Sleep Oscillations

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Introduction

The discovery that the brain oscillates during sleep is almost as old as the discovery of the electroencephalogram (EEG). The first human EEG recordings reported oscillations, the type, frequency, and amplitude of which highly depend on behavioral state. In an alert, awake subject, the EEG is dominated by low-amplitude fast activity (‘desynchronized EEG’) with high-frequency oscillations (beta, gamma), whereas during slow-wave sleep, the EEG shifts to large-amplitude, slow oscillations. The early stage of slow-wave sleep is associated with EEG spindle waves, which occur at a frequency of 7–14 Hz. As sleep deepens, waves with slower frequencies (0.3–4 Hz), including delta waves and slow oscillations, appear and progressively dominate the EEG. During paradoxical sleep, also called rapid eye movement sleep, EEG activities resemble those of wakefulness.

The cellular bases of slow-wave sleep oscillations have been investigated since the first extracellular and intracellular recordings in mammals. The major brain regions identified are the thalamus and cerebral cortex, which are intimately linked by means of reciprocal projections. The activities of thalamic and cortical neurons during sleep have been largely documented by electrophysiological studies. The cellular mechanisms underlying these oscillations depend on many factors, such as the connectivity and intrinsic properties of the different types of thalamic and cortical neurons. To determine these cellular mechanisms, it is necessary to use computational models, which are based on experimental data, and to suggest mechanisms and, if possible, predictions to test them. This type of interaction has been quite successful in the (still ongoing) exploration of the mechanisms of sleep oscillations, which this article attempts to summarize.

Sleep Spindle Oscillations

Sleep spindles are found during the early stages of sleep (sleep stage 2 in humans) and constitute an electrographic landmark for the transition from waking to sleep. Spindle oscillations consist of 7–14 Hz waxing and waning potentials, grouped in sequences lasting 1–3 s and recurring every 3–10 s. Spindle oscillations constitute an interesting and well-constrained problem to investigate by computational models for several reasons. First, these oscillations are generated in the thalamus, which is a well-known structure anatomically, with well-defined connectivity between the different cell types (see circuit in Figure 1(a)). Second, spindles are remarkably well documented experimentally and have been extensively characterized both in vivo and in vitro. Third, this oscillation is generated by an interplay of complex cellular properties (schematized in Figure 1(b), left), such as burst firing, and synaptic interactions via multiple types of postsynaptic receptors (see Figure 1(b), right). Computational models are needed to understand this complex interplay.

The typical electrophysiological features of spindle oscillations are shown in Figure 1(c). The two cell types involved, thalamocortical (TC) and thalamic reticular (RE) neurons, oscillate synchronously and display burst discharges according to a mirror image: RE cells display bursts following excitatory postsynaptic potentials while TC cells burst following inhibitory postsynaptic potentials. While RE cells tend to burst at every cycle of the oscillation, TC cells produce bursts only once every few cycles. These features are typical of spindles recorded in thalamic neurons in different mammals.

Several hypotheses for the genesis of oscillations by thalamic circuits have been proposed. These involve reciprocal synaptic interactions between TC neurons and local inhibitory interneurons, loops between TC and RE neurons, or loops within the RE nucleus. The involvement of the RE nucleus was firmly demonstrated in a series of experiments by Steriade’s group. In particular, the deafferented RE nucleus in vivo can exhibit spindle rhythmicity in extracellular recordings. In contrast, the RE nucleus does not display autonomous oscillations in vitro, but spindles have been observed in thalamic slices based on TC–RE interactions. These in vitro spindles display the same intracellular features as in vivo (Figure 1(c)).

