REVIEW

Large-scale functional brain networks in human non-rapid eye movement sleep: insights from combined electroencephalographic/functional magnetic resonance imaging studies

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This paper reviews the existing body of knowledge on the neural correlates of spontaneous oscillations, functional connectivity and brain plasticity in human non-rapid eye movement (NREM) sleep. The first section reviews the evidence that specific sleep events as slow waves and spindles are associated with transient increases in regional brain activity. The second section describes the changes in functional connectivity during NREM sleep, with a particular focus on changes within a low-frequency, large-scale functional brain network. The third section will discuss the possibility that spontaneous oscillations and differential functional connectivity are related to brain plasticity and systems consolidation, with a particular focus on motor skill acquisition. Implications for the mode of information processing per sleep stage and future experimental studies are discussed.

Keywords: non-rapid eye movement sleep; spindle; functional connectivity; graph theory; small-world; plasticity

1. Introduction

The brain is endowed with the remarkable ability to generate very different dynamics, ranging from transient versatile oscillations underpinning cognition to circadian and seasonal rhythms preserving the long-term adaptation to the environment. Among this wealth of rhythms, the inescapable recurrence of sleep suggests that its characteristic neural dynamics exert important functions and potentially help in maintaining the integrity of brain physiology. A number of important advances were made in our understanding of sleep rhythms by careful

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One contribution of 11 to a Theme Issue ‘The complexity of sleep’.
neurophysiological studies conducted in animals [1]. In humans, the study of sleep has long been restricted to scalp electroencephalographic (EEG) recordings with a limited number of sensors. These studies were critical in characterizing the regulation of sleep by circadian and homeostatic processes [2,3], but provided little information about the underpinning of neural activity within the brain. Recently, advanced neuroimaging (high-density EEG, magneto-encephalography (MEG), combined EEG and functional magnetic resonance imaging (fMRI)) allowed for the first characterization of the neural correlates of human sleep rhythms [4–9].

This paper focuses on the neural correlates of non-rapid eye movement (NREM) sleep. NREM sleep is characterized by a coalescence of rhythms whereby a slow oscillation (about 1 Hz) organizes the occurrence of other rhythms, such as spindles, theta or gamma oscillations [1,10]. Such nested frequencies have also been observed in non-harmonic fluctuations during NREM sleep [11]. The first section reviews the evidence that transient increases in regional brain activity are associated with specific sleep events as slowwaves and spindles. The second section describes the changes in functional connectivity associated with sleep onset and NREM sleep, and illustrates that ‘small-world’ network properties as observed in wakefulness [12] change in the descent from wakefulness to slow wave sleep (SW). The third section will discuss whether spontaneous oscillations and differential functional connectivity are related to brain plasticity and systems consolidation, with a particular focus on motor skill learning.

2. Neural correlates of non-rapid eye movement sleep oscillations

(a) Neural correlates of slow oscillations

The slow rhythm (<1 Hz) constitutes the fundamental rhythm that characterizes NREM sleep. Intracellular recordings in cats showed that neuronal membrane potential oscillates at low frequency (around 1 Hz). This oscillation shapes neuronal activity, by alternating a depolarizing phase, associated with important neuronal firing (‘up state’), and a hyperpolarizing phase, during which cortical neurons remain silent for a few hundred milliseconds (‘down state’) [13,14]. This so-called slow oscillation (<1 Hz) is recorded during NREM sleep in all major types of neocortical neurons (both excitatory and inhibitory) and occurs synchronously in large neuronal populations. At the population level, the activity is therefore made up of the alternation of ‘ON’ states and ‘OFF’ states. Because these events represent massive and synchronous changes in large neuronal populations, they can be reflected in EEG recordings as large-amplitude low-frequency waves [15]. The slow oscillation is generated by the cortex as it can be observed after thalamic destruction [15], in cortical slabs isolated from thalamic influence [16] or in cortical slices [17]. However, two intrinsic conditional thalamic oscillators also participate in the generation of the slow oscillation [18].

In humans, the taxonomy of slow waves is not always clear. A slow rhythm was initially identified in scalp EEG recordings as the recurrence of spindles [19] or their grouping by slow waves [20]. More recently, high-amplitude slow waves themselves were taken as realization of the slow rhythm [21]. On the other hand, historically, the power density in the 0.75–4 Hz frequency band, usually referred to as ‘slow-wave activity’ (SWA), has proved a very useful and popular parameter because it quantifies the dissipation of homeostatic sleep pressure during NREM.
The frequency bounds of SWA do not respect the dichotomy between slow (\(<1\text{ Hz}\)) and delta rhythms (1–4 Hz), which is based on differences in the respective cellular correlates of these rhythms in animals [15]. In the temporal domain, the amplitude of slow waves is classically larger than 75 \(\mu\text{V}\) [23], but only the largest waves (\(>140\ \mu\text{V}\)) were taken as realizations of the slow oscillation (\(<1\text{ Hz}\)) [20,21]. This approach suggests that relatively smaller waves (amplitude between 75 and 140 \(\mu\text{V}\)) correspond to delta waves (1–4 Hz). These faster waves of smaller amplitude would also be an expression of the slow oscillation, but arise when the synchronization in the network is less marked [24,25].

