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Origin and dynamics of cortical slow oscillations

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Slow oscillations are the coordinated activity of large neuronal populations consisting of alternating active (Up states) and silent periods (Down states). These oscillations occur in the corticothalamocortical network during slow-wave sleep and deep anesthesia. They also spontaneously occur in isolated cortical slices or in disconnected 'cortical islands' in brain damage. This rhythmic activity emerges in the cortical network when there are no other driving inputs and is considered its default activity pattern. During Up states, neocortical neurons receive barrages of synaptic inputs and fire action potentials. During Down states, neurons remain silent; rather they are hyperpolarized, and synaptic activity is almost nonexistent. From a dynamic perspective, this pattern is often referred to as a state-dependent bistability. During Up states, the activity expresses coherent oscillations at high frequencies in the beta and gamma ranges, sharing properties with wakefulness. The impact of Up/Down states on synaptic transmission and plasticity and its relationship with sleep are discussed.

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Introduction

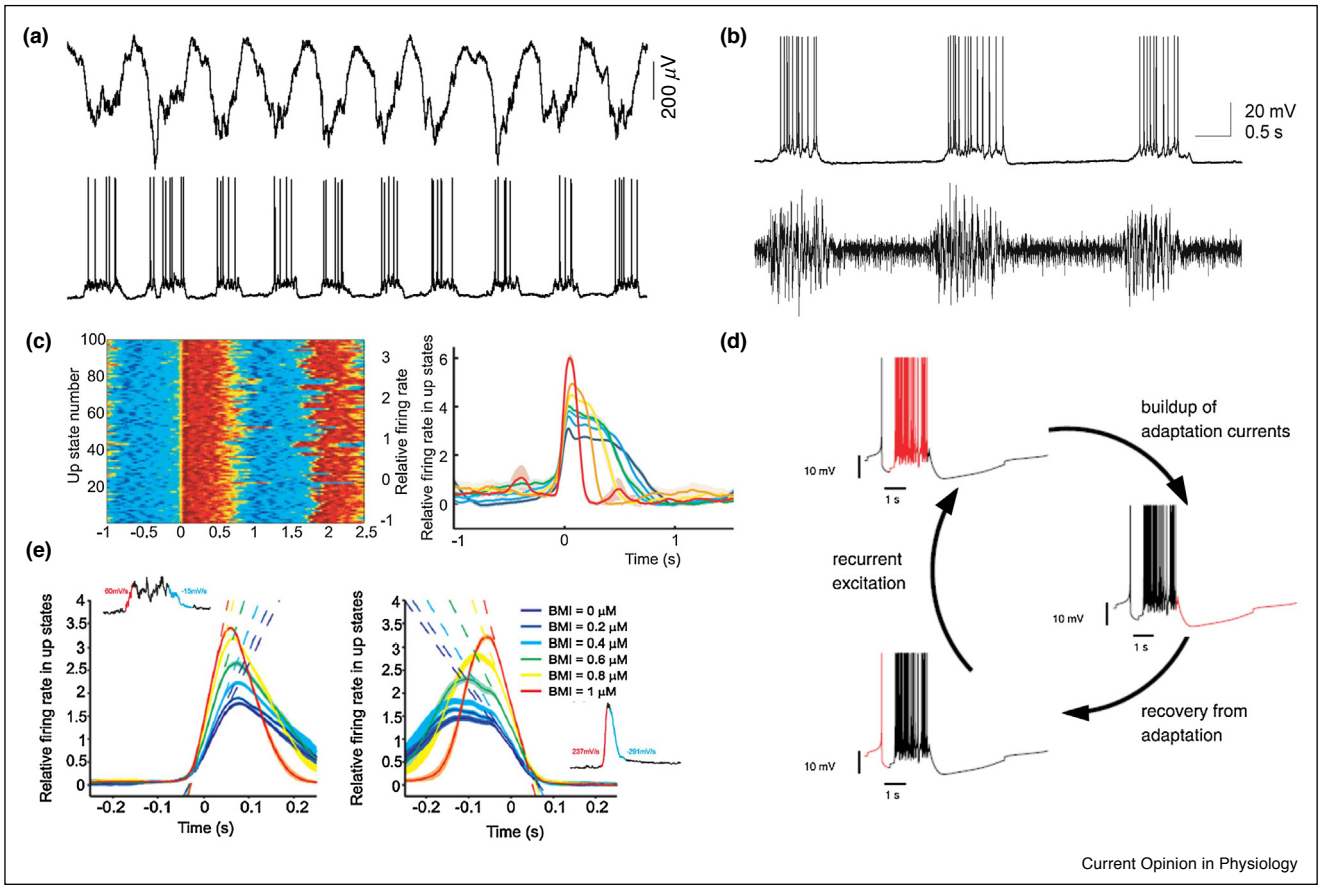
Slow waves were first recorded using electroencephalography in the 1930s, but were not described in detail until decades later, in a series of studies by Mircea Steriade and collaborators in 1993 [1,2•,3]. These studies showed slow oscillation frequency to be below 1 Hz, and largely between 0.2 and 0.5 Hz. Slow oscillations are prominent in the cerebral cortex during slow-wave sleep and deep anesthesia (Figure 1). Steriade *et al.* noted that slow oscillations seemed to persist in the cortex even after the connected thalamus was destroyed [4], a finding strongly suggestive of their origin in the cortical recurrent connectivity. Indeed, the non-stationary bistability underlying slow oscillations is also expressed under conditions of physical disconnection of the cerebral cortex, in what appears to be strong evidence in favor of their cortical origin. This is the case for large pieces of disconnected cortex like the isolated gyrus [4], for cortical slabs [5], and for cortical slices maintained *in vitro* (Figure 1b) [6•], which spontaneously generate slow oscillations largely similar to those the whole brain *in vivo*. Slow oscillations are also expressed in clinical conditions where a 'cortical island' is generated as a result of pathological disconnection [7]. Perilesional slow oscillatory activity is also common in acute ischemic cortical stroke and can persist for months and even years [8]. They are also recorded in pathological states associated to unconsciousness, such as unresponsive wakefulness syndrome [9]. This tendency of the disconnected cortical circuit to generate slow oscillations suggests that this is a default emergent pattern of the cortical network [10,11•]. The default rhythmic pattern is then modulated by different factors, such as excitability levels [12•], by neuromodulators [13•,14•] or by inputs from other connected areas. The reciprocal interaction between the cortex and various subcortical structure shapes the resulting emergent pattern recorded *in vivo*, and the interaction with the thalamus is particularly significant, since the thalamus produces slow oscillations in coordination with those of the cortex [3,15,16]. Indeed, thalamic inactivation reduces the frequency of cortical slow oscillations [17]. The influence of the thalamus over Up/Down states (e.g., [18•,19•] could be mediated not only over excitatory neurons, but also by driving cortical parvalbumin-positive interneurons during Down states [20•].

