Oscillating circuitries in the sleeping brain

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Abstract | Brain activity during sleep is characterized by circuit-specific oscillations, including slow waves, spindles and theta waves, which are nested in thalamocortical or hippocampal networks. A major challenge is to determine the relationships between these oscillatory activities and the identified networks of sleep-promoting and wake-promoting neurons distributed throughout the brain. Improved understanding of the neurobiological mechanisms that orchestrate sleep-related oscillatory activities, both in time and space, is expected to generate further insight into the delineation of sleep states and their functions.

Electroencephalography (EEG). The gross electrical activity non-invasively recorded from dipoles at the level of the skull or scalp; this activity is largely considered as a proxy of neocortical activity.

Local field potentials (LFPs). Oscillations recorded directly from the extracellular space, resulting from the firing of localized groups of neurons.

Slow oscillations Bimodal oscillations (<1 Hz) of the cell resting membrane potential, typically cortical or thalamic neurons, between hyperpolarized (DOWN) and depolarized (UP) states.

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https://doi.org/10.1038/s41583-019-0223-4

Since the first recordings of electrical activity in the brain[1,2], scalp electroencephalography (EEG) has been commonly used to measure the differences in generalized brain activity between wakefulness and sleep. The classical descriptions of sleep-related brain activity, which were derived from low spatial resolution EEG, led to the distinction between rapid eye movement (REM, also termed paradoxical) sleep and non-REM (NREM) sleep (FIG. 1a). However, the multifaceted organization of sleep-related brain activity in space and time has only been appreciated in the past decade. Theta and gamma rhythms are the hallmarks of REM sleep as recorded by scalp EEG or intracranial local field potentials (LFPs, FIG. 1a), whereas the predominant oscillations during NREM sleep are slow oscillations, delta waves, spindles and sharp wave–ripples (SWRs). These typical sleep-related oscillations result from the synchronous activity of neural circuits restricted to the thalamus, neocortex or hippocampus. Their amplitudes correlate with the level of synchronization of underlying neuronal firing, and strongly depend on the intrinsic properties of ion channels, transporters and receptors expressed at the cell membrane, cell morphology, and extrinsic influences from synaptic inputs and background neural activity (that is, noise). At the network level, neural circuit oscillations might also result from monosynaptic interactions between fast excitatory and inhibitory neurons, feedback loops (for example, recurrent thalamocortical resonance) and slower forms of neuromodulation.

Advances in multichannel surface and intracranial electrophysiological recordings in humans and rodents, together with functional imaging of brain activity across sleep states, have revealed a complex landscape of region-specific activity. For example, 21-channel EEG recordings in humans showed a marked increase of oscillatory activity in the theta band concomitant with a decrease in the alpha band at the onset of NREM sleep; this increase initially occurred in midline but not lateral cortical areas, and later propagated to posterior areas[3]. Similarly, low-frequency oscillations resembling those of NREM sleep have been detected during wakefulness in local brain areas in rodents and humans[4–7], suggestive of fragments of sleep during wakefulness. Collectively, these advances have triggered a shift in the understanding of sleep states and the need for their delineation in time and space. In particular, the nature and mechanisms of region-specific sleep oscillations and the boundaries between sleep and awake states have attracted increased attention.

Novel imaging and recording techniques in rodents have opened new perspectives in understanding the brain mechanisms of sleep, from cortical EEG activity at the mesoscale level down to multiple, local, cell-defined signatures of sleep states[8]. Optogenetic technologies have enabled the selective recording, activation and silencing of targeted cells in freely moving rodents and non-human primates. The application of these experimental techniques in sleep research has led to the identification of several single circuits (defined here by a given cell population and its input–output map) that are either sufficient or necessary for triggering states of wakefulness, NREM or REM sleep[9], or at least some aspect of those states (BOX 1; FIG. 1b). These investigations have demonstrated that high-resolution modalities for investigating sleep-relevant oscillatory mechanisms have increased our understanding of the control and function of sleep.

This Review focuses on the neurobiological mechanisms underlying neuronal network oscillations in the sleeping mammalian brain, their orchestration in space and time across state transitions, and their possible connection with identified NREM and REM sleep-active neurons. The coalescence of heterogenic sleep oscillations during consolidated sleep states is reviewed in light of their role in sleep architecture and function. Note that highly species-specific oscillations that are

absent in mammals (such as mu and alpha rhythms[10], low-beta (12–20 Hz) oscillations[11], vertex waves[12] and sawtooth waves[13]) are outside the scope of this article. Respiration-coupled[14,15] and heartbeat-coupled[16,17] oscillations, which have been recorded in the sensory cortex, hippocampus or amygdala, are not discussed because their underlying mechanisms remain unclear; however, the reader should note that such oscillations could have a confounding effect on some of the rhythms described here, in particular on delta wave synchronization. The circadian[18], genetic[19], metabolic[20], developmental[21] and immune[22] regulation of sleep are likewise not covered, as these topics have been extensively reviewed elsewhere.

Network oscillations in NREM sleep

In mammals, NREM sleep is associated with a reduced response to external stimuli (for example, auditory and tactile stimuli), a fall in body temperature, stabilization of heart rate and sequential reductions in awareness of the environment. The original Rechtschaffen and Kales sleep scoring system[23] used in polysomnography studies divided NREM sleep in humans into four distinct stages (S1–S4) corresponding with changes in oscillatory activity that represent increasing sleep depth. This system was simplified in 2007 by the American Academy of Sleep Medicine, which devised a multimodality scoring system that now includes three stages of NREM sleep (N1–N3; in which N3 represents stages S3 and S4 combined) together with arousals and respiratory, cardiac and movement events[24]. The S1–S4 nomenclature remains in use in experimental settings where the detection of S3-specific brain activity is relevant. However, the use of sleep staging has been criticized owing to its subjectivity, which is attributable both to brief, transient states (such as micro-arousals) and the continuum of complex brain oscillations across states[25].

The transition from quiet wakefulness to eyes closed in humans is characterized by the onset of cortical alpha waves (8–11 Hz), which is followed shortly thereafter by theta waves (4.0–7.5 Hz) in the N1 stage and by intermittent spindles (11–14 Hz) and K-complexes in N2 sleep. The N3 stage is characterized by large-amplitude, slow oscillations (<1 Hz) and delta waves (1.0–4.5 Hz; FIG. 1a). In humans, the onset of NREM sleep can be accompanied by hypnagogic hallucinations reminiscent of the dreams that occur during REM sleep[26,27]. In rodents, the onset of NREM sleep is indicated by distinct slow-wave oscillations (0.5–4.5 Hz), in which spindles irregularly occur (FIG. 1a,c). Despite the presence of these oscillations in EEG or LFP recordings, only one NREM stage is classically described in rodent species, although the results of one study (which so far has been published only in preprint form) suggest that additional NREM stages can be defined[28].

This Review emphasizes the brain activities recorded in rodent NREM sleep, which is analogous to human stages N2 and N3. These NREM sleep oscillations originate mainly from reverberating circuits described as 'feedback loops', between thalamic and neocortical cells. Although the mechanisms contributing to these oscillations have been extensively studied at a molecular, cellular and network level, current understanding of their origin, features and synchronization at a network level has largely been derived from correlational approaches that measured activity across brain regions. However, perturbational studies have demonstrated that functional connectivity is necessary for the coordination of sleep oscillations in time and space. These oscillations are described in the following sections.

Slow waves. Slow waves (0.5–4.5 Hz) were among the first brain activity patterns recorded from the human scalp during sleep[29,30] and include two independent components, namely slow oscillations (<1 Hz)[31,32] and delta waves (1.0–4.5 Hz)[33]. During NREM sleep, slow oscillations reflect variation in the resting membrane potentials of thalamic and cortical neurons, which switch between depolarized 'UP' (also termed 'active') and hyperpolarized 'DOWN' (also termed 'quiescent' or 'inactive') states. The terms UP and DOWN refer to oscillations of the resting membrane potential derived from intracellular recordings described first in cats[31] and subsequently in rodents[7], whereas the terms active (ON) and inactive (OFF) refer to the neuronal firing patterns (often recorded extracellularly) associated with these UP and DOWN states in humans[34,35] and rodents[36]. These terms describe different manifestations of slow waves. During the UP state, thalamocortical cells (relay neurons) and corticothalamic cells show intense synaptic activity (both excitatory and inhibitory) and fire bursts of action potentials whereas, during the DOWN state, their membrane hyperpolarization induces a period of relative quiescence[4,36]. UP and DOWN states last for a few hundred milliseconds each, depending on species, the time and site of recordings, and experimental conditions (for example, anaesthesia versus natural sleep)[6,35–38] (BOX 2). Thus, the alternation of UP and DOWN states during NREM sleep generates a slow oscillation at <1 Hz frequency measurable by both EEG and LFP electrodes across thalamocortical structures, including primary sensory, association and motor cortices[39,40], thalamic relay areas[41] and the thalamic reticular nucleus (TRN)[42,43] (FIG. 2a). Mechanistic studies of the transition from the DOWN state to the UP state showed that the onset of the UP state originates in layer 5 neocortical neurons, possibly from a subset of pacemaker pyramidal neurons[44–46], whereas its termination involves astrocytes[47] and inhibitory cortical interneurons[48,49] (FIG. 2b). Activation of corticothalamic cells during the UP state further exerts strong excitatory feedback control on thalamic relay cells, leading to an increased probability of spindle generation (discussed further below; FIG. 2c), which is associated with slow waves in rodents[42,50,51], cats[42] and humans[52].