In scalp EEG recordings, the power density corresponding to slow waves (0.75–4 Hz) predominates over frontal areas [26], where indeed the largest waves are typically recorded. However, an analysis of individual waves demonstrated the spatial variability of slow waves. Each wave originates at a specific site and travels over the scalp following a particular trajectory [21]. Waves originate more frequently in frontal regions and travel backwards to posterior areas. Beyond this variability, slow waves seem to recruit systematically various brain regions. Early studies based on cerebral blood flow measurement by positron emission tomography (PET) reported that the power density of delta waves (1.5–4 Hz) during NREM sleep was negatively correlated with regional cerebral blood flow in the ventromedial prefrontal cortex, the basal forebrain, the striatum, the anterior insula and the precuneus [27]. The interpretation was that the decrease in blood flow predominated in areas that generate prominent synchronous oscillations at low frequency. Using simultaneous EEG and event-related fMRI, it was possible to show that slow waves were associated with transient increases in regional brain activity, thus reconciling human physiology with animal data [6]. Slow waves were associated with significant increases in activity in pontine tegmentum, midbrain, cerebellum, parahippocampal gyrus, inferior frontal gyrus, middle frontal gyrus, precuneus and posterior cingulate cortex. When compared with baseline activity, the largest waves (\(>140\ \mu\text{V}\)) were associated with significant activity in the parahippocampal gyrus, cerebellum and brainstem, whereas delta waves were related to frontal responses.

These results are remarkable for two reasons. First, they show that the slow oscillation recruits a widespread set of brain areas, not only in the cortical but also in the subcortical structures. The transient responses observed in the brainstem are consistent with rhythmic neuronal firing patterns time-locked to the cortical slow oscillation recently reported in latero-dorsal tegmenti nucleus [28] and the locus coeruleus [29]. Collectively, these data raise the possibility that the brain activity associated with slow oscillations represent microwave states [30], characterized by both a high activity in thalamo-cortical (TC) loops but also by the neuromodulatory context arising from brainstem activity. Second, these results demonstrate that a limited number of cortical areas are consistently recruited during slow waves, which potentially represent preferential initiation or propagation sites for slow oscillations. Source reconstruction of scalp high-density EEG recordings confirmed this interpretation. Although slow waves originate more frequently in the insula and cingulate gyrus, they preferentially involve the precuneus, the posterior cingulate, ventro-lateral and medial frontal areas [31]. It is currently believed that these areas constitute a preferred propagation pathway because they correspond to major structural connectivity nodes in the human brain [31].
(b) Neural correlates of sleep spindles

Spindles constitute the hallmark of light NREM sleep, although they can still be detected in lower amounts during deep NREM sleep. In humans, spindles consist of waxing-and-waning 11–15 Hz oscillations, lasting 0.5–3 s. At the cellular level, spindles arise from the cyclic inhibition of TC neurons by reticular thalamic neurons. Post-inhibitory rebound spike bursts in TC cells entrain cortical populations in spindle oscillations [1]. In addition, two kinds of spindles are described in humans: slow spindles (centred around 12 Hz) and fast spindles (centred at 14 Hz). These two spindling activities differ by their circadian and homeostatic regulations, pharmacological reactivity, development in infancy, evolution during ageing, modulation during menstrual cycle and pregnancy [32], and intriguingly, by their association with general cognitive capabilities [33] and memory processing [34]. Despite these functional differences, it is still debated whether slow and fast spindles reflect the activity of different neural networks or the differential modulation of a single generator.

Little is known on the cerebral correlates of human spindles. Scalp multi-channel EEG recordings showed that slow spindles exhibit a variable topography, primarily over the frontal cortex [35]. Fast spindles are topographically and dynamically limited to the superior central and parietal cortex [35]. Source reconstruction of scalp EEG recordings identified two sources, one for slow spindles in a mesial frontal region and another for fast spindles in the precuneus [36]. Early PET studies reported a negative relationship between thalamic cerebral blood flow and the power spectrum in the spindle frequency band [37]. Taking advantage of the high temporal resolution of combined EEG and fMRI, it was later shown that human spindles were also associated with transient surges in activity in the thalami, paralimbic areas (anterior cingulate and insular cortices) and superior temporal gyri [7]. Slow spindles were further associated with increased activity in the superior frontal gyrus. By contrast, fast spindles recruited a set of cortical regions involved in sensorimotor processing, as well as the mesial frontal cortex and hippocampus. The recruitment of partially segregated cortical networks for slow and fast spindles further supports the existence of two spindle types during human NREM sleep, with potentially different functional significance. However, one has to keep in mind that slow and fast spindles detected by EEG recordings might represent only a fraction of human spindles, potentially related to the recruitment of the distributed TC system. In contrast, MEG sleep recordings identified multiple asynchronous and focal generators of associated sleep spindles, which would correspond to the recruitment of the core TC system [38].