Initiation and maintenance of Up states

Recordings obtained simultaneously from different cortical layers provide a layer profile of activation during Up states [21•]. Studies performed *in vivo* and *in vitro* on a number of species have consistently shown the important role of deep or infragranular layers—in particular layer 5—in the initiation of Up states [6•,22•,23,24]. Neurons in layer 5 also display a more intense and longer discharge during Up states, while those of layer 2/3 display weaker and shorter firing [6•,22•,25•]. In addition, layer 5 neurons (but not layer 2/3 neurons) can be optogenetically activated to initiate Up states and entrain slow oscillations [26•,27•].

Several mechanisms have been proposed for how layer 5 neurons initiate the firing that by reverberation in closed loops results in the initiation of new Up states. Layer 5 neurons have a larger intrinsic excitability that leads them to begin firing during Down states [6•,22•,28], stochastic release of synaptic vesicles [5] or specific pacemaker cells

Figure 1



Slow oscillations *in vivo* and *in vitro*.
(a) Top Local. Cortical recordings in rat V1 under anesthesia. Top, local field potential. Bottom, intracellular recording. The scale is the same as for the intracellular recording in (b). **(b)** Spontaneous slow oscillations in ferret V1 slices. Top, intracellular recordings of layer 5 neuron. Bottom, multiunit activity. **(c)** Raster plots of 100 aligned Up states and (right) waveform average of the relative firing rate under increasing blockade of GABAA receptors. Notice how the firing rates increase and shorten for lesser inhibition. **(e)** Down-to-Up and Up-to-Down transition for different levels of GABAA blockade. Insets are corresponding intracellular recordings. (c) and (e) are courtesy of Sanchez-Vives *et al.* [45]. **(d)** Proposed mechanism of generation of Up states and Down states cycle, courtesy of Compte *et al.* [28].