To attempt clarifying these contrasting results, the genesis of spindle oscillations was investigated with computational models. First, models investigated whether the RE nucleus is capable of displaying oscillations consistent with experiments. Models found that RE neurons interacting through γ-aminobutyric acid (GABAergic) synapses can generate spindle rhythmicity and suggested different mechanisms. GABAergic interactions between RE neurons can make them oscillate synchronously through mutual inhibitory rebound interactions, either with slow GABAergic synapses or with fast (GABA<sub>A</sub> receptor-mediated) GABAergic synapses with extended connectivity. Synchronized oscillations can also be generated...
Figure 1  Modeling the interactions between intrinsic and synaptic properties to generate spindle oscillations. (a) Circuit of interconnected thalamocortical (TC) and thalamic reticular (RE) neurons with different receptor types. (b) Models of the intrinsic properties of thalamic neurons (left) and of the synaptic receptor types (right) mediating their interactions. (c) In vitro recordings of TC (LGNd) and RE (PGN) neurons from the visual thalamus during spindle oscillations. (d) Computational model of spindle oscillations in circuits of interconnected TC and RE cells. The expanded trace below shows the phase relations of the two cell types. (e) Phase relations of TC cells during spindle oscillations in a different computational model. AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; GABA_A, γ-aminobutyric acid class A receptor; LGN, lateral geniculate nucleus; LGNd, dorsal lateral geniculate nucleus; PGN, perigeniculate nucleus. (a, b, d) From Destexhe A, Bal T, McCormick DA, and Sejnowski TJ (1996) Ionic mechanisms underlying synchronized oscillations and propagating waves in a model of ferret thalamic slices. Journal of Neurophysiology 76: 2049–2070. (c) From von Krosigk M, Bal T, and McCormick DA (1993) Cellular mechanisms of a synchronized oscillation in the thalamus. Science 261: 361–364. (e) From Wang XJ, Golomb D, and Rinzel J (1995) Emergent spindle oscillations and intermittent burst firing in a thalamic model: Specific neuronal mechanisms. Proceedings of the National Academy of Sciences of the United States of America 92: 5577–5581.
from RE neurons connected with depolarizing GABA-ergic synapses. The presence of gap junctions in the reticular nucleus was also incorporated in models and also reinforced its propensity to oscillate in the spindle frequency range. Thus, models suggest that the intrinsic properties of thalamic RE neurons, combined with their synaptic or electrical interactions, support the RE pacemaker hypothesis.

Second, models including TC and RE cells showed that spindle oscillations can also be obtained from TC–RE loops. This TC–RE loop model is shown in Figure 1(d). Neurons were modeled using Hodgkin–Huxley type representations of Na⁺, K⁺, and Ca²⁺-voltage-dependent currents, which were based on voltage-clamp data on thalamic neurons. These models reproduced the most salient intrinsic properties of thalamic neurons, such as the production of bursts of action potentials (Figure 1(b)). Synaptic interactions were modeled with conductance-based kinetic models, which were used to simulate the main receptor types (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), GABA_A, and GABA_B) identified in thalamic circuits (Figure 1(b), right). Under these conditions, the circuit generated 7–14 Hz spindle oscillations with the typical features identified intracellularly in the different thalamic neuron types. The model reproduced the typical mirror image between TC and RE cells during spindles, as well as the phase relations between cells (see Figure 1(d)). In particular, TC cells produced bursts once every two or three cycles, a feature consistently observed experimentally (compare with Figure 1(c)). More-irregular behavior, similar to the experiments, was obtained in larger networks (Figure 1(e)) or in the presence of the cortex (see the section titled ‘Propagation or large-scale synchrony’). The oscillations also showed the typical waxing-and-waning envelope of spindles; this property was due in the model to Ca²⁺-mediated slow regulation of the hyperpolarization-activated current, a prediction that was verified experimentally.

Thus, models show that the complex bursting properties of thalamic neurons, combined with their interactions through well-defined types of synaptic receptors, account for both RE pacemaker oscillations and spindle oscillations arising from TC–RE loops without assuming pacemaker activity in the RE nucleus. How may such an apparent inconsistency be resolved? This question was addressed by a computational model of the RE nucleus which took into account the action of neuromodulators (such as noradrenaline) in depolarizing RE cells. This model produced oscillations only when a sufficient level of neuromodulator was present. The difference between in vivo and in vitro preparations may therefore be explained by the limited connectivity between the RE neurons in the slice and/or by the fact that slices lack the necessary level of neuromodulation to maintain isolated RE oscillations. The main prediction from this model is that applying neuromodulators to slices of the RE nucleus should induce oscillations similar to those observed in vivo. This prediction still awaits testing.

**Propagation or Large-Scale Synchrony?**

How spindle oscillations are initiated and distributed in large circuits was investigated with multiple recordings in vivo and in vitro. Spindle oscillations in vitro showed traveling wave patterns, with the oscillation typically starting on one side of the slice and propagating to the other side, at a constant propagation velocity. Traveling spindle waves were simulated by computational models of networks of interconnected TC and RE cells (one-dimensional extensions of the circuit shown in Figure 1), in two independent modeling studies. These models were similar in spirit to the circuit shown in Figure 1(a) but assumed that there was a topographic connectivity between TC and RE layers, consistent with anatomical data. Under these conditions, the models generated traveling waves consistent with in vitro data.