Slow oscillations persist in the neocortex after thalamectomy[33], pharmacological blockade of thalamic activity[53] and in isolated cortical slabs[32,46,54], but disappear in the thalamus of decorticated animals[55], which suggests that slow oscillations have a cortical origin. Nevertheless, emerging experimental evidence supports a contribution of midline and dorsal thalamic structures to the generation of cortical slow waves (for example, at the onset of local cortical UP states) in anaesthetized and spontaneously sleeping mice[6,56], rats[57] and humans[58]. In addition, thalamic lesioning[59] and pharmacological

Thalamus
A symmetrical collection of nuclei in the diencephalon, with functions including sensory relaying to neocortex, alertness, consciousness and motoric output, which is heavily implicated in the genesis of sleep oscillations.

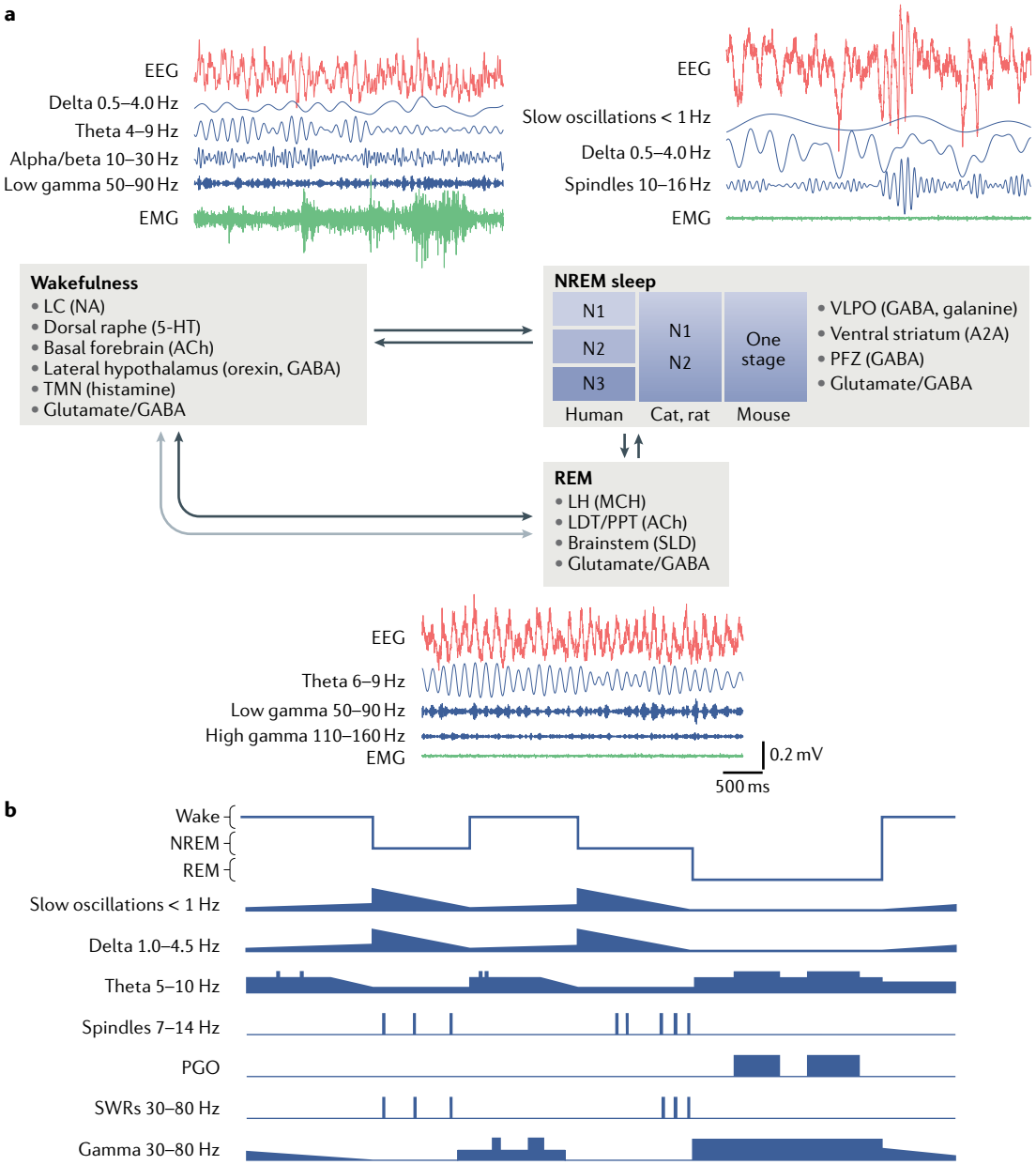
Resonance
The natural frequency of an oscillating circuit without any external inputs.

State transitions
Changes from one vigilance state to another (that is, from wakefulness to non-rapid eye movement sleep), which are associated with transient network activity.

Polysomnography
A multiparametric test, including the electroencephalogram, electromyogram, electrooculogram and electrocardiogram, commonly used to measure sleep.

Slow waves
A term often used to define low frequency high amplitude electroencephalography events (0.5–4.0 Hz) predominating during deeper non-rapid eye movement sleep and including both slow and delta oscillations.

Bursts
Neuronal firing pattern consisting of regular periods of intense activity interspersed with periods of relative quiescence (also referred to as phasic activity).



blockade[53] transiently abolish slow waves in connected areas of the neocortex, although similar waveforms then reappear through unknown, possibly compensatory, mechanisms. These observations suggest a thalamic contribution to sleep-related slow waves (FIG. 2c). Of note, optogenetic approaches have successfully been used to induce slow-wave activity[6,60,61]. Together, the results of these studies suggest that slow waves can originate from cortical or thalamic sources, or both, and that these waves can overlap both temporally and spatially[59,62].

The original descriptions of highly synchronous slow waves throughout the cortex suggested that they represent a global, uniform cortical event. However, multichannel recording technologies subsequently revealed that spontaneous slow waves show regional specificity in rodents[4] and humans[5,63,64]. According to these findings, slow waves behave as travelling waves that originate from discrete cortical areas predominantly located in the frontal region (as shown by EEG source modelling and EEG analyses)[5,63,65] and preferentially propagate along a frontoparietal axis and along cingulate pathways in cats[66,67] and humans[34,64]. Only a small proportion of these waves reach posterior cortices[62,68] (FIG. 2b). The consistent origin and stability of slow-wave propagation over several nights' observation[63], together with their sensitivity to thalamic[59] or cortical[69] lesioning, suggest that brain-wide synchronization of slow waves relies on the recruitment of circuits that encompass both cortical and thalamic structures. Their recurrent nature after perturbation (for example, lesion or receptor blockade) suggests the existence of compensatory mechanisms that are essential to NREM sleep maintenance or homeostatic functions.

Human brain functional imaging has revealed that, compared with wakefulness, NREM sleep is associated with reduced whole-brain (global) and regional metabolism, as measured by either brain glucose utilization or

◀ Fig. 1 | **Sleep-state specificity of oscillations. a** | Typical electroencephalography (EEG) grapho-elements associated with vigilance states in freely moving mice are composed of state-dependent oscillations generated by a series of cardinal cellular networks. During wakefulness, multiple cortical and subcortical networks show high frequency and/or low amplitude activity, including theta and gamma oscillations, which signal interactions with the environment, whereas high electromyography (EMG) activity signals body movements. At the onset of non-rapid eye movement (NREM) sleep, EMG activity is low and EEG activity is dominated by high-amplitude, low-frequency slow waves (<4.5 Hz) that include slow oscillations (<1 Hz) and delta waves (0.5–4.5 Hz). Spindles (10–16 Hz) are transient events generated by the interplay between neocortical and thalamic circuitries. During REM sleep, EEG activity predominantly comprises theta (6–9 Hz) and gamma oscillations (30–150 Hz) generated by the hippocampus and cortical networks, respectively. EMG tone is further reduced, reflecting postural muscle atonia (sleep paralysis). The mammalian sleep–wake cycle is composed of three vigilance states: wakefulness, NREM sleep and REM sleep. In humans, NREM sleep is divided into three stages (N1–N3), versus two stages (N1, N2) in cats and rats, and one stage in mice. Black arrows indicate transitions between sleep–wake states. Transitions from wakefulness to REM sleep (grey arrow) can occur in humans but are rare in rodents. According to current views (BOX 1), NREM sleep results from the activity of anterior hypothalamic cells in the ventrolateral preoptic area (VLPO) and median preoptic nucleus, whereas REM sleep results from the activity of neurons located in the brainstem: sublaterodorsal nucleus (SLD), ventrolateral periaqueductal grey, gigantocellular nucleus and lateral hypothalamus (LH). Wakefulness results from activation of the ascending reticular formation, which is composed of brainstem arousal systems: locus coeruleus (LC), dorsal raphe, laterodorsal tegmentum (LDT) and pedunculopontine tegmentum (PPT), together with neurons located in the hypothalamus and basal forebrain. Note that only the major systems and connectivity maps are shown to illustrate the key nodes implicated in brain control of sleep–wake states. Importantly, this representation does not take into account the region-specific activity of the brain during sleep or its temporal dynamics. **b** | Representative hypnogram of the mouse sleep–wake cycle, showing network oscillations associated with vigilance states. Sleep oscillations represent a continuum of brain activity across sleep–wake states. Thus, at any point in time, one type of oscillation tends to dominate, although other bands are always present to a variable extent. During active wakefulness, slow wave and delta power are low and theta and gamma oscillations are high. The former increase during quiet wakefulness before the onset of sleep and become the dominant frequency during NREM sleep. Slow wave amplitude progressively reduces over the course of an NREM episode as sleep pressure dissipates. Note that during NREM sleep, spindles and sharp wave–ripples (SWRs) occur concurrently as isolated events. The start of REM sleep is characterized by increased theta power. Theta rhythm is high before the onset of REM sleep and becomes predominant during stable REM sleep, with switches between tonic (low power) and phasic (higher power) theta rhythms. The latter are associated with ponto-geniculo-occipital (PGO) waves of brainstem origin. Gamma oscillations are high during active wakefulness and wane as the onset of sleep approaches. At the onset of REM sleep, a large increase in gamma power is coupled (phase-amplitude locked) to theta oscillations. 5-HT, 5-hydroxytryptamine (serotonin); A2A, adenosine A2A receptor; ACh, acetylcholine; MCH, melanin-concentrating hormone; NA, noradrenaline; PFZ, parafacial zone; TMN, tuberomammillary nucleus.

cerebral blood flow[70,71]. Thus, the observed reduction in activity in the thalamus and cortex during NREM sleep might not relate to the origin of NREM sleep oscillations but rather could reflect a state of low energy consumption that is inversely proportional to the amplitude of the slow-wave activity[72]. Human brain functional imaging further confirmed recruitment of the frontal cortex during slow waves[63,65,70,72].