[29]. In humans, Up states have been reported to start in supragranular layers of the cortex [30], which is a critical difference in cortical function requiring further study.

What is the excitation driving Up states? From the early characterizations of slow oscillations both *in vivo* [3] and *in vitro* [6•] a contribution of both NMDA non-NMDA receptors was reported, even when the blockade of NMDA receptors was found to result in just a partial blockade of Up states, while the blockade was complete with non-NMDA antagonists. It is possible that the relative contribution of glutamate receptors varies by cortical area, since NMDA contribution has been reported to be more relevant in barrel cortex than in entorhinal cortex [31]. The blockade of NMDA receptors in prefrontal cortex is often used as a model of schizophrenia, and this strategy *in vitro* reduces the frequency of Up states while increasing beta-gamma synchronization during Up states (see below) [32]. Another mechanism that contributes to Up states during slow wave sleep *in vivo* is spindle waves that have been proposed to foster dendritic plasticity during these periods [33].

As originally reported, both excitatory and inhibitory neurons fire during Up states [2•]. Conductance measurements during Up states reveal that the weights of excitation and inhibition are well-balanced *in vivo* [34] and similarly *in vitro* [35], as argued theoretically [28]. Increases and decreases in excitatory and inhibitory conductances at the beginning and end of Up states occur in close association with each other *in vitro* [35]. The timing of these synaptic events also accumulates during the rise of Up states both *in vitro* and *in vivo*, although it is 1.4 times faster *in vivo* [36]. A similar coincidence also occurs in Up

state termination. Simultaneous recordings of nearby pairs of cortical neurons also show this interlocking of excitation and inhibition [37]. Inhibition tightly regulates firing rates during Up states and the blockade of $GABA_A$ receptors induces a significant increase in the firing rates during Up states and a subsequent shortening of them (Figure 1c, 43). At the beginning of Up states, both excitatory and inhibitory synaptic conductances are high and tend to progressively decrease; however, their ratio remains constant and close to 1:1 in anesthetized and *in vitro* preparations [34,35]. Inhibitory conductance has been reported to be significantly larger than the excitatory conductance during Up states in natural sleep [38].

Mechanisms of termination of Up states

The synaptic reverberation that generates the Up state is terminated by a transition from the Up to the Down state. What is the main mechanism triggering this transition? Several mechanisms have been proposed that could contribute to the termination of Up states. They include arrival of excitation [34,35], synaptic depression [39] but see Ref. [40], thalamic dysfacilitation [41], fast inhibition [42], activation of K^+ currents [6•,28], or extracellular K^+ dynamics [43]. In order to understand how these mechanisms act, it is important to consider that the Up state is a synchronized persistent network activity, and different mechanisms could break the balance that maintain the Up state, and in that moment the network switches into a 'Down state', as in a relaxation oscillator [44]. An activity-dependent fatigue variable that provides an inhibitory feedback can exert this effect (Figure 1d), and indeed the time course of the slow after-hyperpolarization observed in intracellular recordings during Down states (as in Ref. [45]) suggests that slow K^+ currents could be a relevant factor in the termination of Up states and maintenance of Down states. Different mechanisms involving K^+ currents have been proposed, including ATP-dependent K^+ current [46], $GABA_B$ receptor-mediated responses [47,48] and Ca^{2+} and Na^+-dependent K^+ currents [6•]. Slow K^+-mediated after-hyperpolarizations are blocked by neurotransmitters (acetylcholine, noradrenaline) that control the transition from sleep to awake states [49,50], providing a mechanism for stopping the Up/Down bistability when entering the awake state. Finally, the fact that the transition from Up state to Down state has been reported to be highly synchronous across separate cortical areas-indeed more synchronous than Down-to-Up transitions is highly suggestive that *in vivo*, the beginning of the Down state could be driven or facilitated by a subcortical input [16,51].

