than the whole organism, even though a brain cannot adopt a species-specific posture. This is, however, where the consensus ends and the discussions become lively. This is in part because our preferred definition of a sleep unit may very well be influenced by our tacit or explicit assumptions about the function of sleep. To Jan Born, who studies the effects of sleep on human memory, 'sleep is a complex, systems process' (Born *et al.*, 2006) and the minimal sleep unit is the entire brain. For James Krueger and David Rector, individual cortical columns, consisting of approximately a thousand neurons in the rat, alternate between two states, wake-like or sleep-like (Krueger *et al.*, 2008; Roy *et al.*, 2008). A proponent of the hypothesis that sleep plays a key role in the regulation of neuronal connectivity and plasticity is unlikely to accept the isolated neuron as the minimal sleep unit whereas the proponents of the 'sleep replenishes energy stores of the brain' may very well accept the neuron as the minimal unit. The intermingling of descriptive and functional elements is not uncommon and even at the level of the whole organism functional elements are included in the definition of sleep. For example, current definitions of sleep include the requirement that it is 'homeostatically regulated', i.e. that loss of it must be compensated for by a subsequent increase in either its intensity or duration, or both (Tobler, 1983; Zimmerman *et al.*, 2008).

The consensus which emerged was that it is permissible that definitions of sleep contain function-oriented elements because, after all, sleep researchers search for the contribution of sleep to brain function. It is, however, questionable that we can develop a definition of the minimal sleep unit in the absence of a clear understanding of sleep's function at the level of the whole organism. Because we are in this catch-22, spending much time on the definition of the minimal sleep unit may not be productive. It may be more fruitful to accept that sleep- and wake-like phenomena can be observed in units that are smaller than an organism, a brain, a hemisphere, a network, etc. Studying sleep-like phenomena and their function in sleep units of all sizes, and relating these phenomena at the 'smaller unit level' to sleep and its functions as observed at the level of the ultimate sleep unit, i.e. the whole organism living in its 24-h environment, is the most promising avenue to further progress.

During these discussions about sleep function and the minimal sleep unit it also emerged that another contentious issue was whether we

should assume that sleep has one primary function or many. If we accept that sleep may have multiple (very important) functions, some of these functions may be fulfilled at the cellular level, e.g. energy balance-related functions, whereas other functions of sleep, e.g. plasticity or memory consolidation, may only emerge at the network or systems level. Abolishing the quest for the ultimate function of sleep may be liberating and may open our eyes to a multitude of sleep functions, but the desire to identify a primordial function of sleep remains strong because this function would have been the driver for the emergence of sleep during evolution.

'Top-down' or 'bottom-up' control of sleep–wake states?

According to some (Krueger & Obal, 1993), sleep is a self-organizing property of any viable neuronal assembly. According to this view, alternating active ('wake') and silent ('sleep') phases will emerge in any neuronal network. Sleep is thus a local network process that emerges from the bottom up and that would proceed in the absence of top-down regulation by specialized neuroanatomical circuits or nuclei. It is the local activity within a network or minimal sleep unit that will determine the likelihood of sleep to occur and it is at this local level that clues about the function of sleep are to be found.

A bottom-up view is consistent with the local differences in the intensity of NREM sleep SWA as induced by local activation during wakefulness and the local regulation of 'sleep states' in cortical columns, as well as the remarkable persistence of sleep-like phenomena after widespread lesions across the brain. The bottom-up view is, however, to a first approximation inconsistent with the highly orchestrated nature of the occurrence of vigilance states and the accompanying changes in multiple state variables across the brain and body. In mammals, the complex phenomena of NREM and REM sleep emerge through interaction of local networks and top-down control by neuroanatomical circuitry (Saper *et al.*, 2005; Luppi *et al.*, 2006; Fort *et al.*, 2009, this issue), disruption of which leads to disruption of the normal characteristics of sleep and wakefulness. A prominent example of loss of top-down control is narcolepsy, in which disruption of the orexinergic systems leads to severe disruption in the regulation of behavioural state transitions, including pathological transitions between wakefulness and REM sleep and co-occurrence of consciousness and muscle atonia (Nishino, 2007). Another prominent example of top-down control is the circadian control of sleep, in the absence of which the temporal organization of sleep and wakefulness into long episodes of wakefulness (e.g. 16 h) and sleep (e.g. 8 h) is lost, but sleep and its homeostatic regulation persist (Trachsel *et al.*, 1992; Edgar *et al.*, 1993). The existence of top-down orchestration, however, does not imply that essentials of sleep function could not be related to some of the 'bottom processes' that determine local variation in the probability of being in a sleep-like state, i.e. variation in sleep propensity. Understanding local variation in sleep propensity may provide important clues to sleep function and it seems reasonable to assume that bottom-up phenomena emerged first in evolution and later became controlled by specialized sleep-regulatory centres, to optimize spatial and temporal organization of vigilance states which in turn should contribute to behavioural adaptation (Krueger *et al.*, 2008).