3. Functional connectivity in sleep: a large-scale network approach

(a) Resting network activity throughout non-rapid eye movement sleep

Ultraslow spontaneous fluctuations (<0.1 Hz) of the blood oxygen level dependent (BOLD) signal as measured with fMRI show temporal correlations in functionally related networks [39]. The neural circuitry of these networks is consistent throughout various time-series analyses, such as correlation against the time course of a particular seed region [39–41] or spatiotemporal independent...
component analysis [42,43]. Such networks are referred to as resting state networks as they can be derived from spontaneous BOLD fluctuations during rest, without engaging in a particular task. Nonetheless, the neural circuitry of these networks matches fMRI activations in specific sensory, motor and cognitive tasks [39]. Accordingly, networks can be divided into primary sensory resting networks (e.g. sensorimotor, auditory and visual networks) and into cognitive networks such as the dorsal and ventral attention networks, the frontoparietal networks and the ‘default mode network’ (DMN) [43,44]. The DMN, consisting of the medial prefrontal cortex, posterior cingulate, precuneus (and retrosplenial cortex and hippocampal complex) and the bilateral parietal lobules, has received most attention because of its task-negative activity pattern and because of its proposed involvement in episodic memory retrieval [45], imagination of future outcomes [46] and internal versus external awareness [47], and its possible role as a marker for psychiatric [48] and neurological disorders [49].

Previous EEG/fMRI studies have examined these resting networks also during sleep and reported that, in general, functional connectivity was maintained in light sleep. Horovitz et al. [50] observed that DMN connectivity persisted in light sleep, and also found an increase in BOLD signal fluctuations in the visual and auditory cortices and the precuneus, among others [50]. An increase of activity in the left precuneus and bilateral inferior parietal lobules has been observed in early sleep stage 1 specifically [51]. Larson-Prior et al. [44] reported no significant changes in functional connectivity in various sensory and cognitive resting networks from wakefulness to light sleep, while an increase in functional connectivity was observed in the dorsal attention network. Sämann et al. [52] noted the continued presence of the DMN in light sleep, but with reduced contribution from the posterior cingulate, retrosplenial cortex and parahippocampal gyri. These results are largely in line with the EEG studies, which reported increased neocortical connectivity (EEG synchronization) in specific frequency bands during sleep [53–55].

A breakdown of intra-network connectivity was observed in SW, specifically in the correlation between the anterior and posterior nodes of the DMN [52,56], with the posterior areas maintaining or even strengthening their connectivity [56]. This breakdown of cortico-cortical connectivity in SW parallels a combined high-density EEG and transcranial magnetic stimulation (TMS) study during sleep [57], which reported that TMS-induced activation spread over the cortex during wakefulness but remained local in SW.

The breakdown in functional connectivity during SW is in accord with the fading of consciousness in NREM sleep [58], but the preservation or even increase in functional connectivity in light sleep stages appears more puzzling and counterintuitive. However, according to an information integration of consciousness, not the connectivity per se but the capacity of a network to integrate information is proposed critical for high complex cognitive functions such as consciousness [59]. This would mean that a possible increase in connectivity in light sleep could be compatible with fading consciousness if the network’s capacity to integrate information would be reduced, which may occur owing to exclusion of pivotal nodes (such as the thalamus) or increased randomness in the network. In order to examine such hypotheses, a focus on a large-scale functional brain network is required.
A large-scale functional brain network throughout sleep

Large-scale functional brain networks as derived from fMRI time series can be examined by graph-theoretical analysis; such analysis has revealed a small-world organization of human functional brain networks during wakefulness [60], with high local clustering and short path length [61]. A small-world topology is a promising model for large-scale brain networks [62] as it supports both specialized processing in local clusters and integrated processing over the entire network [63]. Small-world properties of large-scale brain networks have helped in characterizing ageing processes [64,65], intelligence [66], psychiatric disorders like schizophrenia [67] and neurodegenerative disorders [68,69].