Propagation of slow oscillations and travelling waves

The term slow oscillations refers to the temporal organization of the cortical activity during the dynamical regime of state-dependent bistability described so far. However, when we refer to 'slow waves', we allude to the spatial component, since waves propagate. Slow oscillations propagate along the cortical network as waves (Figure 2). Propagation has been reported during slow-wave sleep or anesthesia (Figure 2a–d) and also in the cortex *in vitro* (Figure 2e). During wave propagation, the deep or infragranular layers lead the front of the wave [25•]. Deep layers, and in particular layer 5, also displays higher firing rates and longer Up states, such that mapping these properties to space leads to an anatomical identification of layers 4–5 (Figure 2e–g). The maintenance of physiological propagation speed also involves though columnar interactions between superficial and deep layers [52]. The propagation is continuous along the cerebral cortex (Figure 2b), and locally generated Up states can be recorded along the wave propagation in all cortical layers. The reported values of the propagation speed vary across species and conditions: 1.2–7 m/s (humans/EEG, slow-wave sleep [53]; 100 mm/s in the anesthetized cat [2•]; around 30 mm/s in the anesthetized mouse [27•,54•] and 4–10 mm/s in neocortical slices *in vitro* [6•,25•]. In the olfactory cortex, which is not neocortex but paleocortex, propagation is an order of magnitude faster (114 mm/s in Ref. [55]). Cortical gabaergic inhibition slows down propagation [56,28] and the gradual blockade of $GABA_A$-mediated inhibition progressively increases the propagation speed [45,41]. Once the wave is transformed into an epileptiform discharge due to inhibition removal, propagation speed increases by one order of magnitude [45]. Wave propagation is characterized by its speed, but both its spatiotemporal profile and associated variability provide information about the underlying network and the complexity of the network interactions. Thus, increasing the excitability of the network either by current injection [57] or by decreasing anesthesia levels (Dasilva *et al.*, in review) increases the entropy of the spatiotemporal patterns associated with wave propagation.

Fast rhythms during Up states

Nested fast oscillations that span the beta (15–30 Hz) and the gamma (30–90 Hz) range are displayed during Up state network activity *in vivo* [54•,58,59•]. In these relatively high frequency ranges, inhibitory synaptic potentials have a pivotal role and often synchronously inhibit nearby pyramidal cells [59•,60]. *In vitro* studies have shown that the emergent activity of the cortical network can also be synchronized in the beta and gamma band, typically with the application of cholinergic agonists, kainate, or electrical tetanic stimulation of the tissue [59•,61–63]. Although these neuromodulators potently modulate and induce high frequencies, robust beta/gamma oscillations still spontaneously emerge in the absence of externally applied neuromodulatory agents and without any particular stimulation pattern during physiological *in vitro* network function [60]. Comparing systematically across different cortical areas of beta and gamma power in the mouse *in vivo*, prefrontal cortex Up

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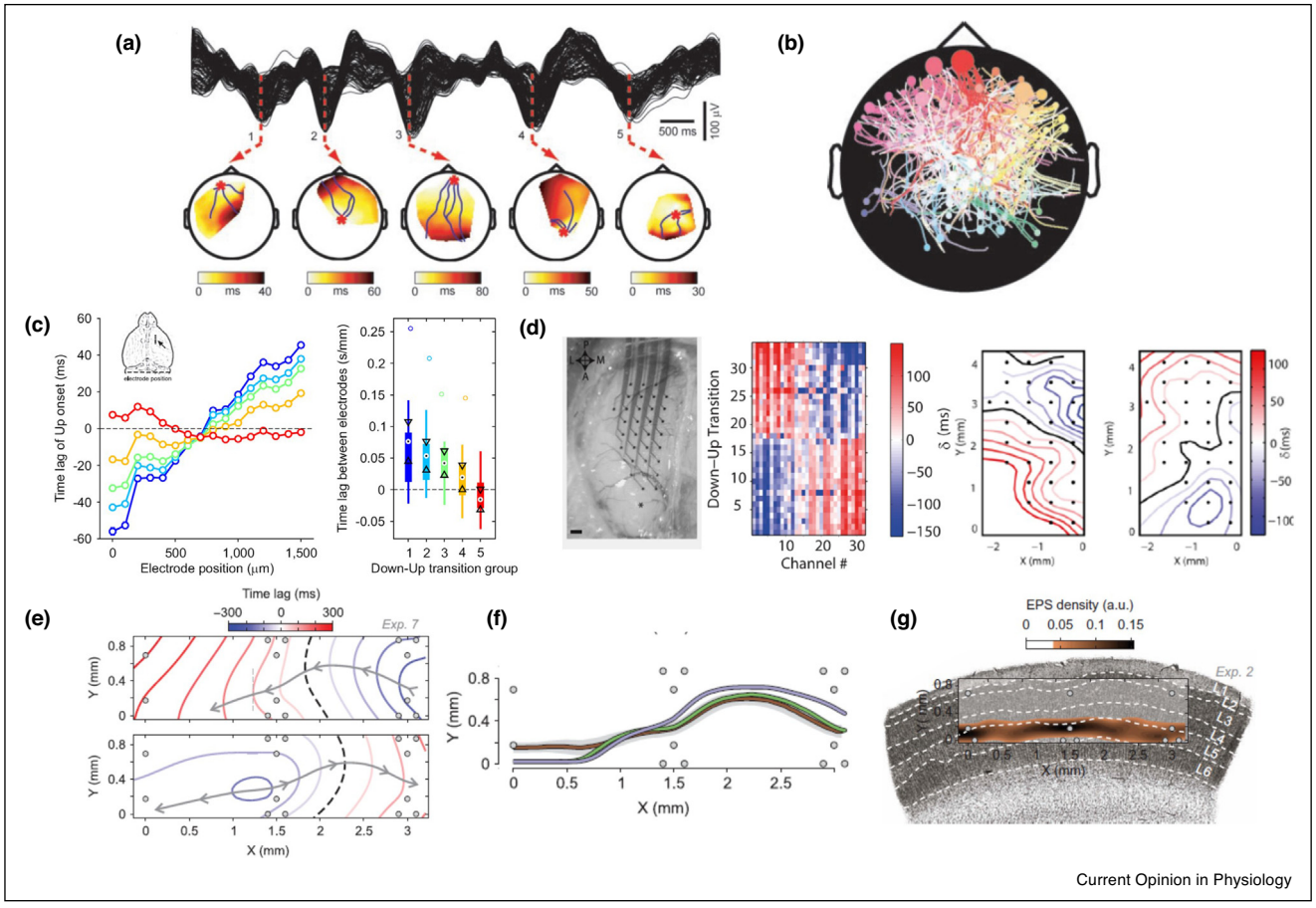
Figure 2