The regulation of global and local sleep propensity

Global organization of sleep propensity: circadian and homeostatic components

Searching for alterations in brain function following sleep deprivation has been a popular paradigm in the study of sleep function. It has been established beyond doubt that sleep deprivation leads to sleepiness and changes in subsequent sleep duration and structure. These responses to sleep deprivation are one manifestation of sleep-homeostatic regulation, which in essence implies that sleep propensity and the contents of sleep depend on vigilance state history. The phenomenon of sleep homeostasis is very well established and understanding the mechanisms underlying sleep homeostasis has almost become a proxy for understanding sleep function.

It may be thought that measuring sleep propensity is a good approach to monitoring the time course of the sleep homeostat during a normal waking episode, but it is not. This is because at the global level sleep propensity is regulated through interactions of sleep homeostasis and circadian rhythmicity (Borbély, 1982; Daan *et al.*, 1984; Dijk & Czeisler, 1995). In this conceptualisation, time spent awake results in physical changes in brain neural networks. During the day (in the case of diurnal species such as humans) these changes do not, however, lead to an overt and proportional increase in sleepiness (sleep propensity) (Dijk *et al.*, 1987) or to performance deterioration (Dijk *et al.*, 1992). It is thought that the mechanism underlying the absence of an increase in sleep propensity and performance deterioration is related to wake-promoting (activating) inputs at the level of either the hypothalamus or the cortex (Edgar *et al.*, 1993; Saint-Mleux *et al.*, 2007). Whereas during the day this activating input 'masks' the effects of sustained wakefulness on sleep propensity and performance, during the night these activating inputs diminish and the effects of sustained wakefulness on the brain can now manifest themselves as increased sleep propensity or, in the case of attempting to stay awake, deteriorating performance. The circadian pacemaker, in mammals located in the suprachiasmatic nucleus of the hypothalamus, is thought to drive these activating inputs and, in a top-down manner, organise the temporal pattern of sleep and wakefulness (Dijk & von Schantz, 2005).

Thus sleep propensity and performance are not really directly reflecting time awake and its effects on neural networks. Shadows of the covert effects of sustained wakefulness on neural networks can, however, be observed at the global level in the EEG while the brain is awake: as mentioned above, slow/delta and theta wave activity increase with increasing duration of wakefulness (Franken *et al.*, 1991; Cajochen *et al.*, 2002). These changes in neural networks manifest themselves most prominently during NREM sleep: SWA in the EEG during repeated nap sleep increases monotonically with increasing duration of wakefulness (Dijk *et al.*, 1987). When we override the circadian control on sleep propensity and sleep is initiated during the day, SWA during NREM sleep is very little affected by the circadian pacemaker. Thus even though many aspects of sleep, i.e. sleep propensity, sleep spindles (which are oscillations in the 10–15 Hz frequency range; Table 2) and REM sleep, are under circadian control, SWA and its decline during sleep are nearly independent of circadian phase (Dijk & Czeisler, 1995). This is strong evidence in support of the hypothesis that wakefulness leads to unidentified changes in the brain and that these changes are reversed during sleep, i.e. sleep homeostasis. Because of its response to sleep deprivation and its near independence of the circadian process, SWA is considered a good marker of sleep homeostasis.

SWA vs. the duration of NREM sleep: how good is SWA as a marker of sleep homeostasis?