Delta waves (1.0–4.5 Hz) are most common during deeper stages of NREM sleep in humans and have two proposed mechanisms, one originating in the thalamus and the other in layer 5 cortical neurons[46]. In the thalamus, membrane hyperpolarization activates the hyperpolarization-activated cation current (I_h), resulting in increased sodium conductance and gradual membrane depolarization. In turn, this depolarization induces the opening of T-type calcium channels, which increases calcium conductance and activates the transient, low threshold calcium current (I_T); subsequently, this activation induces low-threshold calcium spikes. Cortical layer 5 neurons also exhibit an intrinsic delta oscillation, as revealed in the deafferented cat cortex[33], which is dependent on acetylcholine-sensitive potassium conductance[46]. Which of these two mechanisms is most important for delta oscillations during sleep remains unclear; however, investigations using optogenetic silencing of midline and dorsal thalamic neurons have demonstrated a reduction of oscillation amplitude in delta frequencies in cortical regions[6], which suggests that the thalamus has a driving role.

K-complexes. K-complexes occur as spontaneous events during stage N2 sleep in humans but remain less well described in rodents. K-complexes were originally described as consisting of a slow component, ~1 s in duration and with a signal strength of several hundred microvolts, followed by a regular 14 Hz rhythm "superimposed on the slow waves [that] may persist for several seconds afterwards" (REF.[29]). This 14 Hz rhythm was probably a spindle accompanied by an alpha burst, which corresponds to a refractory period during which sensory stimuli fail to either evoke a slow wave or induce a transition to wakefulness. Thus, spontaneous K-complexes and spindles reflect two sides of the same coin — inhibitory and excitatory microstates, respectively[34].

K-complexes can be evoked by sensory (auditory, tactile or somatosensory) stimulation. Originally discovered in responses to auditory stimuli (K refers to knock) or modality-independent stimulation (such as arousal related to respiratory effort) during NREM sleep in humans, cats and rats, these complexes cannot be elicited during REM sleep[29,68,73]. Moreover, not every peripheral stimulus during NREM sleep will evoke a K-complex, presumably owing to their temporal coincidence with thalamic and cortical DOWN states[32,45,74], during which cells are refractory to excitatory inputs. A functional implication of this temporal concordance is that the arousal threshold (that is, whether a sensory stimulus causes awakening from sleep) might depend on the timing of the stimulus — and, presumably, its modality — in relation to the level of ongoing brain activity in the corresponding cortical area[71,74]. In this context, the classical view that the thalamus 'gates' sensory input during sleep[75] has been revisited in the light of experimental evidence showing that information from the periphery (for example, an auditory stimulus) still reaches the cortex even during NREM sleep[76,77]. Where in the thalamic circuitry and when this sensory gating occurs during sleep remain to be investigated.

Spontaneous and evoked K-complexes show similar EEG graphoelements independent of topography, suggesting that they are a modality-independent and sleep-specific response to sensory stimulation that does not involve primary thalamocortical relay pathways[73], although responses to auditory stimuli are seen in primary and secondary auditory cortices of sleeping rats[77] or monkeys[76]. Following investigations in humans and anaesthetized cats, K-complexes were suggested to be a manifestation of the slow oscillation at the cortical level that is temporally coupled to spindles and periodically synchronizes with delta waves in the thalamus[78].

Arousal threshold
The level of external stimulation (that is, acoustic or somatosensory) to produce behavioural arousal from sleep.

Box 1 | **Models of sleep–wake states**

The flip-flop 'switch' model

According to this model, mutual inhibition creates a bistable feedback loop, that is, with two stable patterns of firing and a tendency to avoid intermediate states — features that are considered crucial to the production of defined sleep–wake states[265]. The preoptic area of the anterior hypothalamus contains sleep–active inhibitory neurons that reciprocally inhibit wake–active neurons located in the hypothalamus (orexinergic and histaminergic), basal forebrain and brainstem (noradrenergic and serotonergic). This model was later extended to include the control of rapid eye movement (REM) sleep[266], taking into account the influence of circadian rhythmicity, homeostatic control of sleep and energy homeostasis[132,265].

The reciprocal interaction model

According to this model, an ultradian oscillator in the mesopontine junction controls the regular alternation of REM and non-REM (NREM) sleep periods[267] through pontine REM-active (ON) cholinergic and non-cholinergic cells and REM-inactive (OFF) noradrenergic and serotonergic systems[267]. This model was later extended to include GABAergic and glutamatergic neurons after studies in cats showed that the pontine peri-locus coeruleus (a region corresponding to the sublaterodorsal nucleus in rats) is responsible for REM sleep onset[268]. Accordingly, glutamatergic neurons in the sublaterodorsal nucleus are considered REM-promoting cells, although cholinergic neurons might also be involved in the modulation of theta rhythm[215]. The projections of these neurons to the basal forebrain and thalamic nuclei modulate cortical activity, whereas their innervation of glycinergic premotor neurons located in the ventral gigantocellular reticular nucleus is responsible for REM sleep atonia[268].

The thalamocortical loop model

The switch and reciprocal interaction models share the basic principle of reciprocal inhibition between sleep–active and wake–active circuits, the causal nature of which has been experimentally confirmed in some respects[9]. According to the thalamocortical loop model, however, sleep is initiated locally at the neuronal level as a consequence of previous activity and is only afterwards consolidated by central mechanisms[8]. Thus, the homeostatic regulation of sleep occurs in multiple brain circuits in response to prior cellular or network activity, as reported for the local modulation of slow waves in rats[4] and humans[5]. In this Review, we emphasize the role of thalamocortical circuits in controlling cortical oscillations (those detectable by cortical electroencephalography during REM and NREM sleep).

In the NREM thalamocortical loop model, slow oscillations, delta waves and spindles during NREM sleep reflect coordinated network activity between thalamic and cortical networks. Thus, "…rather than simply [acting as] relays, thalamic neurons have sui generis intrinsic electrical properties that govern their specific functional dynamics and regulate natural functional states such as sleep and vigilance"[269]. In support of this model, bursting midline and thalamic reticular nucleus neurons contribute to cortical slow waves and spindles, respectively, and have an important role in the consolidation of NREM sleep after extended periods of wakefulness[6,56,59]. During wakefulness, activation of the ascending reticular activating system (including brainstem monoaminergic systems) and other wake-promoting neurons is associated with tonic activity of midline and thalamic reticular nucleus neurons, which attenuates these slow oscillations and thereby promotes faster rhythms[149].

The functional and behavioural implications of K-complexes remain unknown; however, these data collectively suggest a role for K-complexes in the global synchronization of sleep delta waves and spindles.

Sleep spindles. Spindles are transient, waxing and waning (that is, with a variable amplitude peaking at 100 μV) 11–15 Hz oscillations of 0.5–2.0 s in duration that persist for ~6–15 cycles. Spindles are observed during NREM sleep in humans[79,80], cats[42] and rodents[81–83] (FIG. 2a,c) and propagate across the cortex[84,85]. The features of spindles are influenced by genetic background[86], pharmacological treatments[87] and circadian rhythm[88]. Spindles are single events that are frequently, but not exclusively, associated with the UP state of a slow wave[52,89–91]. In humans, spindles predominate in central and parietal neocortical areas, where they display an average frequency of 14 Hz (REFS[42,64,79]). Fast and slow spindles are distributed across frontal and occipital areas, respectively[92,93], although the available detection methods show poor agreement[94]. Spindles are temporally associated with distinct haemodynamic changes in the lateral and posterior thalamus, the anterior cingulate cortex, and insular and neocortical structures, which suggests the existence of two functionally distinct spindle generators[95,96] involving the thalamus[52,97]. This hypothesis awaits confirmation in further investigations, particularly in rodents, in which spindle executive circuits have increased accessibility to electrophysiological recordings[88].

During spindles, thalamocortical cells transiently exhibit strong burst firing, which generates typical spindling activity within thalamocortical cell circuits. Volleys of TRN inputs in the spindle frequency range provide strong inhibition by evoking inhibitory postsynaptic currents in thalamocortical cells with inputs from the sensory thalamus, resulting in a large hyperpolarization[42]. This hyperpolarization itself triggers the depolarizing I_h current. An I_T current immediately following this depolarizing I_h current produces a burst of action potentials in thalamocortical neurons[98]. These bursts of spikes directly excite layer 4 pyramidal neurons in the corresponding cortical area, where they elicit excitatory postsynaptic potentials and spindle oscillations that are detectable by scalp EEG electrodes. The pacemaker activity of TRN cells and functional inputs to TRN cells from the cortex are sufficient to generate spindle-like activity[60], whereas cortical inputs to the TRN are responsible for spindle termination[99,100]. Similarly, bipolar stereo-EEG recordings in humans suggest that convergent cortical DOWN states lead to thalamic DOWN states and thalamic cell hyperpolarization, hence triggering spindles, which are transmitted to the cortex at DOWN to UP transitions[101]. Thus, reciprocal interactions between the thalamus and the cortex shape the duration and amplitude of spindles[82]. Of note, spindle-like oscillations have been reported in the hippocampus of people with epilepsy[102]; however, whether these oscillations result from a circuit architecture similar to that underlying thalamocortical spindles or support related brain functions remains to be investigated.