In a recent study [70], we applied graph-theoretical analysis on the correlations between extracted BOLD signal time courses of 90 atlas-defined cortical and subcortical regions [71] in wakefulness, light sleep stages 1 and 2 (S1, S2) and SW, and we observed three patterns in the descent from wakefulness to SW. First, we found a widespread increase in cortico-cortical connectivity in light sleep stages S1 and S2, but a strong reduction of cortico-cortical connectivity in SW. Second, TC correlation values sharply decreased in light sleep stage S1 and were partially restored in deeper sleep stages. Third, there was also a significant effect of sleep on small-world properties, in particular on local clustering values, which were highest in SW and lowest in S1 and S2 when compared with values of randomly rewired networks as a reference. See figure 1 for the average wavelet correlation values per stage.

The decrease in TC correlation values was specific to light sleep stage 1. This stage has been proposed to signify a transition period rather than a sleep stage per se [72,73]; sleep stage 2 would reflect more consolidated sleep. Here, the subclassification of stage 1 into early stage 1 sleep (stage 1a) and a deeper stage 1 sleep (stage 1b) may be informative, as auditory detection levels in stage 1a are comparable with waking levels, whereas in stage 1b sleep, they appear more reduced to levels typical for consolidated sleep [74]. An increase in TC correlation values in later sleep stages could be a consequence of sleep-specific phenomena either originating in the thalamus or mediated by the thalamus, such as sleep spindles [7,75]. A question is whether the thalamus becomes anti-correlated with neocortical regions in light sleep, as for instance observed in propofol-induced anesthesia [76]. One recent study observed a positive correlation during sleep between EEG spectral power in the 0.05–0.1 Hz frequency band and BOLD signal fluctuations in the thalamus, and a negative correlation between this ultraslow EEG fluctuation and BOLD signal fluctuations in mostly neocortical association areas [77]. In the fMRI data reported in Spoormaker et al. [70] and in figure 1, about 30 per cent of the correlations of the left and right thalamus were (weakly) negative in S1, whereas this percentage was 15–20% in deeper sleep stages and 0 per cent in wakefulness. Note that no global mean regression was used during preprocessing of the fMRI-data, which may induce artificial anti-correlations [78,79], and that the reported correlations do not represent linear correlations but coherence measures. A negative sign in non-global mean-regressed wavelet correlations, albeit weak, can be considered truly negative, however more theoretical and experimental work is needed to understand the nature of negative correlations in BOLD signal fluctuations [80,81] and how these may be affected by the deactivation of the thalamus at sleep onset [82,83].
Figure 1. Average group correlation matrices in wakefulness and sleep stages. The matrices provide the correlations of maximum overlap discrete wavelet transform coefficients at a frequency band of 0.03–0.06 Hz of 90 (sub)cortical regions as defined in the Automated Anatomical Labeling (AAL) atlas [71], listed in alphabetical order. BOLD signal time courses were extracted from 92 epochs of one continuous sleep stage, measured in forty 26.7 min runs in 25 subjects, reported in Spoormaker et al. [70]. Note that the correlation values are highest in sleep stages 1 and 2, although the same functional modules are visible in the matrices, such as occipital (visual), frontal and para-/precentral (pre-motor) cortices. The subcortical basal ganglia regions were the only regions with (nominally) stronger connectivity in wakefulness than in sleep. In deep sleep, one functional module had moderate to high correlation values: frontal regions, which only show within-module correlations and no between-module correlations as obvious in other stages. This could be related to the role of prefrontal cortices in the generation of slow oscillations [6,21]. S0, wakefulness; S1, sleep stage 1; S2, sleep stage 2; SW, slow wave sleep; hipp., hippocampus. The colour bar depicts wavelet correlation values. (Online version in colour.)

Moreover, the counterintuitive increase in cortico-cortical connectivity in light sleep is accompanied by a move towards randomness of the large-scale functional brain network. This is reflected in critical network properties such as the clustering coefficient that were closest to random network values in light sleep. The unspecific increase in functional connectivity in light sleep, paralleled with a more random network organization, limits the entropy of a network and the capacity to integrate information, in line with an information integration theory of consciousness [59]. In contrast, SW was characterized by a breakdown in cortico-cortical connectivity and by an increase in local clustering compared with random values. Although there were no significant differences in characteristic path length (topological distance between nodes), the correlation values of physical
Figure 2. (Caption opposite.)
Figure 2. (Opposite.) Differential connectivity graphs illustrating the differences in connections of 90 cortical and subcortical regions in the transition from wakefulness (S0) to light sleep stages 1 (S1) and 2 (S2) and finally to SW, with lines depicting a differential correlation value more than 0.20 between two stages. Linear mixed models revealed that connectivity differences were robustly significant across sleep stages for neocortical regions (association, primary sensory and paralimbic cortices) but not for limbic regions [70]; the only subcortical region showing (multiple test corrected) significant differences across sleep stages was the thalamus. The reduction in TC correlation values is illustrated in the upper left panel, while the panels S2 > S1 and SW > S1 illustrate the partial (trendwise) restoration of TC connectivity in light sleep stage 2 and SW. S1 > S0 and S2 > S0 visualize the statistically robust increase in neocortical connectivity in light sleep stages, and the three S0/S1/S2 > SW panels illustrate the subsequent breakdown of neocortical connectivity in SW. Interestingly, prefrontal cortical regions had a trend for increased connectivity in SW compared with wakefulness. Note that the current depiction threshold is an arbitrary yet consistent threshold as z-values for correlation differences were not significant in univariate tests owing to modest group sizes. Reproduced with permission from the Society for Neuroscience [70].