SWA is widely considered to be a good marker of sleep homeostasis by researchers who use it as their proxy for sleep need. However, although the variation in SWA upon sleep onset, and its decline during NREM sleep, can be accurately predicted on the basis of prior sleep–wake

history, it has been known for many years that SWA fails to predict sleep duration. Thus, rats that were sleep-deprived for 24 h showed a marked increase in SWA above baseline values during the initial 4 h of recovery sleep ('positive sleep rebound'). SWA then quickly declined to values below baseline and remained below baseline until 36 h into recovery ('negative rebound'). Yet throughout this period rats slept more than baseline (Franken *et al.*, 1991). SWA does not, therefore, reflect the human or animal's apparent sleep need and this has led to the notion that sleep intensity and sleep duration are regulated separately (Borbély, 1982). The take-home message is that only one aspect of sleep homeostasis is accounted for by SWA and understanding SWA may not necessarily hold clues to all functions of sleep.

Local correlates of sleep propensity: sleep-regulatory substances (SRSs) and synaptic strength

Although sleep homeostasis is well established, a key unanswered question is in what form, i.e. metabolic, molecular, structural or bioelectrical, is past waking and sleep activity recorded? In other words, what does the sleep homeostat sense? To answer this question, total sleep deprivation is the obvious paradigm to use but other paradigms in which the contents of wakefulness are changed, through specific (learning) tasks or stimulation of specific sensory pathways, can also be used and may be more informative.

Biochemical correlates of the effects of sleep–wake history have long been sought. Originally it was shown that sleepiness could be transferred from one animal to another, using material extracted from the cerebrospinal fluid or brain of sleep-deprived animals (Pappenheimer *et al.*, 1975). More recently, sleepiness, or at least some aspects of the consequences of sleep deprivation, were successfully transferred to a dish: the responsiveness of orexin neurons to noradrenaline remarkably changes from excitatory to inhibitory when the hypothalamic slices that contain them are taken from animals having undergone 2 h of sleep deprivation rather than from animals allowed to sleep. These effects appear mediated by postsynaptic mechanisms (Grivel *et al.*, 2005). Sleep deprivation has also been shown to increase the strength of glutamatergic synapses on orexin neurons (Rao *et al.*, 2007). Thus at the local level, sleep homeostasis is reflected by changes in neuronal responsiveness and synaptic strengths of, in this case, orexin neurons. These changes in the orexinergic system provide us with mechanisms by which wakefulness may lead to an increase in the propensity to fall asleep, yet they do not necessarily provide us with clues about sleep's contribution to neural function.

One molecule that has received much attention as a potential biochemical mediator of sleep homeostasis is adenosine. Some cells release adenosine triphosphate (ATP) from synaptic vesicles together with neurotransmitters, possibly providing an index of prior synaptic use. This ATP is rapidly hydrolyzed to adenosine (Krueger *et al.*, 2008). During prolonged wakefulness extracellular concentrations of adenosine increase, in particular in basal forebrain areas (Porkka-Heiskanen *et al.*, 2000). Adenosine's effects on A1 receptors and associated activation of K^+ channels and inhibition of Ca^{2+} entry leads to inhibition of neural activity, an increase in sleep propensity and ultimately to SWS (Basheer *et al.*, 2000). Adenosine may only be a member of the group of SRSs, which include interleukin-1β, tumor necrosis factor α (TNFα), brain-derived neurotrophic factor (BDNF) and epidermal growth factor, all of which have been shown to induce sleep and/or to be induced by sleep loss (Krueger *et al.*, 2008). It is thought that electrical activity patterns and associated postsynaptic events that prevail during wakefulness, and maybe in particular during specific behaviours such as exploration, lead to the production of these 'somnogenic growth factors'. Such effects can be observed in the intact animal. For example, expression of BDNF is correlated with time spent in exploratory behaviour (Huber *et al.*, 2007) and BDNF expression is thought to depend on neuronal firing rates. This growth factor and others such as TNFα are on the one hand somnogenic and on the other hand thought to activate the molecular machinery required for synaptic plasticity (see below).

Sleep deprivation studies in which appropriate controls for circadian processes were implemented have also been used to identify changes in gene expression profiles in association with vigilance state and circadian rhythmicity. Early rat studies (Cirelli *et al.*, 2004) and more recent mouse studies indicate that there is specific variation around the clock in brain RNA expression, driven to a large extent by the alternation between sleep and wakefulness and to a smaller extent by circadian rhythmicity (Maret *et al.*, 2007). In a recent study in which it was attempted to identify those transcripts that were specifically up- or down-regulated, in the brain and not the liver, by 6 h of enforced wakefulness rather than by circadian rhythmicity, and in three different mouse inbred strains, one cDNA stood out: *Homer1a* (Maret *et al.*, 2007). This *Homer1* gene alternate transcript is induced by neuronal activity. This finding may be interpreted within the context of the function of *Homer1a* in plasticity or protection and recovery from glutamate-induced neuronal activity imposed by wakefulness. Gene expression microarray studies are informative with respect to brain-specific response to sleep loss but they are blind to translational and post-translational regulations, and no causality can be ascribed: genes which are functionally implicated in sleep regulation are not distinguished from genes whose expression merely follows sleep–wake history.