Sharp wave–ripples. SWRs consist of non-periodic transient field potentials, known as the sharp wave, on which is superimposed a fast, periodic oscillation (150–200 Hz), referred to as the ripple[103,104]. SWRs last 50–100 ms and occur prominently in the hippocampal CA1 pyramidal layer during NREM sleep but have been observed in all regions of the hippocampal formation (including CA3, subiculum, presubiculum, parasubiculum and the entorhinal cortex) in rodents[105,106], non-human primates[107] and humans[108]. SWRs are highly irregular in their occurrence and their incidence rate has been reported to vary from 0.01 Hz to 2.00 Hz during awake immobility, rearing or goal-directed behaviours such as eating and drinking[109] (BOX 3).

The basic mechanisms supporting the generation and propagation of SWRs in the hippocampus remain undetermined. The bursting of CA3 cells onto the CA1

Tonic activity
Neuronal firing pattern in which each action potential occurs at a regular sustained interval with no quiescent period.

Circadian rhythm
Oscillations of physiology and behaviour with a 24-hour periodicity, synchronized to the revolution of the Earth.

stratum radiatum is thought to generate the sharp wave, whereas local CA1 excitatory and inhibitory circuits are thought to generate the ripples via an interplay between CA1 and CA3 neuronal circuits[110]. This interplay might have its trigger in CA2 (REF.[111]). During each ripple cycle, pyramidal cells fire initially and provide a sufficient level of excitation in the hippocampal network to tonically drive parvalbumin (inhibitory) interneuron firing[112]. This firing in turn leads to recurrent $GABA_A$ receptor-mediated inhibition (at ~200 Hz), while also inducing synchronous pyramidal cell firing in CA1–CA3 during intermittently decreased inhibition at the ripple frequency[112,113].

Interestingly, neocortical structures are active during hippocampal SWRs, whereas brainstem and subcortical structures are metabolically quiescent (as indirectly shown by decreases in measures associated with metabolic activity)[114], in particular the mediodorsal nucleus of the thalamus[115]. Hippocampal ripples can be triggered by both cortical spindles and DOWN to UP transitions, and are central to the reactivation of fragments of wake-related experiences that are best exemplified by the 'replay' of place cell sequences. Hence, SWRs have been proposed to play a critical part in consolidating memory traces within the hippocampus and in transferring previously acquired information from the hippocampus to the neocortex, specifically to frontal and association cortices[106,116] (BOX 4). Finally, the network activity underlying spindles and SWRs during NREM sleep is predictive of firing decreases observed during subsequent REM sleep, which is suggestive of long-lasting interactions between the oscillatory circuits of NREM and REM sleep[117].

Infra-slow oscillation. Infra-slow oscillations (<0.1 Hz) have been observed in multiple brain regions, including the hippocampus, basal ganglia, locus coeruleus and thalamus, in humans and rodents[118]. In thalamocortical cells, such oscillations are modulated by periods of hyperpolarization thought to be mediated by inward rectifying potassium channels (K_{ir}) and the adenosine A1 receptor, which implicates astrocytes in the regulation of these oscillations[118]. In both mice and humans, infra-slow oscillations are localized to primary and secondary somatosensory cortices and are correlated with spindle activity[119]. A specific infra-slow oscillation (0.02 Hz) reported in mice and humans occurs as the result of an oscillation in sigma power during NREM sleep[119]. An increased likelihood of waking was noted when acoustic stimuli occurred during the descending phase of this oscillation, whereas this propensity was reduced when acoustic stimuli occurred during the ascending phase, which suggests a role for this oscillation in the maintenance or stability of NREM sleep[119].

A role for subcortical cells?

Multi-channel recordings of cortical EEG signals in humans reveal a strong heterogeneity of oscillations, both in space and time, at the onset of NREM sleep. Slow waves and low-frequency (<8 Hz) oscillations predominate in the frontal neocortex, together with an occipital theta rhythm[62,120,121]. In addition, transient parahippocampal low-frequency (1.5–3.0 Hz) activity in humans has been proposed to be a substrate of hypnagogic hallucinations, which can occur at the early stage of NREM sleep[27,122]. Although the frontal predominance of slow waves and spindles persists with increasing depth of NREM sleep[64,79,80], local cortical EEG signals show interhemispheric asynchronous activity[123]. In addition, intra-individual[124] and inter-individual[125] variations in both humans and animals[36,126] have been described, together with distinct layer-specific oscillations within a single cortical column[66].

Similar to cortical areas, subcortical structures exhibit a strong heterogeneity of temporal activity dynamics at NREM sleep onset. In humans, both the thalamus and the hippocampus display neural activities typical of NREM sleep (for example, slow wave activity and spindle-like oscillations, respectively) minutes before clear signs of NREM sleep are detectable in the neocortex[102,127,128]. Once stable NREM sleep is reached, increased firing rates of midline and dorsal thalamic neurons consistently precede cortical UP states in frontal but not parietal cortices in rodents[6,57] and humans[128,129], consistent with a region-specific control of sleep oscillations and the presence of slow waves of thalamic origin (these waves occur concomitantly with slow waves of cortical origin).

These region-specific changes in network oscillatory activities are consistent with the brain-wide anatomical distribution of sleep-active neurons and the multicentric origins of sleep[9,57,62,124,128,130–132]. Initial studies of the neuronal mechanisms of NREM sleep generation,

Box 2 | Shared and divergent features of sleep and general anaesthesia

General anaesthesia and sleep were long considered behaviourally and electrophysiologically similar (for example, slow oscillations, delta waves and spindles are seen in both) but growing evidence indicates that these two states are not identical[270].

The most important advance in understanding slow waves came from work in the 1990s that identified the UP and DOWN states of the membrane potential underlying the slow oscillation in anaesthetized cats[31,33]. Both non-rapid eye movement sleep and general anaesthesia were associated with a breakdown in cortical connectivity[271], which supported a common mechanism for the disruption of large-scale information integration[272]. However, the networks recruited by general anaesthetics and their resulting oscillations are highly agent specific (reviewed elsewhere[273]).

Experimental evidence has demonstrated that general anaesthetics recruit sleep-relevant circuitry to produce unconsciousness, particularly in the hypothalamus and brainstem[133,274], thalamus[57,275] and neocortex[271]. One study also showed that anaesthesia-tagged or sleep recovery-tagged neurons from the lateral preoptic area of the hypothalamus were able to induce non-rapid eye movement sleep, with an accompanying drop in body temperature[133], suggesting that the mechanisms that control sleep are not purely involved in consciousness control.

Moreover, general anaesthesia dramatically increases the synchrony of both global and local slow waves across cortical and thalamic neurons and across brain hemispheres[276], possibly through the corpus callosum. However, cortical UP and DOWN states and sleep spindles have differing characteristics during sleep and anaesthesia[270]; although both states produce cortical membrane fluctuations between UP and DOWN states, anaesthesia produces longer hyperpolarized DOWN states and less variability in UP state durations. Furthermore, anaesthesia produces a fairly uniform distribution of slow waves across the neocortex, whereas during natural sleep slow waves were more pronounced in association and frontal areas[270]. This observation suggests that anaesthesia alters the cellular and network properties of slow oscillations. Whether this finding is related to dose-dependent factors or to the specific molecular targets of general anaesthetics remains to be investigated.