Table 1. Hubs per stage.

<table>
<thead>
<tr>
<th>stage</th>
<th>hubsa</th>
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<tbody>
<tr>
<td>wakefulness</td>
<td>superior parietal lobule (L), precentral gyrus (R), inferior and middle temporal gyrus (L,R)</td>
</tr>
<tr>
<td>sleep stage 1</td>
<td>superior frontal gyrus (L; dorsal), paracentral gyrus (L,R), postcentral gyrus (L,R), precentral gyrus (L,R), precuneus (L,R), inferior, middle and superior temporal gyrus (L,R)</td>
</tr>
<tr>
<td>sleep stage 2</td>
<td>calcarine gyrus (L), inferior frontal gyrus (L; orbital), medial frontal gyrus (L), superior frontal gyrus (L,R; dorsal), lingual gyrus (L,R), postcentral gyrus (L,R), precentral gyrus (L,R), precuneus (L,R), supramarginal gyrus (L), superior temporal gyrus (L,R)</td>
</tr>
<tr>
<td>deep sleep</td>
<td>inferior frontal gyrus (L,R; orbital), precuneus (L), supramarginal gyrus (L)</td>
</tr>
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aHubs are defined as nodes with ≥ 45 connections (out of 89 possible connections) in a binary matrix that was generated at a connection probability of 30%. This threshold was chosen because the network was both sparse and fully connected (no fragmentation). L, left; R, right.

long-distance connections (more than 75mm) were sharply reduced in SW. As a result, the large-scale functional brain network in SW demonstrated both high ‘cliqueness’ and fewer physical long-range connections, which reflects a move towards a regular network [12].

(c) An unspecific increase in neocortical connectivity in light sleep

The increase in connectivity in light sleep stages was accompanied by a network organization that was notably different from the organization of the large-scale functional brain network in wakefulness or in SW. Examining the sleep-specific correlation matrices reveals an unspecific increase in correlation strength (figure 1), and we computed the differential correlations (figure 2) to visualize the differences between the correlation matrices of wakefulness and sleep stages.

Both wakefulness and deep sleep are characterized by fewer hubs than light sleep stages (table 1), whereas wakefulness is the only stage with a parietal hub. Light sleep hubs are predominantly located in the (pre-)motor and temporal cortices.
These results are relevant to the debate on whether low-frequency BOLD signal fluctuations allow us to describe changes in consciousness [84,85] and may shed light on reorganization of a large-scale functional network during sleep. A move of the large-scale functional brain network towards more regularity in SW provides a functional brain state optimal for reprocessing information in segregated functional systems, which is more in accord with a memory-reprocessing hypothesis than with a memory-transfer hypothesis of SW [86]. The functional relevance of a move towards more randomness in light sleep needs further attention as it may comprise a stage suitable for global information transfer, which could be relevant in the light of systems consolidation of memories (see below). In short, network reconfiguration in sleep may well be a key mechanism for our understanding of brain plasticity taking place during sleep [54], and may have particular relevance for neuroimaging studies on sleep impairments [87–90].

4. Brain plasticity and connectivity

(a) Brain plasticity in general

Human beings rely on experience, learning and memory to shape their culture and to adapt to the particular environment they live in. For this, learned and stored information gathered from previous experience is vital in guiding the control of appropriate behaviour. The importance of being able to adapt to one’s surroundings is reflected in the extraordinary plasticity of the human brain [91]. With the advent of modern brain imaging methods and advancements in the measurement of electrical brain activity, human brain plasticity has been explored extensively using neuroanatomical and neurophysiological techniques.

Brain areas involved in the control of a task for which subjects demonstrate particular expertise exhibit different neuroanatomical and neurophysiological features. For example, professional (and semi-professional) musicians have specific anatomical features in the motor system (for controlling the hands with which the musical instruments are manipulated), in the entire auditory system (for processing the musical sounds) and in the cognitive system (for controlling memory and attention functions) [92]. Such distinctive neuroanatomical features are not restricted to musicians. Other groups with specific expertise reveal associated specific neuroanatomical features, including professional golf players [93], academic mathematicians [94], professional taxi drivers [95], subjects with a long background of bilingual experience [96] and even typists with extensive practical experience [97].