Local correlates of sleep propensity: slow/delta waves and synaptic strength

Another approach in the search for sleep's contribution to neural function has been to follow the EEG slow/delta waves, as a marker of sleep homeostasis, to their origin. What are the underlying mechanisms of slow/delta wave generation? Intracellular recordings during SWS have revealed that many cortical and thalamic neurons are triggered to enter a characteristic burst–pause mode of firing when excitatory inputs from diffuse neuromodulator systems are low and their resting membrane potentials become hyperpolarized. This hyperpolarization allows T-type Ca^{2+} channels (also referred to as low-voltage-activated Ca^{2+} channels) to de-inactivate, mediate Ca^{2+} entry and initiate a burst of action potentials (Steriade *et al.*, 1993).

Evidence that T-type Ca^{2+} channels are critical players in the rhythmic synchronized burst discharges characteristic of SWS was provided through analysis of mice bearing gene-targeted mutations in T-type Ca^{2+} channel pathway components. Thalamocortical relay neurons from mice deficient for one of the three T-type Ca^{2+} channels (the α1G-subunit, also called $Ca_v3.1$) strikingly fail to enter the burst mode of firing action potentials, whereas the tonic firing mode is unimpaired (Kim *et al.*, 2001). These mutant mice exhibit disrupted sleep continuity, with a higher incidence of awakenings lasting > 16 s, but not of brief awakenings lasting < 16 s, when compared to wild-type mice (Lee *et al.*, 2004; Anderson *et al.*, 2005). Oscillatory bursting in neurons of the nucleus reticularis of the thalamus (nRT) also appears important for slow/delta wave generation. Mice lacking SK2, a K^+ channel selectively expressed on dendrites of nRT neurons and coupled to T-type Ca^{2+} channels, show a NREM sleep EEG

characterized by weakened slow/delta and spindle oscillations, and fragmented sleep (Cueni *et al.*, 2008). Thus T-type Ca^{2+} channel de-inactivation is thought to constitute a triggering event in slow/delta wave generation and associated processes (Destexhe *et al.*, 2007).

However, what underlies the gradual increase in slow/delta waves in the EEG as observed after sustained wakefulness and their gradual dissipation during sleep? In one scenario it reflects the variation in levels of the wake- or arousal-promoting neuromodulators mentioned above, namely monoamines, acetylcholine and orexins, and/or variations in adenosine levels (McCarley, 2007). In a different scenario, most relevant to the role of sleep in plasticity, variations in slow/delta waves reflect changes in connectivity within cortical neuronal networks. Krueger & Obal (1993, 2003) proposed that changes in sleep propensity are related to local and use-dependent changes in synaptic strength and hypothesized that sleep serves the maintenance of the 'synaptic super structure'. Tononi & Cirelli (2003, 2006) proposed that neuronal connections would become on average stronger during wakefulness due to synaptic potentiation associated with learning, and would weaken during sleep due to sleep-dependent synaptic depression or homeostatic downscaling.

Here it may be useful to note that synaptic depression and synaptic downscaling, although they may share molecular steps, were defined as distinct phenomena. 'Homeostatic plasticity', which encompasses 'synaptic scaling' as well as a wide variety of other processes, refers to mechanisms thought to counteract the destabilizing effects of experience-dependent Hebbian events, such as long-term potentiation (LTP) and long-term depression (LTD) (Table 2) (Turrigiano & Nelson, 2004; Nelson & Turrigiano, 2008). It is now still too early to conclusively identify the specific synaptic plasticity processes that occur during sleep and in which slow/delta waves are thought to be involved, and the field remains equivocal in the use of these terms.