Slow wave propagation in human, mouse and slices.
(a) Signals recorded from all electrodes during five consecutive cycles of the slow oscillation and their corresponding delay maps. Each wave has a different origin and spreads over the scalp with a distinct pattern of propagation. **(b)** Displays the streamline map from the first hour of sleep in one subject (slow oscillation cycles affecting _20 channels are excluded). The size of each dot is proportional to the number of cycles originating from each electrode. Note that virtually any pattern of origin and propagation is possible, although anterior electrodes tend to start more slow oscillations, and streamlines traveling in the anteroposterior direction are more numerous. **(c)** Unidimensional measure of propagating with linear arrays. Average time lags of up state onsets recorded with arrays of 16 electrodes in primary motor cortex of the mouse. **(d)** 2D recordings of mouse cortex. Time lags matrix. Average waves from front to back and back to front after principal component analysis classification of waves. **(e–g)** a and b courtesy of Massimini *et al.* [53]. c modified from Ruiz-Mejias *et al.* [54•]. d modified from Dasilva *et al.* (under review). e–g courtesy of Capone *et al.* [25•].

state activity presents significantly stronger fluctuations than in the motor, somatosensory and visual cortex, in particular in the gamma range (one order of magnitude larger power) [54•]. Interestingly, in pathological conditions where the generation of beta/gamma frequencies during Up states is reduced, the generation of these frequencies in the awake animal is also reduced [64,65]. This finding suggests that the spontaneous organization of activity patterns during slow oscillations has a predictive value of how the cortical network functions in the awake state.

Slow oscillations, sleep and cortical plasticity

Slow (<1 Hz) potential oscillations predominantly arise from the prefrontal neocortex, although they can be generated anywhere in the cortex [53]. They propagate across the cortical network alternating activity and silence, the periods of silence being referred to, in EEG, as delta waves. Such large, synchronized waves are the hallmark of slow wave sleep. Thalamic spindle waves are phase-locked with slow oscillations [66] as are hippocampal sharp-wave ripples [67,68]. Slow wave sleep has been associated with different critical roles such as homeostasis [69•] and synaptic scaling [70]. Furthermore, slow oscillations have been consistently associated with synaptic plasticity, replay and memory consolidation (for a review see Ref. [71]) and the induction of slow oscillations has been associated with memory potentiation [72]. A fine-tuned coordination between the different rhythmic patterns, sharp wave-ripples, delta waves and spindles could be the key to this memory consolidation [73].

Conflict of interest statement

Nothing declared.

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