The impact of these experience and practice-related adaptations can be seen at macro-anatomical levels. This is reflected in increased volume and grey matter density in brain areas involved in the control of the practiced task. In addition, anatomical measures that index inter- and intra-hemispheric connectivity demonstrate experience-dependent change. For example, fractional anisotropy (FA) and diffusivity, which are measures that reflect the integrity of the fibre tract system, indicate differences in experts compared with non-experts. In pianists, there is a linear correlation between the number of practice hours and the FA and diffusivity in several fibre tracts (including the corpus callosum, the longitudinal fasciculus and other fibre tracts) [98]. In addition, the corticospinal tract has been shown to have different FA and diffusivity values correlated with
the commencement of musical training [99]. More recent evidence shows that the fasciculus arcuatus, connecting temporal and frontal brain areas, is differently organized in professional musicians [100].

Experience and practice-related adaptations can also be identified at the level of neurophysiological activation, as indexed by changes in haemodynamic responses in EEG–MEG-based measures of brain areas responsive to the task. Typically, activation in the involved brain areas decreases with increasing experience, thus indicating increased neural efficacy with increasing practice (optimization of neurophysiological activation) [101,102]. In addition to optimization of neural activity, a change in the activation pattern occurs with new areas becoming active in the experienced state [103,104]. The more efficient those brain areas that were primarily engaged in a given task become, the more other secondary brain areas engage with these primary areas in the control of behaviour. This means that over the course of learning, change in activation pattern reflects a change in the contribution of psychological functions to the control of the particular task.

Structural and neurophysiological remodelling has been observed in the human brain over periods of weeks to months. However, the fastest plastic changes have been identified at the microscopic level, with dendritic spines sprouting not later than 30 min after presynaptic tetanic stimulation [105]. Using multi-modal pharmaco-neuroimaging, acute D2 receptor blockade has been demonstrated to induce reversible striatal volume changes and structural–functional decoupling in motor circuits within several hours [106]. In addition, these anatomical and neurophysiological changes were strongly related to motor deficiencies.

In summary, the human brain is highly plastic and can adapt rapidly to environmental changes. A major finding of plasticity research is that experience-dependent anatomical and neurophysiological changes can fade away as practice stops, indicating that plasticity is possible in both directions. This leads to the metaphor ‘use it or lose it’ in emphasizing the reliance of the neural networks on use-dependent influences. Although brain plasticity is an important mechanism for the human brain, it is also associated with the same practical problems. For example, rapid changes in the brain need to be monitored to ensure that only those changes are maintained that are necessary for further cognitions and behavioural control. Sleep, with its associated neurophysiological activation stages, is one such mechanism that most probably facilitates the retention of more important and loss of less important plastic changes.

(b) Sleep and learning: theoretical models

The brain passes through several stages during sleep, with each stage being associated with a particular neurophysiological activation pattern. Human NREM sleep (and particularly SW) has been demonstrated to be beneficial for the consolidation of several types of memory [86,107]. Evidence supporting a memory consolidation hypothesis of NREM sleep has been converging for declarative memory tasks (for a recent review, see [86]). Although evidence for the role of sleep in the consolidation of motor memory has been accumulating [107–114], some design and task-induced confounds have been highlighted that challenge the main hypothesis [115]. A recent study that controlled for circadian rhythm and massed practice effects [116] found no beneficial effects of sleep on motor memory.
Another recent study [117] specifically controlled for task-related inhibition owing to massed practice in a finger-tapping task (with 30s blocks of tapping and rest), and observed a pattern of skill deterioration during the day and stabilization during the night. This is inconsistent with the typically observed pattern of enhancement during sleep, however, it is not in disagreement with a network reconfiguration and systems consolidation perspective of sleep. We will focus on how NREM oscillations and functional connectivity may be related to brain plasticity and systems consolidation of motor memories, and we will first briefly recapitulate two current models of information transfer and consolidation during sleep.

According to the so-called synaptic homeostasis hypothesis [118], synaptic strength is changed during the slow wave sleep stage (SWS). The basic assumption is that there is a net-increase in synaptic strength during wakefulness. This increase of synaptic strength is the result of experience and learning during wakefulness. As mentioned earlier, even short-term exposure to some environmental stimuli or even short-term motor training induces changes in synaptic strength in some networks. Therefore, many necessary and unnecessary synaptic connections are strengthened during wakefulness. Slow oscillating brain activity during the SWS is proposed to facilitate downscaling of the synaptic strengths. This downscaling is proposed to be necessary to keep energy and volume demands constant and enable reuse of synapses that are no longer required. Downscaling of synaptic strengths is thought to be associated with the elimination of weak synaptic connections. The net result of this is a kind of an enhanced signal-to-noise-ratio between strong and weak synaptic connections. This means that memory engrams, which are stored in networks with strong synaptic strengths, may become stronger, while memory information stored in networks with weak synaptic strengths is eliminated.