In any event, local synaptic strength (or weight, i.e. the input–output relationship of a synapse) within cortical networks is thought to vary over the sleep–wake history. Mechanistically, stronger synaptic connections would increase network synchronization whereas weaker connections would reduce network synchronization. According to this view, which is supported by computer simulations and models of the thalamocortical system (Hill & Tononi, 2005; Esser *et al.*, 2007), these variations in synaptic strength result in variations in slow/delta waves within cortical networks, which appear as changes in SWA at the level of the EEG. Across the sleep–wake cycle, changes in synaptic strength are thus driving changes in SWA.

Furthermore, SWS-associated neuronal firing patterns, including the slow/delta waves, are in turn assumed to alter synaptic strength. As discussed below, the burst-firing mode of activity can induce LTD (Birtoli & Ulrich, 2004; Czarnecki *et al.*, 2007). Thus slow/delta waves may both reflect and drive changes in synaptic strength.

Synaptic depression and/or downscaling are required because otherwise all the experiences incurred during wakefulness would lead to unconstrained synaptic weight growth. In this view, and at this level of organization, the function of NREM sleep is synaptic weight homeostasis, a process initially described in the developing nervous system (Turrigiano & Nelson, 2004).

Electrophysiological and molecular evidence for sleep-related changes in synaptic strength

Mathematical models of neuronal networks have shown that SWA and other EEG variables, e.g. the slope of individual slow/delta waves (in voltage over time, nV/s), as well as the slope and amplitude of evoked potentials during sleep and wakefulness, can indeed be a measure of network connectivity (Esser *et al.*, 2007). These parameters have now been shown in rat and humans to increase with wake and decrease with sleep (Riedner *et al.*, 2007; Vyazovskiy *et al.*, 2007, 2008). To what extent these variables are a simple monotonic function of time awake and time asleep or are also modulated by the circadian phase remains, however, to be established. Nevertheless, there is electrophysiological evidence for changes in synaptic strength in synchrony with the sleep–wake cycle.

There are, however, contradictory reports on the direction of synaptic plasticity occurring during sleep using molecular markers of plasticity. Vyazovskiy *et al.* (2008) compared phosphorylation levels of GluR1-containing AMPA receptors and other markers of LTP and LTD after 6 h of predominant sleep vs. wakefulness in rats, and provided evidence for net potentiation after wakefulness and depression after sleep.

In contrast, other authors emphasize the role of sleep in the consolidation of cortical plasticity associated with synaptic potentiation. Using the classical plasticity paradigm of remodelling of ocular dominance in the visual cortex of kittens submitted to monocular deprivation, Frank and colleagues recently reported observations seemingly at odds with the synaptic depression or downscaling hypothesis (Aton *et al.*, 2009). These authors initially showed that sleep enhances ocular dominance plasticity and that this effect depends on cortical activity during sleep through unknown mechanisms (Jha *et al.*, 2005). They now report, using some of the same molecular markers of potentiation or depression of glutamatergic synapses as those used in the Vyazovskiy *et al.* (2008) study described above, that sleep-dependent enhancement of visual cortex remodelling is associated with synaptic potentiation (Aton *et al.*, 2009). They also show that sleep-dependent ocular dominance plasticity is inhibited by antagonists of NMDA receptors or cAMP-dependent protein kinase, known to inhibit LTP. Altogether, it is proposed that 'off-line' secondary waves of synaptic potentiation events occur in the primary visual cortex during sleep that follows initial plasticity, and act to reinforce cortical map remodelling.

Slow/delta waves and sleep spindles: effects on measures of plasticity

EEG phenomena such as slow/delta waves may not just reflect changes in synaptic strength but may actually play a causal role in bringing about these changes. A systematic electrophysiological study of how specific patterns of sleep-related neuronal firing affect synaptic plasticity in cortical pyramidal neurons of rat brain slices was performed by Daniel Ulrich and co-workers, as described below.

The two most conspicuous neuronal firing patterns of NREM sleep, slow/delta waves and sleep spindles, are not only different in their frequency range but are also very different in their regulation. Slow/delta waves decline during sleep but sleep spindle activity remains constant or even increases during sleep (Fig. 1). Whereas slow/delta waves are not affected by circadian phase, sleep spindles are under circadian control and are not markedly affected by sleep deprivation (Dijk *et al.*, 1997). At the behavioural level, variation in both delta oscillations and sleep spindles have been reported to be associated with consolidation of procedural and declarative memory (Huber *et al.*, 2004; Schabus *et al.*, 2004; Schmidt *et al.*, 2006; Aeschbach *et al.*, 2008).