However, in contrast to thalamic slices, the intact TC system in vivo does not display clear-cut propagation, but spindle oscillations are synchronized over extended thalamic regions and show little signs for traveling wave activity (Figure 2(a)). This large-scale synchrony was lost when the cortex was removed, suggesting that although the oscillation is generated by the thalamus, its synchrony depends on the cortex. To investigate the mechanism underlying large-scale synchrony, a TC network model was developed by combining the previous model of thalamic slices with a model of deep cortical layers. The principal prediction of this model was that, in order to generate large-scale coherent oscillations, the powerful action of cortex on thalamus (via corticothalamic fibers) must be included, and most important, the cortex had to recruit the thalamus primarily through the RE nucleus. Because of the powerful inhibitory action of RE cells, the action of corticothalamic input is ‘inhibitory dominant’ on TC cells, a property essential to maintain large-scale synchrony by synchronizing the rebound bursts of TC cells. This property of inhibitory dominance is generally observed intracellularly in thalamic neurons when the cortex is stimulated. In these conditions, the same model was capable of generating large-scale synchrony in the presence of the cortex, as well as traveling wave activity in the isolated thalamus (Figure 2(b)). Consistent with these models, propagating activity has indeed been observed in the thalamus of decorticated cats in vivo.
The cortical control of thalamic relay cells through dominant inhibitory mechanisms has important consequences, not only for explaining large-scale synchrony, but also for explaining pathological situations such as absence epileptic seizures. As a result of inhibitory dominance, a too strong corticothalamic feedback can overactivate thalamic GABAB receptors and entrain the physiologically intact thalamus into hypersynchronous rhythms at \( \frac{\pi}{24} \) Hz. This scheme may explain the genesis of absence seizures, which are hypersynchronous \( \frac{\pi}{24} \) Hz rhythms that appear suddenly in the TC system. These seizures can be provoked experimentally by increasing cortical excitability in a physiologically intact thalamus. The TC model accounts for those experiments and can simulate seizures based on inhibitory-dominant corticothalamic feedback. This model directly predicted that manipulating corticothalamic feedback should entrain intact thalamic circuits to generate hypersynchronous rhythms at \( \sim 3 \) Hz, a prediction verified by two independent studies. A similar mechanism, with a different balance between GABA_A and GABA_B receptors, can also generate faster hypersynchronous rhythms (around 5–10 Hz), as observed in rat or mouse experimental models of absence seizures.

**Slow-Wave Oscillations**

During the deepest phases of sleep (stages 3 and 4 in humans), as well as for some anesthetized states, cortical activity is dominated by delta and slow oscillations, in a frequency range of 0.3–4 Hz. The intracellular
correlate of these slow waves is the alternation between depolarized states (up states) and hyperpolarized states (down states), which occurs in perfect synchrony with the EEG (Figure 3(c)). Thus, entire cortical regions are simultaneously switching between up and down states, as also shown by multiple extracellular studies. The origin of these oscillations seems to be cortical because they survive extensive thalamic lesions, and they are also observed in cortical slices.

One of the interesting features of up states is that this activity is very similar to that during the awake state. This is supported by several observations. First, during the up state, the EEG is of low amplitude, and fast activity is similar to desynchronized EEG. Second, extracellular recordings have shown that the up states obey the same dynamics of firing, have similar local correlations, and display similar relations between EEG and unit firing as wakefulness does. Third, simulating nuclei participating in the ascending arousal system induces periods of desynchronized EEG corresponding intracellularly to prolonged up states. Fourth, conductance measurements from intracellular recordings in anesthetized or EEG-activated states show similar conductance patterns during both states. The absolute conductance is lower in activated states than in up states, but both states are characterized by similar ratios between excitatory and inhibitory conductances. Fifth, computational models of up/down states and of activated states in cortical circuits suggest that both can be generated by similar mechanisms.

Computational models have investigated the genesis of slow-wave oscillations and the associated up- or down-state patterns. These models were based on recurrent circuits of excitatory and inhibitory cortical neurons (Figure 3(a)). The two main electrophysiological types of cortical neurons were considered, as well as their synaptic interactions through glutamate (AMPA) and GABAergic (GABA_A) receptors (Figure 3(b)). These models showed that up states can be generated by recurrent excitatory and inhibitory connections, which self-sustain the activity (Figure 3(d)). Different exact mechanisms by which up states begin and terminate have been proposed. Up states can start either by the interaction between subthreshold Na currents (persistent Na current) and miniature excitatory synaptic potentials. Another possible mechanism is spontaneously active cells that would initiate the wave of activity in the network. In either case, none of the mechanisms has been verified experimentally. The termination of the up state is apparently due to a progressive run down of synaptic activity, as indicated by conductance measurements. What causes this run down could be either an intrinsic property, such as the progressive buildup of a slow potassium conductance, or simply depression of excitatory synapses. Both hypotheses are supported by experimental data and are also consistent with the refractoriness of the up states found in slices (this refractoriness could be due to the potassium conductance, or recovery from synaptic depression).

Another property of up/down states is that the duration of the down state is proportional to network size. Down states are typically short in vivo (a few hundred milliseconds) whereas they can last up to 20 s in slices. Cutting cortical slabs of different sizes in vivo confirmed that the down-state duration varies inversely in proportion to slab size. Here again, this property is consistent with the two mechanisms of initiation outlined above as they both depend on coincident activation of either miniature or spontaneously active cells, both of which will occur more often in large networks.