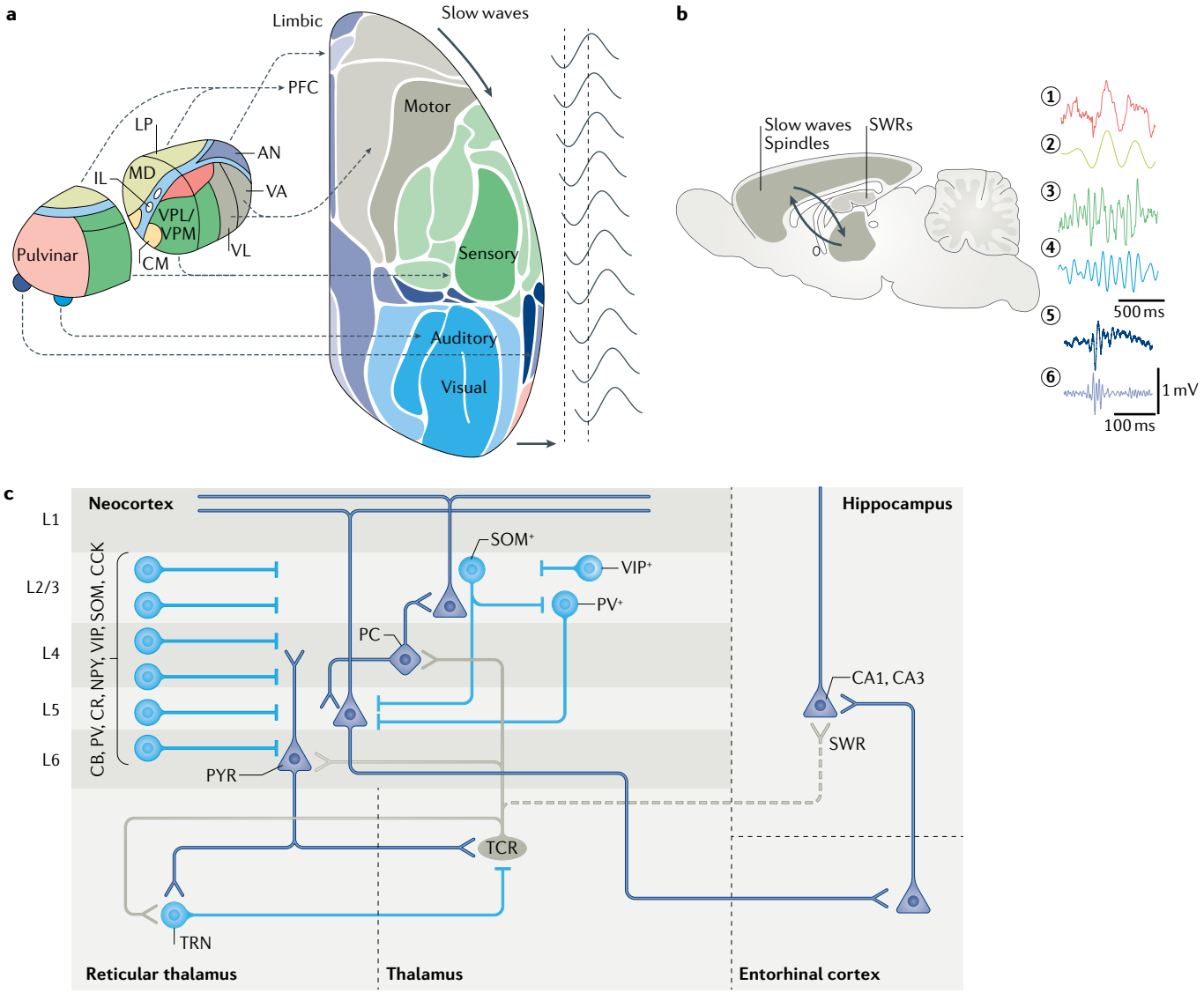


Fig. 2 | **Circuit mechanisms of NREM sleep-specific oscillations.** **a** | Parcellation of the mouse thalamus indicating different anatomical and functional areas: primary sensory (green), higher-order (pink), mediodorsal (yellow-green), midline (yellow), motor (grey) and intralaminar (blue) nuclei. Note that each functional area of the thalamus projects to a discrete primary (dark colour) and secondary (pale colour) sensory area of the neocortex. During non-rapid eye movement (NREM) sleep, slow-waves predominantly propagate across the neocortex in an anterior-to-posterior direction in mice and humans (arrow). **b** | Representative 1 s samples of NREM events recorded in mice: (1) raw cortical electroencephalography (EEG); (2) slow waves (1.0–4.5 Hz); (3) a single sleep spindle in the raw cortical EEG; (4) a band-filtered spindle trace (11–15 Hz); (5) hippocampal raw local field potentials; (6) sharp wave–ripples (SWRs; 100–250 Hz). Cortical EEG recordings during NREM sleep are characterized by slow waves, which are synchronized with sleep spindles in thalamocortical circuits and SWRs in the hippocampus, and are important for sleep integrity and sleep-dependent memory formation. **c** | The circuit mechanisms of oscillations occurring during NREM sleep. Slow wave oscillations reflect recurrent excitatory inputs between the thalamus and neocortex, which are shaped by inhibitory interneurons in layers 2/3 and 5 of the neocortex[31]. Excitatory inputs from both the neocortex and thalamus to inhibitory thalamic reticular nucleus (TRN) neurons drive a hyperpolarizing input to thalamocortical relay (TCR) cells, which causes rebound burst firing that sends a volley of excitatory activity to the neocortex, giving rise to sleep spindles[81]. At the same time, collateral inputs to hippocampal area CA1/CA3 as well as inputs from the entorhinal cortex drive SWRs[110], which co-occur with spindles. AN, anterior nuclei; CB, calbindin; CCK, cholecystokinin; CM, centromedial nucleus; CR, calretinin; IL, internal (medullary) lamina; LP, lateral posterior nucleus; MD, mediodorsal nucleus; NPY, neuropeptide Y; PC, principal neuron; PFC, prefrontal cortex; PV, parvalbumin; PYR, pyramidal neuron; SOM, somatostatin; VA, ventral anterior nucleus; VIP, vasoactive intestinal peptide; VL, ventrolateral nucleus; VPL/VPM, ventral posterior lateral nucleus/ventral posterior medial nucleus.

later referred to as the 'sleep switch'[132], implicated hypothalamic sleep-active GABA-releasing or galanin-releasing neurons of the ventrolateral preoptic area and median preoptic nucleus in humans and rodents (BOX 1). The involvement of these neurons in the onset and maintenance of NREM sleep was confirmed by activity tagging and retrograde labelling in optogenetic, pharmacogenetic and chemogenetic experiments[133–135]. Strikingly, the states of sleep induced by selectively targeting these neurons were also accompanied by a reduction in body temperature, as occurs spontaneously in mammals during REM sleep[133], which is suggestive of a dual function

Box 3 | **Homeostatic control of sleep**

During extended periods of wakefulness (that is, sleep deprivation), the urge to sleep (sleep pressure) accumulates and then progressively dissipates during rebound sleep through an evolutionarily conserved phenomenon called sleep homeostasis (or process S)[277]. Glial cells[278], genetic factors[19], molecular factors[279,280], protein phosphorylation and cerebrospinal fluid ionic composition or flow[281] all contribute to sleep homeostasis.

A widely accepted physiological indicator of sleep pressure is an increase in cortical slow-wave activity, which correlates with prior (global) wakefulness duration[5,126,282] and with local changes in neuronal and non-neuronal network activity induced by somatosensory stimulation[283], arm immobilization[284] and transcranial magnetic stimulation[237,285] during prior wakefulness in humans. However, one study found that neuronal fatigue from sustained firing was unlikely to account for the increased slow wave activity occurring after sleep deprivation[286]. Along with the decreased amplitude of slow waves in consecutive non-rapid eye movement (NREM) sleep episodes in sleep-pressured individuals, the incidence of slow spindles decreases while that of fast spindles progressively rises[93].

Rapid eye movement (REM) sleep pressure also accumulates during waking periods and/or NREM sleep periods[287] and dissipates during rebound REM sleep, revealing homeostatic regulation[288]. Acute homeostatic responses implicate a hypothalamic modulation of brainstem executive circuits[289]. Similarly to NREM sleep, both the quantity and electroencephalographic spectrum of REM sleep are influenced by genetic factors[19,290] and NREM–REM sleep cycling[117,291], and strongly depend on prior region-specific activity[292,293]. Local slow waves during spontaneous or rebound REM sleep[211,294] and high-frequency gamma oscillations during rebound NREM sleep[294] suggest the existence of interdependent or shared homeostatic mechanisms and ultimately point to the need for a refined characterization of sleep states in time and space.

for these cells. Further work has implicated GABAergic neurons in the parafacial zone[136,137], adenosine receptor-expressing cells in the nucleus accumbens[138], zona incerta neurons[139] and clusters of glutamatergic or GABAergic neurons in the midbrain[140], brainstem[141] and cortex[142] in the mechanisms of NREM sleep.

Although the existence of multiple sleep-active systems is now well established, how these systems regulate oscillating circuitries in time and space and, ultimately, the progressive transition from wakefulness to NREM sleep (the sleep switch)[132] are still poorly understood. In this context, thalamo-cortico-thalamic circuits[6] could represent 'sleep units'[143] that act as anatomical and functional hubs by integrating inputs from subthalamic and cortical structures and modulating core circuitries that generate NREM sleep K-complexes, slow waves and spindles.

The parcellation of thalamic nuclei might further support region-specific modulation of cortical oscillations during sleep or anaesthesia[6,53,56,59] (BOX 2). For instance, the activation of brainstem cholinergic inputs to the thalamus, and to the TRN in particular, induces sleep-like thalamocortical oscillatory states[144,145] and promotes NREM but not REM sleep, possibly by either increasing sleep spindle occurrence[146] or inhibiting wake-promoting midline thalamic circuits[147]. Similarly, noradrenergic neurons from the locus coeruleus maximally discharge during wakefulness and become progressively less active during NREM sleep until they are eventually silent during REM sleep[148,149]. In contrast to their wake-promoting actions[150], the low firing activity of these noradrenergic neurons during NREM sleep is phase-locked to the slow oscillation[151]; this phase-locking was proposed to serve NREM sleep-dependent cognitive functions[152], a hypothesis further supported by the finding that norepinephrine increases midline thalamic neuron excitability[153]. Furthermore, experimental findings indicate that the activity of thalamic neurons is phase-locked with hippocampal SWRs or theta rhythms[154]. Together, these findings are consistent with a central position of thalamocortical circuits in modulating brain activity during NREM sleep.

Network oscillations in REM sleep

During REM sleep, also called paradoxical sleep, cortical EEG recordings show marked changes that resemble N1 NREM sleep in humans or wakefulness in rodents. The EEG features of REM sleep include low-voltage, high-frequency activity termed theta (6–9 Hz in rodents, 4–6 Hz in humans) and gamma (30–90 Hz) oscillations. Unlike the monophasic sleep observed in humans, rodents have polyphasic sleep — only ~25% of transitions from NREM sleep episodes result in REM sleep episodes in mice[155].