Is there electrophysiological evidence that these phenomena may contribute to plasticity and, if yes, in a similar or dissimilar way? One approach to investigating how NREM sleep may contribute to plasticity has been to investigate the effects of these specific firing

patterns on phenomena such as LTP and LTD, which have been widely implicated in learning and memory.

In these studies, cortical pyramidal neurons were stimulated by bursts of action potentials, which are the characteristic of slow/delta waves, paired with application of an excitatory postsynaptic potential (EPSP). This electrophysiological profile led to LTD (Birtoli & Ulrich, 2004; Czarnecki *et al.*, 2007). In contrast, if the EPSP was paired with a firing pattern mimicking a spindle oscillation, LTP was generated (Rosanova & Ulrich, 2005). It is noteworthy that, in the same experimental setup, application of a profile characteristic of the waking state, i.e. individual action potentials mimicking tonic rather than burst firing, generated LTP. In summary, these studies suggest that the two hallmarks of NREM sleep both contribute to synaptic plasticity, albeit in opposite directions.

A role for SWS beyond synaptic depression and downscaling?

Synaptic depression or downscaling during SWS may recalibrate the strength of synapses within a functional responsive range, but could it enhance the signal-to-noise ratio of stored (learned) information? Could it actively contribute to memory consolidation? In a first modelling attempt it was shown that an SWS-mediated downscaling could indeed keep synaptic weight in check and maintain selectivity of information that was stored (learned) during the waking day as well (Sullivan & De Sa, 2008).

A parallel question is whether the well known negative effects of extended periods of wakefulness and the positive effects of sleep on performance (which are particularly clear in the absence of the circadian confound; Wyatt *et al.*, 1999), may be associated with these changes in synaptic weight over the sleep–wake cycle. Currently, no direct evidence for this link is available. However, irrespectively of the mechanisms involved, there is some experimental evidence that SWS is beneficial for performance and memory consolidation.

Consolidation can be defined as the progressive post-acquisition stabilization, and sometimes enhancement, of memory that occur even in the absence of training. Researchers such as Jan Born, Robert Stickgold, Pierre Maquet and their co-workers believe indeed that sleep does more for memory than synaptic scaling. For a variety of memory tasks that are improved by sleep, brain activity was monitored by brain imaging using positron emission tomography (PET) or functional magnetic resonance imaging (fMRI), before or at initial training, during post-training sleep or at retesting. During post-training SWS they observed (re)activation of activity patterns evoked during learning (Peigneux *et al.*, 2004; Rasch *et al.*, 2007). The reactivations were reported to correlate positively with the improvement in performance on the subsequent day. Much earlier, using multi-unit electrode recordings in rats during SWS, McNaughton and colleagues reported 'replay' in hippocampal 'place cells' of similar spatial and temporal firing patterns as were evoked in those cells when the rat was engaged in spatial exploration and navigation across an arena (Wilson & McNaughton, 1994). More recently it was reported that post-training replay also occurs in cortical neurons, and this takes place specifically during up-states of SWS (Ji & Wilson, 2007). Cortical and hippocampal replays were found to be coupled temporally. It could not be determined whether these replays contribute to, or only reflect, memory consolidation. Nevertheless, the concept that memory consolidation evolves from repeated covert reactivation of newly encoded memory traces during sleep has gained ground.

In addition, memory traces can undergo slow and major structural changes in a sleep-dependent manner. The retesting 48 h (Fischer *et al.*, 2005) or 12 h (Walker *et al.*, 2005) after initial training of a nondeclarative procedural motor task (finger tapping) in humans revealed profound alterations in task-concomitant patterns of brain activation as detected by fMRI. These alterations were sleep-specific and associated with gains in performance. They were interpreted as a reorganization of the memory representations of the skill.

The scale of reorganizations of memory representations may be such that retrieval of hippocampus-dependent memories becomes over time hippocampus-independent, presumably due to a gradual transfer to cortical networks, in particular to the prefrontal cortex (Maviel *et al.*, 2004; Euston *et al.*, 2007).

Well beyond 'synaptic consolidation', sleep is thus thought to contribute to memory by promoting a process of 'system consolidation' that leads to a redistribution of the memory representation involving new neuronal networks not involved at initial encoding (Dudai, 2004; Born *et al.*, 2006). This may imply a 'qualitative' change in the memory, which can be manifested for example as the memory may become less dependent on context, but richer in schematic, abstract structure (discussed in Hoffman *et al.*, 2007).