Models were also used to simulate the transition to the sustained and irregular firing activity during wakefulness. Self-sustained irregular states similar to activated states have been simulated by various models. Only a few models, however, provided the transition from up/down states to activated states. For all such models, up states and activated states are very similar and differ only by the level of excitability of the neurons (mostly by downregulating potassium conductances). Some of these models were confronted to input resistance or conductance measurements and reproduced qualitatively the values measured experimentally. The fact that up states and activated states can be simulated with few differences by the same models is another indication that those two states stem from similar network activity.

A final property of slow waves is that the up states clearly show propagating properties in vitro. This propagation can be reproduced by computational models (Figure 3(e)), assuming that synaptic connections are made locally in the cortical network. In contrast, there is evidence that up states are highly synchronized in vivo, because the local EEG is always phase locked with intracellular activity (Figure 3(a)). Multiple extracellular recordings in natural sleep also demonstrated that the up states of slow waves are highly synchronized across distances up to 7 mm in cortex. A detailed investigation of this synchrony, and the conditions under which up states can propagate in vivo, as well as the modeling of such phenomena, still await.

**What Is the Role of Slow-Wave Sleep Oscillations?**

As mentioned above, the up states during slow waves share many different features of the sustained activity during wakefulness, and thus, up states can be viewed
Intracellular recordings in vivo

Figure 3  Computational models of slow-wave oscillations in cerebral cortex. (a) In vivo recordings of a morphologically identified pyramidal neuron during slow waves. (b) Schematic circuit showing the two main types of cortical neurons, pyramidal cells (PY) and inhibitory interneurons (IN). Those neurons are connected via different types of synaptic receptors, with the two main types illustrated here. (c) Models of the intrinsic properties of cortical neurons (left) and of the synaptic receptor types (right) mediating their interactions. (d) Computational model of slow-wave oscillations arising from reverberation of activity through recurrent connections in networks of cortical circuits. The network displays up and down states with different frequency of occurrence, depending on the level of spontaneous activity. (e) Snapshot of activity in the network, showing the initiation and propagation of the up state. AMPA, 
as brief periods of activity in which network dynamics are very similar to the dynamics during wakefulness. This is consistent with the fact that up states would represent ‘replayed’ events that have occurred previously during the wake state. There is abundant experimental evidence, from birds to higher mammals, for such a replay during sleep.

Why would such a replay occur during sleep and not during wakefulness? There is presently no clear answer to this question, but it was proposed that another type of sleep oscillation, sleep spindles, may be implicated in gating of long-term plasticity mechanisms (for example, permanent changes that require protein synthesis). Computational models of reconstructed pyramidal neurons, combined with intracellular measurements of thalamic inputs during spindles, have shown that the pattern of synaptic bombardment during spindles in the cortex is a strong excitatory-driven depolarization in dendrites, with an equally strong inhibition around the soma, preventing the cell from excessive firing. This pattern is likely to induce massive calcium entry at around 10 Hz in the dendrites, which is an ideal signal to activate molecular gates, such as protein kinase A. Sleep spindles would therefore provide a physiological signal similar to the repeated tetanus used to induce long-term synaptic changes in slices. However, instead of inducing potentiation directly, spindles may in fact provide a ‘priming’ signal, opening a gate that allows permanent changes to subsequent inputs (‘replayed’ events mentioned earlier) following the sleep spindles.

Taking those two observations together leads to the following scenario for how these different mechanisms may contribute to memory consolidation during sleep. During conscious experience, latent memories are formed throughout the cortex, together with links to the hippocampal formation that allow top-down retrieval to occur. During the early stages of sleep, spindle oscillations would mobilize the molecular machinery needed for memory consolidation in cortex. In the deeper phases of slow-wave sleep, during the brief periods of wake-like activities (up states), the hippocampal formation would activate latent memories stored in the neocortex (‘replay’) and induce permanent changes in intrinsic or synaptic conductances. This hypothetical mechanism of memory consolidation during sleep is consistent with all electrophysiological characteristics of sleep oscillations, and it predicts that special correlations between hippocampal and cortical activities should occur during the up states of slow waves. Such correlations have been found recently between cortical slow waves (up states) and hippocampal sharp waves. No computational model has been proposed to date to explain these observations, and certainly they constitute one of the most exciting directions to pursue toward exploring the role of sleep oscillations.

See also: Electroencephalography (EEG); Electrophysiology: EEG and ERP Analysis; Epilepsy; Executive Function and Higher-Order Cognition: EEG Studies; Gap Junctions and Neuronal Oscillations; Sleep and Sleep States: Thalamic Regulation; Sleep Oscillations and PGO Waves; Sleep-Dependent Memory Processing.

Further Reading


Relevant Website
http://senselab.med.yale.edu – ModelDB, database of freely available model codes, some of which simulate sleep oscillations.