REM sleep is further characterized by rapid and irregular eye movements on electro-oculography, the absence of muscular tone on electromyography, increased brain temperature, and irregular respiration and heart rate[23]. Dreaming was classically considered to occur during REM sleep, although studies published in the past three years have shown that dreams also occur during NREM sleep[156]. The term desynchronized, previously used to describe brain activity in cortical EEG recordings during wakefulness and REM sleep, has been rendered obsolete by the discovery that a highly synchronized gamma-frequency oscillation (30–90 Hz) is active during these states[109]. Similarly, the term 'synchronized', previously used to describe brain activity during NREM sleep, has been superseded owing to the discovery of local brain activity resembling wakefulness during this state[157].

Theta rhythm. The theta rhythm (5–8 Hz in animals, 4–7 Hz in humans[122,158]) is a prominent feature of hippocampal activity during REM sleep in cats[159], dogs[160] and humans[161]. Two types of theta rhythms have been identified[162]: type I and type II theta oscillations. Type I theta oscillations (5–8 Hz) are atropine insensitive and predominantly occur during locomotion and REM sleep in animals and humans[130,135,136] (FIGS 2b,3a), and have been causally linked to contextual memory consolidation during REM sleep in some[163,164] but not all[165,166] studies (reviewed elsewhere[167]). Type II theta oscillations (4–7 Hz) are atropine sensitive and are not discussed further in this Review because they occur during fear-induced freezing and urethane-induced general anaesthesia but not during sleep.

The theta rhythm observed in human REM sleep is more phasic than the tonic theta oscillations observed in rodents[161,168], possibly owing to species-related differences in the molecular or anatomical architecture of the underlying neuronal circuitries. Furthermore, theta oscillations are present during awake cognitive tasks and are coupled to gamma oscillations during REM sleep in rodents and humans[169]. In rodents, theta power decreases and its phase-lag increases as the distance between the recording site and its hippocampal source increases[170,171], consistent with the idea that

Electro-oculography
The electrical activity resulting from eye movement used to help determine sleep stage.

Electromyography
Electrical activity of musculature, which shows distinct patterns dependent on behavioural state and is used to help determine sleep stage.

Synaptic scaling
Refers to a non-Hebbian form of homeostatic plasticity that adjusts synapse strength (synaptic 'renormalization') in a network or neuron up or down in response to global changes in activity so that total synaptic inputs are tuned whilst the relative strength of all synapses is constant.

Ocular dominance plasticity
Refers to the plastic rearrangement of cortical visual areas following monocular deprivation, which triggers a shift in the response of individual neurons towards the non-deprived eye. Sleep is required for the expression of plasticity in the developing visual cortex.

the hippocampus is the main source of theta rhythm in the mammalian brain. Yet, locally generated theta oscillations, although smaller in amplitude than their hippocampal counterparts (presumably owing to the smaller size of the circuits involved), have been recorded in the prefrontal cortex[172] and amygdala[173] in rodents and humans[174] during wakefulness and REM sleep.

The medial septum encompasses glutamatergic, GABAergic and cholinergic neurons and is required for normal hippocampal theta rhythm activity, as shown by evidence from electrolytic lesioning or pharmacological blockade[109] (FIG. 3b). Of note, an intra-hippocampal mechanism for theta rhythm generation has been proposed[175,176]. Medial septum GABAergic neurons fire rhythmically at theta frequencies that are phase-locked to hippocampal theta rhythms during sleep[109]. Their intrinsic 'pacemaker' rhythmicity results from the expression of hyperpolarization-activated and cyclic nucleotide-gated non-selective cation channels[177]. These medial septum GABAergic neurons postsynaptically inhibit hippocampal interneurons, ultimately resulting in the rhythmic disinhibition of pyramidal cells, as shown in vitro[178,179] and in vivo[163]. By contrast, medial septum cholinergic neurons show a slower firing pattern than their GABAergic counterparts and fine-tune, rather than drive, the amplitude of the hippocampal theta rhythm — although they can still increase the power and coherence of the theta rhythm or reduce peri-theta oscillations (for example, slow waves and beta-frequency waves)[180]. A subpopulation of medial septum glutamatergic neurons spontaneously fire at theta frequencies (reminiscent of medial septum GABAergic neurons) and project to the hippocampus, where they have the ability to entrain the theta rhythm in vivo[181], possibly through direct excitation of CA3 pyramidal cells. Additional inputs from entorhinal cortex, posterior hypothalamus and brainstem circuits further contribute to the modulation of REM sleep theta oscillations. Accordingly, theta oscillations during REM sleep show a nonlinear, dynamic and transiently 'phasic' period[182], which is associated with transient ponto-geniculo-occipital (PGO) waves of brainstem origin (discussed in the next

Box 4 | **Consolidation of previously acquired information during sleep**

Compelling optogenetic evidence supports a role for sleep in memory consolidation: manipulations of sleep theta rhythm, sharp wave–ripples (SWRs) or slow waves lead to memory and/or sensory impairment or improvement[60,61,163,165,295]. However, the underlying mechanisms are still unclear. Hebbian and non-Hebbian theories provide conceptual and experimental frameworks that account for the observed findings across multiple experimental scales. Importantly, these theories are not mutually exclusive.

Sleep reactivation
This Hebbian theory posits that strengthening of newly acquired knowledge or skills occurs with transformation of short-term memories into neocortical long-term storage during sleep[296]. This model is supported by observations in rodents that hippocampal place cells and entorhinal grid cells that encode spatial information during wakefulness are reactivated during rapid eye movement (REM) sleep theta rhythm and non-REM (NREM) sleep SWRs as well as during quiet wakefulness. Electrical disruption of hippocampal SWRs impairs, to a variable extent, the consolidation of previous awake experiences[297,298], in particular newly acquired information[299]. Consistent with this finding, task-related auditory or olfactory cueing is further enhanced or weakened upon stimulus re-exposure during sleep in humans and rodents[300]. This phenomenon is not limited to hippocampal circuits and has been observed in the ventral striatum[301], midbrain ventral tegmental area[302] and prefrontal cortex[303].

Synaptic homeostasis
This non-Hebbian theory posits that sleep contributes to a net downscaling of synapses that were strengthened during awake periods[304]. This model is supported by specific sleep-dependent and wake-dependent regulation of gene expression, decreased AMPA receptor expression in glutamatergic neurons after sleep, a net reduction of dendritic spines in adolescent rats and structural changes of cortical synapses[305,306]. Collectively, these changes lead to synaptic scaling during sleep. By contrast, alterations in firing dynamics during NREM sleep occurred entirely in delta-dominated inter-SWR periods, whereas within-SWR firing and synchrony actually increased over the course of sleep[291]. Furthermore, plasticity-inducing molecular mechanisms that support new dendritic spine formation also contribute to NREM-dependent and REM-dependent behavioural performance[307,308], which suggests that local morphologic changes occur during the proposed global effect.

Network excitability
This theory proposes that hippocampal neuron firing rates are distributed over several orders of magnitude in a highly skewed distribution that is conserved across states and time[214]. Firing rates of hippocampal pyramidal cells and interneurons are lower during REM sleep than during NREM sleep and show a net decrease across the sleep period that correlates with electroencephalographic theta power[309]. This observation suggests that theta rhythm is involved in this downscaling of neuronal firing. Interestingly, SWR-associated cells show higher firing rates and increased synchrony during NREM sleep episodes that are interspersed by REM sleep episodes, which indicates that cycling of NREM and REM sleep influences the consolidation of memories during sleep[116,163].

Investigations into the role of sleep in synaptic plasticity have used ocular dominance plasticity elicited by monocular deprivation as an experimental model. Ocular dominance plasticity is enhanced by sleep and blocked by sleep deprivation (in particular by REM sleep deprivation) and requires visual cortical activity, protein synthesis and phosphorylation[310,311]. Ocular dominance plasticity is associated with a decrease in inhibitory cell firing and increased cortical excitability that is consistent with Hebbian principles. By contrast, during recovery from monocular deprivation, excitatory neuron firing rates show an increase (that is, upscaling) restricted to wake periods and absent from both NREM and REM sleep[312], in line with a non-Hebbian theory of sleep function.