Memory consolidation can be thought to consist of synaptic and system consolidation and, although much remains to be understood, there is evidence for contribution of SWS to both processes. The next near irresistible question is: are the slow/delta waves themselves instrumental in SWS-dependent memory consolidation?

Local changes in SWA during the first half-hour of post-training sleep are correlated with the overnight improvement in performance on a procedural visuomotor learning task (Huber *et al.*, 2004).

Slow waves can be manipulated to shed light on their causal links with memory formation. Application of transcranial direct current stimulation in humans can lead to an increase in < 3 Hz activity and improvement in declarative memory (Marshall *et al.*, 2004). In contrast, brain stimulation with oscillations at 5 Hz (theta) left declarative memory unchanged (Marshall *et al.*, 2006). It is to be noted, however, that the protocol used to enhance slow/delta waves also enhanced spindle activity.

Furthermore, it has been reported that acoustic disruption of slow/delta waves prevents the sleep-dependent improvement in performance on a perceptual learning task (visual texture discrimination). In this study, the improvement in performance correlated with SWA, when the control and experimental conditions were combined in those 16 individuals (out of 20) who met a specific initial performance criterion (Aeschbach *et al.*, 2008).

Additional evidence for a role of SWS in memory consolidation was derived by re-exposing sleeping subjects to an odor that had been presented as context during the learning of a declarative memory task (Rasch *et al.*, 2007). This odor exposure led to a boost in post-sleep memory retrieval if the odor was presented during SWS, but not if it was presented during REM sleep. fMRI imaging revealed significant hippocampal activation during SWS upon odor re-exposure. This suggests that reactivation during sleep of a part of a complex memory 'engram' can have access to, and functionally alter, the wider memory traces associated with it.

The evidence for an association between slow/delta waves and plasticity is growing, but important unanswered questions and issues remain. The quantitative relation between SWA and measures of plasticity, and even, as mentioned above, the direction of this association, as well as sleepiness levels and performance, have not always been firmly established across the circadian cycle. Early, well-controlled studies have failed to identify a specific role for SWS in the regulation of daytime performance (Bonnet, 1986) and results of recent studies have not always been supportive of a role for SWS in memory consolidation (Genzel *et al.*, 2009; Schabus, 2009).

Furthermore, whether the positive effects of sleep on declarative memory is mediated by the slow/delta waves or the sleep spindles remains unresolved (Schmidt *et al.*, 2006). For some procedural memory tasks, the case for a role of stage-2 sleep (i.e. NREM sleep with few slow/delta waves and many sleep spindles) in consolidation is much stronger than the case for SWS (Nishida & Walker, 2007).

In summary, there is a growing consensus that NREM sleep contributes to plasticity and memory consolidation, although the relative contribution of specific NREM phenomena such as spindles and slow/delta waves remains to be established. The data in support of a role for sleep in memory consolidation should not detract from the observation that these effects may be learning-task-specific, and that consolidation also occurs during wakefulness (Doyon *et al.*, 2009).

A role for REM sleep in memory consolidation?

What about REM sleep? Is it also associated with memory trace reactivation? Does it also contribute to memory consolidation? Evidence that brain structures activated during learning are reactivated selectively during subsequent REM sleep was obtained in humans using PET imaging during and following visuomotor skill and other implicit memory tasks (Maquet *et al.*, 2000; Peigneux *et al.*, 2003). From these and other studies the notion emerged that, while declarative, hippocampus-dependent memories would be strengthened particularly during SWS, non-declarative, procedural memories (i.e., perceptual and motor skills) would benefit to a greater extent from REM sleep (Born *et al.*, 2006). Amygdala-dependent emotional memories were also shown to benefit specifically from late REM sleep-rich sleep (Wagner *et al.*, 2001).

More recently, Born and co-workers cast doubt on the concept that procedural skills benefit from REM sleep. They reported that suppression of REM sleep by selective serotonin and noradrenaline reuptake inhibitors did not impair consolidation of two different motor skill tasks. In fact, accuracy in finger sequence tapping was significantly enhanced by drug administration and the gain in accuracy was positively correlated with the increase in number and density of fast spindle oscillations (> 13 Hz) during stage-2 sleep and SWS (Rasch *et al.*, 2009). Therefore EEG-defined REM sleep appears not to be required for memory consolidation of this particular procedural task and in fact may be detrimental. A compilation of many recent studies indicates that the hypothesis that REM sleep benefits the consolidation of procedural tasks and SWS is for the benefit of declarative tasks is too simple (Schabus, 2009).