An alternative model focuses on explicit memory processes and argues that there is also a specific consolidation process operative during the SWS (reprocessing and systems consolidation hypothesis) [86]. The basic assumption of this hypothesis is that information during waking is encoded in both neocortical and hippocampal networks. In subsequent SWSs, the representations in the hippocampus are reactivated. In addition, the slow oscillations present during SW are thought to enable an effective hippocampus-to-neocortex transfer of the reactivated information. However, sleep-related plasticity and systems consolidation in cerebello-striato-cortical circuitry subserving motor skills [119] have not yet been integrated into this model. It has been hypothesized that persisting synaptic changes are induced by SW but are nevertheless supported by the following rapid eye movement (REM) sleep. Thus, the succession of SW and REM sleep is proposed to be crucial for the formation of new memory engrams and for transferring new information to the neocortical memory network. This is in accord with studies that observed reactivation of visual and premotor cortices in REM sleep after visuomotor skill acquisition [120], with increased connectivity between the visual cortex and striatum during REM sleep when the visuomotor task involved a predictable (but implicit) sequence [121]. These two models are not mutually exclusive as each seeks to explain memory consolidation during sleep. Evidence for memory consolidation as an active process is increasing (see [86]), and considerations about sleep-related memory consolidation will probably further develop with the growing availability of experimental data.
Could it be that the alteration of different functional connectivity modes informs us about the mechanisms operative during memory (re)processing? During sleep, there is a constant alteration between a distributed functional network (light sleep) and strongly separated functional modules (SW). As they are more or less disconnected from other brain areas, they most probably operate independently of other modules. Undisturbed processing bears the advantage that particular memory information may be activated and maintained in this network without the interfering influence of activity from neighbouring networks or modules. Some of these modules, which have been shown to become active during slow oscillations in SW, strongly overlap with brain areas that are also strongly involved in the control and consolidation of complex motor learning (see below). Thus, motor learning before sleep may well lead to transient motor memory engrams being partly stored in these areas and reactivated and strengthened during sleep but without interfering neural activity.

The parietal areas (inferior parietal lobule (IPL) and superior parietal lobule (SPL)) are strongly involved in the control of complex motor functions, especially in situations when movements are related to external or internal reference information [122,123]. It is conceivable that the motor-related networks located in these areas are reprocessed in sleep too. Neuroimaging evidence for this hypothesis has been provided by Walker and colleagues [109]. Following sleep (relative to wake), the right primary motor cortex (M1), the medial prefrontal lobe, the hippocampus and the left cerebellum demonstrated increased haemodynamic responses on a motor task. In contrast, signal decreases were identified in parietal cortices, the left insular cortex, temporal pole and fronto-polar region. While the former regions are part of the motor control network (except the hippocampus, which obviously plays a special role here), the latter group of brain areas is more involved in conscious spatial monitoring and the processing of emotional associations (e.g. emotional burden to perform the task). Thus, increased activation in the motor areas after a night of sleep can support faster motor output and more precise mapping of key presses. The decreased parietal activation following sleep corresponds to decreasing parietal activation identified during motor skill learning [123], a phenomenon believed to reflect improved sequence automation. In addition, daytime learning of a motor task resulted in an increased amount of NREM SWA over the parietal cortex [124]. Huber et al. [124] showed in a high-density EEG experiment that a visuomotor task (rotation adaptation) triggered a local increase in SWA in the parietal areas (on the delta and fast spindle frequency bands) and that this local increase was correlated to improved performance of the task after sleep. These considerations lead to the view that SWA synaptic strengthening might occur during NREM in parietal networks and be instrumental in improving the functions controlled by this network.

Moreover, sleep spindles could play a mediating role in network reconfiguration and overnight improvement of motor skills [34], as fast spindles have been shown to be associated with activity in the sensorimotor cortices and supplementary motor areas, besides activity in the thalamus, anterior cingulate, insula that was also observed in association with slow spindles [7]. Although spindles are particularly increased in humans after declarative memory tasks [125–128] and also associated with increases in performance on visuospatial memory
tasks [129,130], several studies have noted an increase in spindles after motor skill learning [131–133]. A relationship between sleep spindles and improvements on a motor task has been observed ([134,135] but also see [136]), and this relationship appeared to be mediated by premotor and parietal regions [134]. These findings may relate to the pre- and postcentral gyri being network hubs in stage 2 (table 1), although only the precuneus (not the parietal lobule) is a parietal hub in SW. Here, it is also worth noting that although sleep spindles are a typical characteristic of light sleep stage 2, they also occur in SW—their interplay with hippocampal ripples during an upstate of a slow oscillation has been proposed to be essential for brain plasticity [86]. One study on humans has provided evidence that a finger-tapping task led to an increase of hippocampal (intracranial) EEG power in the low-frequency range and that this was correlated with performance enhancement in epileptic patients [137]. More research is needed to examine how slow and ultraslow fluctuations organize higher frequency fluctuations during sleep [10,11]—and how this is related to skill acquisition in wakefulness.