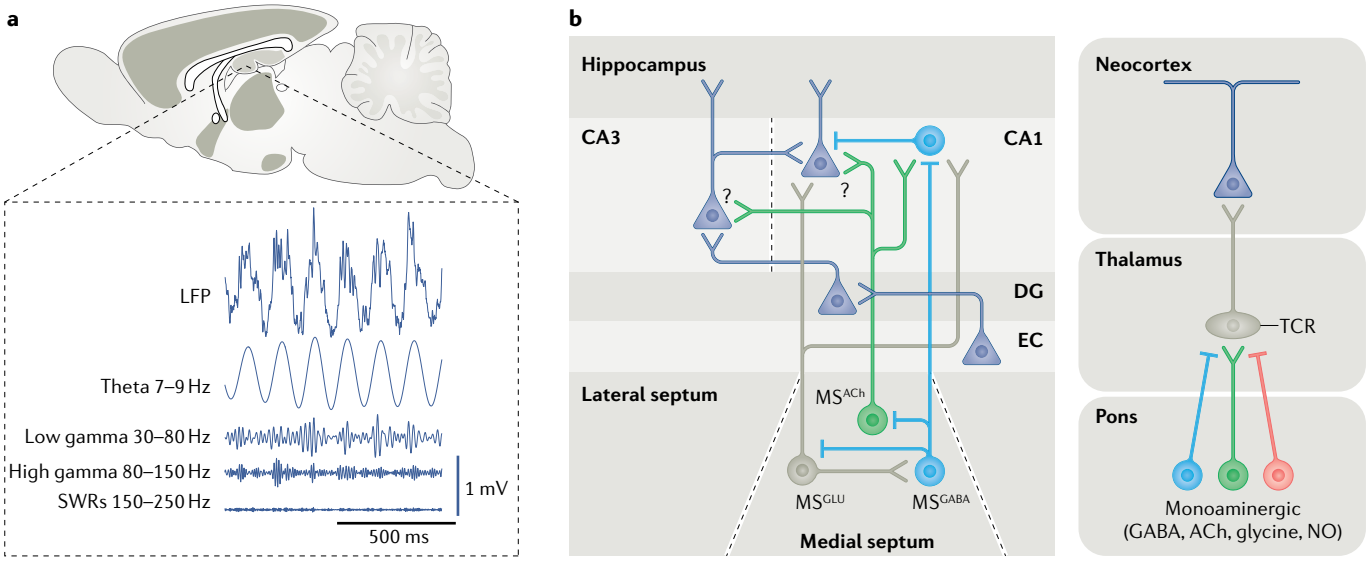


Fig. 3 | **Circuit mechanisms of REM sleep-specific oscillations. a** | Representative 1 s traces of mouse hippocampal local field potentials (LFPs) recorded during rapid eye movement (REM) sleep: raw LFPs, filtered theta activity (7–9 Hz), low-gamma activity (30–80 Hz), high-gamma activity (80–150 Hz) and sharp wave–ripples (SWRs; 150–250 Hz). REM sleep is characterized by the predominance of theta oscillations and the appearance of gamma oscillations in both LFP and cortical electroencephalography signals. Note the coherence (phase-locking) of gamma power to the ongoing theta oscillation during REM sleep. In addition to theta and gamma oscillations, the brainstem generates ponto-geniculo-occipital waves in humans (not shown), which have been suggested to contribute to visual perception during dreaming as well as memory extinction. **b** | Circuit mechanisms underlying REM sleep oscillations in hippocampus and cortical networks. The medial septum (MS) contains genetically distinct cells producing acetylcholine (ACh), glutamate and GABA whose ongoing activity is essential for the generation of theta oscillations in areas CA1 and CA3 of the hippocampus (left panel), together with other inputs from the entorhinal cortex (EC), dentate gyrus (DG) and subcortical structures. GABAergic cells (and to a lesser extent, glutamatergic neurons) in the MS also contribute to theta activity in the hippocampus; however, the precise circuit mechanism and the role of ACh remain unclear. Ponto-geniculo-occipital waves during REM sleep result from bursts of monoaminergic inputs in the brainstem to the lateral geniculate nucleus of the thalamus (right panel), which in turn relays the volley to the visual cortex. NO, nitric oxide; TCR, thalamocortical relay neuron.

paragraph). PGO waves are associated with increased theta-band synchrony both within the hippocampus[182] and between the hippocampus and connected brain structures, such as the amygdala[183], and potentially signal the presence of enhanced information transfer and memory consolidation (BOX 4).

Ponto-geniculo-occipital waves. REM sleep pontine waves, traditionally referred to as PGO waves or P-waves, are large phasic waves that are detectable as pontine LFPs during eye movements, including during REM sleep[184], in rats[185], cats[186] and humans[187] (FIG. 3b). Early experimental recordings in cats showed that these waves result from synchronous bursts of action potentials triggered within the pontine reticulum (that is, in the caudolateral peribrachial and locus sub-coeruleus nuclei) that activate cholinergic neurons in the pedunculopontine tegmentum and laterodorsal tegmentum[188,189]. Activation of these cholinergic neurons is followed by activation of the lateral geniculate and occipital cortex[188,189] (FIG. 3b). PGO waves are modulated by acetylcholine, GABA, glycine and nitric oxide[184,190,191], and spread to various downstream targets, including the amygdala as well as hippocampal and thalamocortical systems[174,184,192,193].

PGO waves have been implicated in nervous system maturation, memory consolidation and visual perception, including visual hallucinations during dreaming (reviewed elsewhere[194]). PGO waves during REM sleep coincide with eye movements[195] and phasic theta rhythms, and are implicated in hippocampus-dependent memory formation[182,183].

Gamma oscillations. Originally described by Jasper and Andrew[196], gamma rhythms occur as short or transient bursts of oscillatory activity at various frequencies (30–150 Hz), often subdivided into low-frequency (30–50 Hz), mid-frequency (50–80 Hz) and high-frequency (80–150 Hz) gamma bands, although these frequency ranges are defined differently between studies and vary with the brain structure considered. Gamma oscillations are classically recorded during wakefulness and REM sleep in almost all areas of the neocortex, hippocampus, amygdala, striatum, thalamus and hypothalamus in humans and rodents[197].

Gamma oscillations result from the synchronization of local neuronal assemblies composed of inhibitory interneurons and postsynaptic $GABA_A$ receptor-mediated inhibition, either via coupling of local interneurons alone (the I–I model) or also involving pyramidal cells (the E–I model), or both[197,198]. In the I–I model, the increased firing of synaptically coupled interneurons results in peri-somatic inhibitory postsynaptic currents followed by the decay of $GABA_A$ receptor-mediated hyperpolarization, from which emerges synchronous

Inhibitory interneurons
GABAergic or glycinergic cells with localized feedback and modulatory control of excitatory neurons.

Synaptic strength
The degree of influence that the input of one neuron has on the activity of its target neuron.

phasic firing of the composing neurons[197]. The frequency of this oscillation is determined by the kinetics of inhibitory postsynaptic potentials (which directly depend on the time constant of $GABA_A$ receptors) and excitation of the interneurons. The E–I model describes reciprocal synaptic volleys between excitatory pyramidal cells and delayed feedback from inhibitory interneurons. According to this model, a certain level of synaptic strength is required for persistence of the oscillation, whereas the phase delay determines the oscillation frequency[197]. Note that local gamma oscillations within multiple distant brain structures (for example, interhemispheric circuits located in the dorsal hippocampus or visual cortex) can show long-range synchronization[199].

The role of gamma oscillations during sleep remains unclear. Interestingly, humans receiving auditory inputs during phasic REM sleep, when gamma power is increased, show less cortical activation than they do when such inputs are received during tonic REM sleep[193]. This finding suggests a role for gamma oscillations in preventing awakening (and therefore in stabilizing REM sleep) during consolidation of awake experiences as memories during sleep. Furthermore, optogenetic induction of gamma oscillations in the cortex of freely behaving mice increased information transfer across circuits in the neocortex or sensory processing areas[200–202]. This observation also supports a role of gamma oscillations in memory consolidation, possibly during UP states or REM sleep, when gamma oscillations are phase-locked to theta rhythms[109,203] (as discussed further in the next sections).

A role for REM sleep executive circuits

During the transition from NREM to REM sleep, cortical EEG signals show a progressive increase in theta rhythm and gamma oscillations in the hippocampus and somatosensory and parietal cortices, concomitant with a progressive decrease and eventual disappearance of slow waves and delta oscillations in the frontal cortex of rodents[170,182,204,205] and humans[161]. Intracranial recordings have revealed that hippocampal theta waves precede the appearance of theta oscillations in the cortical EEG by several seconds in rodents[206,207]. Spindles are irregularly distributed throughout NREM sleep episodes, often in a local manner, but they become highly prevalent prior to transitions from NREM to REM sleep in rodents[208]. Whether spindles are a cause or consequence of this state transition remains unclear. Unlike the decreased amplitude of slow waves, which is observed across successive NREM sleep episodes, theta power is stable and does not correlate with REM sleep episode duration[38]. Additional oscillations, including vertex sharp waves and sawtooth waves, predominate in midline cortical structures during REM sleep and show a steep lateral decrease in humans[209]; no rodent equivalents of these oscillations have been described to date.

Although cortical EEG signals during REM sleep superficially resemble those observed in awake states (both were previously termed 'desynchronized' brain activity states, as noted above), region-specific analysis has revealed marked differences between them. In contrast to theta rhythms in wakefulness, REM sleep theta rhythms in the retrosplenial cortex and hippocampus are strongly synchronized at both the circuit and single-cell levels[38,170,210,211]. Moreover, the prevailing view that theta oscillations are synchronized across the whole hippocampus during REM sleep has been revisited as a result of observations that theta waves travel across the septotemporal axis of the hippocampus in rodents[171], and that coherence of gamma oscillations varies greatly both within and between hippocampal fields (for example, CA1, CA3 and the dentate gyrus) during REM sleep and wakefulness[109,182].

At the cellular level, neocortical excitatory and inhibitory cells generally show higher discharge rates during REM sleep than during wakefulness[126,211,212], although layer-specific and cell-specific differences have been reported[213]. At the hippocampal level, discharge rates of both CA1 pyramidal cells and interneurons gradually ramp up during NREM sleep episodes but decrease during the intervening REM sleep episodes[214]. Whether discharge rates also follow this pattern in non-hippocampal cells remains unclear, but such a pattern would be consistent with the low firing rate of pyramidal cells in the hippocampus during REM sleep. Other subcortical structures involved in theta rhythm modulation during REM sleep include medial septum GABAergic neurons[163], pontine (cholinergic) cells[215,216] and supramammillary glutamate neurons[217], and possibly neurons from the thalamus[154]. Glutamate-releasing neurons of the supra-mammillary region are also involved in theta rhythm modulation during wakefulness[218].