A role for sleep in plasticity during development?

A role of sleep in neuronal network plasticity is in accordance with the predominance of NREM and in particular REM sleep in the early postnatal animal life. Sleep amount is maximal at the time when plasticity is maximal. As mentioned above, ocular dominance plasticity during the critical period in kittens is enhanced by sleep and this effect depends on postsynaptic cortical activity during sleep (Jha *et al.*, 2005). However, a related but distinct paradigm of plasticity during development, recovery from monocular deprivation, is not enhanced by sleep (Dadvand *et al.*, 2006), showing that different forms of plasticity *in vivo* are regulated by distinct mechanisms whose dependence on sleep may differ. Recently, birds have emerged as models for studying the role of sleep in two classical developmental learning paradigms: imprinting in the domestic chick (Jackson *et al.*, 2008) and song development in juvenile zebra finches (Shank & Margoliash, 2009). Establishing a contribution of sleep to plasticity in early life in mammals and birds is a major contribution to a more general view of the interrelationships between plasticity and sleep throughout the lifespan and across two classes of the animal kingdom.

Gender- and age-related and other individual differences in SWA and other EEG variables: implications for differences in plasticity?

It is intriguing that aspects of sleep such as SWA and sleep spindles which are thought to be implicated in plasticity and learning can display marked interindividual differences under baseline (i.e. not sleep-deprived) conditions. Gender and ageing are major factors affecting sleep parameters. Thus, women have more SWS and higher SWA than men (Dijk *et al.*, 1989; Carrier *et al.*, 2001) and ageing is associated with reductions in SWS and SWA (Landolt *et al.*, 1996) and sleep duration (Klerman & Dijk, 2008). Twin studies indicate that the interindividual differences in certain aspects of the sleep EEG such as SWA have a heritability of well over 90% (De Gennaro *et al.*, 2008). The identity of some of the genes contributing to interindividual differences in sleep has been revealed. Polymorphisms in genes involved in the adenosinergic system (Retey *et al.*, 2005) and the circadian gene *PER3* (Viola *et al.*, 2007) have now been shown to affect SWS and SWA. Although sleep deprivation leads to an increase in SWA in all these individuals, the magnitude of some of these interindividual differences in the baseline EEG, including SWA, dwarf the effects related to sleep deprivation (Tucker *et al.*, 2007). An important question to be addressed in future studies is whether these interindividual differences in sleep measures are indicators of differences in plasticity or, alternatively, reflect individual differences in sleep characteristics, which are independent of the modulation and involvement of the sleep process in plasticity, learning and memory. In this context it will be important to distinguish between individual differences in baseline values of sleep characteristics and individual differences in the response to challenges. In other words, are these differences reflective of differences in EEG-generating mechanisms or in sleep regulatory processes which may be related to differences in plasticity? Studies in mice demonstrate that genetic factors that contribute to inter-strain differences in SWA (analogous to inter-individual differences for humans) (Maret *et al.*, 2005) are distinct from those underlying the inter-strain differences in the sleep deprivation-induced changes in SWA (Franken *et al.*, 2001).

Concluding remarks

Understanding sleep's function and contribution to neuronal function requires convergence of evidence from a variety of independent assays, models, levels of analysis, etc. The research that we have reviewed demonstrates that progress has been made in the understanding of the interrelations between classical EEG markers for NREM sleep and sleep regulation and the associated molecular, cellular and network events that mediate plasticity. Many questions remain unanswered. Continuation and expansion of this multidisciplinary sleep research effort holds great promise for furthering our understanding of mechanisms involved in the brain's ability to interact efficiently with its social and physical environment and adapt its responses based on waking experience.

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Abbreviations

AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; EEG, electroencephalogram or electroencephalographic; fMRI, functional magnetic resonance imaging; GluR1, glutamate receptor 1; LTD, long-term depression; LTP, long-term potentiation; NMDA, *N*-methyl *D*-aspartate; NREM, non-REM; REM, rapid eye movement; SRS, sleep-regulatory substance; SWA, slow-wave activity; SWS, slow-wave sleep.

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