(d) What needs to be shown in future experiments

To delineate the influence of sleep on motor memory consolidation, one has to detail what is consolidated during motor memory consolidation, as motor memory consolidation is in itself a complicated issue.

Motor memory consolidation can be demonstrated using different tasks. For example, repetitive finger tapping is enhanced after practising for several hours, with M1 being the main brain area involved in improving tapping performance [138]. Serial reaction time tasks (SRT; also termed motor sequence learning tasks) are widely used in sleep research. Mostly, these tasks are implicitly controlled, but they partly require the contribution of explicit control (for example, conscious insight into the sequence). The control of SRT requires the processing of response-, stimulus- and effector-based information. Effector-independent information (e.g. the visual–spatial coordinates of the successive locations in SRT) is coded in the IPL. On the other hand, coding of effector-specific information in egocentric space (e.g. motor-response coordination) is identified in early activations within M1 [139]. And the particular stimulus modality (visual, tactile or auditory) plays a specific role too [140]. Thus, motor control for SRT is much more complex than for simple finger tapping and involves, besides M1, premotor areas, the IPL, SPL and, in part, the hippocampus [141]. A further typical and widely implemented motor task setting uses variants of visuomotor association or visuomotor tracking tasks [142,143]. These tasks are much more complicated than the other motor tasks discussed. Most importantly, they require the participation of brain areas that are involved in sensorimotor transformation (IPL and the intraparietal sulcus), stimulus-motor mapping (managed by the lateral premotor cortex), sensory processing and the recall of motor goals from memory (hippocampus and IPL) [139].

A further distinction has to be made as to whether we have to learn a particular motor task anew (motor learning) or adapt a previously learned motor behaviour to changing environmental circumstances (motor adaptation). While motor learning requires the establishment of a motor programme, motor adaptation requires the improvement of motor parameters inserted into the previously acquired motor programmes. It has been shown that motor learning more strongly
relies on the cortico-striatal system, while motor adaptation is more strongly dependent on the cortico-cerebellar system [144,145]. It has been proposed that sleep benefits tasks involving cortico-striatal systems (through interaction with hippocampal systems) rather than cortico-cerebellar systems [119]. Moreover, motor learning and motor adaptation can take place in an early or late training phase. The neurophysiological changes during early learning are different from those obtained during late learning [144]; the hippocampus has been shown to be more strongly involved during late learning [139]. Finally, it makes a difference whether motor learning involves coordination of both hands as opposed to unimanual movements [146].

Taken together, motor consolidation is quite complex. Most motor learning and motor memory tasks investigated thus far in the context of motor memory consolidation require sensory and cognitive information. Thus, sensory and cognitive brain areas have been recruited during most motor memory consolidation studies in the context of sleep. Future experiments should use experimental designs that allow separation of ‘true’ motor memory consolidation from the more ‘sensory and cognitive’ aspects of motor learning and motor adaptation. It has to be demonstrated whether the so-called cognitive brain areas (and the activation pattern therein) and classical motor areas benefit directly or indirectly from particular sleep phases. Current data support the notion that the cognitive areas should benefit more from various sleep phases, but the potential benefit of sleep on classical motor areas is in need of investigation. A further problem that has still to be solved is whether time of day effects, or effects of circadian rhythm are important variables in modulating the sleep-dependent motor memory effects.

5. Conclusion

In the previous sections, we discussed the neural correlates of sleep spindles and slow oscillations during human NREM sleep, and that the large-scale functional brain network moves towards a globally distributed network in light sleep and towards a network consisting of segregated modules in SW. These alterations in network topology during sleep may point to critical network reconfiguration relevant to brain plasticity, with the network in light sleep being optimal for the global transfer of information and the network in SW optimal for isolated reprocessing of information. Sleep-specific oscillations are thought to play a critical role in the transfer and reprocessing of information during sleep, and evidence suggests that regions involved in motor activity and planning are hubs in light sleep stage 2 and are strongly associated with spindles. In conclusion, we propose that a network approach to functional connectivity in sleep may provide greater understanding of the relationship between sleep-specific events and brain plasticity.

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