As with NREM sleep, a gap remains between the executive circuits responsible for the generation of REM sleep and the networks that generate oscillations during REM sleep. REM sleep executive circuits were initially identified in the brainstem, on which hypothalamic and basal forebrain circuits exert a modulatory role[219] (BOX 1). Thus, cortical activity during REM sleep results from both subcortical and cortical circuits originating from the sublaterodorsal nucleus, basal forebrain or laterodorsal tegmentum and/or pedunculopontine tegmentum (cholinergic), and the claustrum or retrosplenial cortex[38,210,215,217,220]. Some of these regions contain neurons that exhibit theta-locked spiking activities. Yet, the mechanisms underlying their modulation of theta rhythm or cortical activity during REM sleep remain unclear[221,222], despite both in vitro[223] and pharmacological evidence: acetylcholine provokes a rapid 'desynchronization' of cortical networks through a direct action on somatostatin interneurons[224]. Finally, neuronal populations that modulate key aspects of REM sleep, such as its frequency and duration, have been identified in the lateral hypothalamus (namely, melanin-concentrating hormone neurons)[155,225,226] and the supra-mammillary nucleus (specifically dual, that is, both glutamatergic and GABAergic, neurons)[210,217]. Some of these neuronal populations project directly to the medial septum or the dentate gyrus, where they might directly modulate REM sleep theta rhythm circuits or function[155].

Awakening from sleep

The initial moments following awakening from sleep are typically marked by hypovigilance, diminished awareness, confusion and impaired cognitive performance, a state referred to as sleep inertia, which dissipates within

minutes in humans[227,228]. The EEG correlates of sleep inertia show the intrusion of sleep-specific features (including slow waves and low-frequency oscillations in general) in posterior cortices as well as persistence of the theta rhythm[219,229], the intensity of which depends on the prior sleep duration[230], the circadian trough of body temperature[231] and the ongoing sleep stage[228]. Although sleep inertia has not been characterized in rodents, brief awakenings (that is, of a few seconds in duration) from NREM sleep or REM sleep are conspicuous owing to the abrupt decrease of slow waves concomitant with an increase in fast oscillations (mainly theta and gamma) and the detection of motor activity.

At the cellular level, transient awakening is preceded by a surge in the firing of wake-promoting neurons in the brainstem, basal forebrain and hypothalamus, which is eventually followed by the resumption of NREM sleep (reviewed elsewhere[9,132,232]). During wakefulness, the activity of each of these cells and circuits is constantly changing in response to ongoing behaviour or stimulation from the environment in a region-specific manner, indicative of a spatiotemporal control[233] reminiscent of that occurring during sleep.

At the circuit level, optogenetic and pharmacogenetic studies have demonstrated that wake-active circuits are sufficient to induce awakening from either NREM sleep or REM sleep, or both[155,234]; however, no single circuit has yet been demonstrated to be necessary for awakening, since neither lesioning nor pharmacological blockade of arousal-related neurotransmitters or neuromodulators has led to a marked sleep increase[132,235]. Collectively, these findings suggest an apparent redundancy among wake-promoting circuits. Instead, emerging evidence supports the specialization of these circuits, as exemplified by activation of NREM but not REM sleep-to-wake transitions in single-circuit optogenetic studies[6,135,234]. This observation might reflect the propensity of each wake-promoting circuit to initiate or maintain a specific behaviour (such as feeding, mating or nesting) during wakefulness, and therefore to be involved in initiating wakefulness for the purpose of conducting that behaviour under specific conditions.

Conclusions and future perspectives

Oscillations are locally generated rhythmic activities that occur simultaneously in multiple circuits and propagate over variable distances in the sleeping brain of mammals, and presumably also other organisms. Some of these sleep oscillations can be transiently observed during wakefulness, with which they share electrophysiological fingerprints. Most oscillations are restricted to local brain circuits (for example, PGO waves) but others propagate over variable distances (for example, slow waves). Despite these differences, all these oscillations are precisely orchestrated in space and time during the sleep–wake cycle to form a continuum of brain activity.

Local manipulation of sleep oscillations can induce marked changes in the global architecture of sleep that inform our understanding of the functional connectivity of sleep-relevant networks. For example, optogenetic activation[83] or disinhibition[234] of GABAergic TRN neurons during NREM sleep increases spindle occurrence in thalamocortical circuits and also increases delta oscillation amplitude. Ultimately, these changes stabilize NREM sleep in rodents. Furthermore, electrical stimulation in animals[36,236] or transcranial magnetic stimulation in humans[237] of local areas of the neocortex initiate single EEG slow waves and deepen sleep. Physiologically relevant sensory inputs, such as auditory[68,238], olfactory (restricted to rats)[239] or vestibular[240] stimuli, stabilize and prolong sleep, including REM sleep[241]. Although the underlying mechanisms remain unclear, these effects could be attributed to the generation and brain-wide propagation of (sensory-evoked) slow oscillations that synchronize with higher frequency oscillations or PGO waves that synchronize with REM sleep executive circuits. Ultimately, direct modulation of sleep oscillations could have immediate and lasting effects on sleep state duration and the overall architecture of the sleep–wake cycle.

These findings raise important questions. Experimental strategies have employed perturbational techniques to induce states of wakefulness[150,234,242], NREM sleep[133,136,138] or REM sleep[141,155] that often have behavioural and cortical EEG features indistinguishable from those observed during spontaneous sleep–wake cycles. Similarly, sleep-related slow waves associated with electric[36], optogenetic[6] or auditory[238] stimuli show waveform profiles that are comparable to those of natural brain waves. Yet, at the network level, these waves might result from the activation of cellular networks that involve smaller, larger or different neuronal populations, or might not correspond to any brain activity detected in a spontaneously sleeping brain. A major challenge lies in improving our understanding of the mechanisms and functions of apparently similar sleep oscillations. For example, we do not yet know whether slow waves originating from cortical or thalamic locations have the same functions.

The precise mode of synchronization of oscillations during sleep might support the many functions of different sleep stages. For example, during NREM sleep, high spiking and synaptic activities of slow oscillations occurring during cortical UP states are often temporally synchronized with higher-frequency oscillations, including spindles and SWRs, as well as beta and gamma oscillations[50,243,244]. This phenomenon might support the transfer of information between brain circuits and the consolidation (or weakening) of memory traces through synchronization-dependent synaptic plasticity and long-term storage of information during sleep in rodents and humans[106,245–249] (reviewed elsewhere[250]). For example, roles have been proposed for spindles in memory consolidation, intelligence and cognition[116,251], as indicated by increased motor memory consolidation and sensory attention upon enhancement of spindle activity in humans[252] and mice[253]. During REM sleep, coherence of theta rhythm between the medial prefrontal cortex, amygdala and hippocampus is correlated with the retrieval of fear memories[173,182,247,248,254]. The coupling of distant oscillating networks transiently occurs through theta–gamma coupling in the hippocampus or cortex (reviewed elsewhere[255]) and prevails during locomotion[256], learning and decision-making in awake rodents[256] and humans[257,258] but also occurs during

Unsupervised sleep staging
Algorithm-defined sleep scoring methods, which are supposedly more objective than the subjective visual scoring of EEG or polysomnography recordings.

REM sleep in rodents[38,205,259], in which its role remains unclear[260]. Thus, synchronization of proximal and distant oscillating networks during sleep expands the complex (and as yet uncharacterized) mechanisms by which oscillations might modulate both neural communication and the synaptic plasticity associated with sleep states. In addition to this functional role, synchronization of distant circuits could orchestrate oscillatory activities underlying the initiation, maintenance and termination of sleep states.

Despite the observation that many sleep-relevant oscillations can be detected across large fields of the EEG, they often originate from local circuits and propagate to distal brain structures where they are essential to support functions such as memory consolidation. For example, slow waves can be generated from many sites of the neocortex and travel in any direction during spontaneous NREM sleep, although they preferentially originate in frontal structures and propagate along an anteroposterior axis[63,261]. Similarly, theta oscillations and spiking of CA1 pyramidal cells propagate along the septotemporal axis of the hippocampus in rodents[171,262]. In this context, each cycle of an oscillation represents a repetitive pattern of local input and output activity that is synchronized with distal circuits[171]; this synchronization might, therefore, offer a window of opportunity for offline information processing during sleep — that is, the consolidation or weakening of information carried by slow oscillations, spindles, SWRs, theta or gamma oscillations. Thus, the temporal coupling of these oscillations is hypothesized to contribute to memory consolidation through long-term potentiation or depression[250], spike timing-dependent synaptic plasticity or the reactivation of behaviourally relevant neuronal sequences[116] (BOX 3). Hence, single oscillations and their temporal orchestration, rather than the global sleep state per se, might be essential to the encoding of specific types of information. In this context, the information content carried by an oscillation cycle is intrinsically linked to the underlying circuit and to its biophysical properties and brain-wide connectivity.

Finally, improved understanding of the origin of sleep oscillations at multiple scales is expected to shed light on their implications for sleep control and sleep functions. Unravelling the large-scale connectivity maps of these oscillations at single-cell resolutions will provide quantitative nonlinear signatures of NREM or REM sleep that could refine the definitions of these sleep states. New analytical methods (such as unsupervised sleep staging)[57,128,263] together with recording and perturbational techniques (optogenetic and non-invasive brain modulation approaches such as transcranial magnetic stimulation) hold promise for characterizing the neurobiological mechanisms of sleep and its function in health and disorders of sleep or consciousness[264] as well as the early pathophysiological changes in sleep oscillations associated with epilepsy, schizophrenia, major depression and dementia.

Published online 15 October 2019

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Acknowledgements
The authors thank all the Tidis laboratory members and M. Schmidt for their helpful comments on a previous version of the manuscript. A.R.A. was supported by the Human Frontier Science Program, Inselspital University Hospital Bern, Swiss National Science Foundation, European Research Council and the University of Bern. T.C.G. was supported by the University of Zürich Forschungskredit. C.G.H. was supported by the Swiss National Science Foundation and the University of Bern.

Author contributions
All authors contributed equally to discussions of the article content, writing the manuscript and its review, or editing before submission.

Competing interests
The authors declare no competing interests.

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