Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Neurobiology

Brain state dependent activity in the cortex and thalamus

David A McCormick, Matthew J McGinley and David B Salkoff

Cortical and thalamocortical activity is highly state dependent, varying between patterns that are conducive to accurate sensory-motor processing, to states in which the brain is largely off-line and generating internal rhythms irrespective of the outside world. The generation of rhythmic activity occurs through the interaction of stereotyped patterns of connectivity together with intrinsic membrane and synaptic properties. One common theme in the generation of rhythms is the interaction of a positive feedback loop (e.g., recurrent excitation) with negative feedback control (e.g., inhibition, adaptation, or synaptic depression). The operation of these state-dependent activities has wide ranging effects from enhancing or blocking sensory-motor processing to the generation of pathological rhythms associated with psychiatric or neurological disorders.

Addresses
Department of Neurobiology, Kavli Institute for Neuroscience, Yale University School of Medicine, 333 Cedar Street, New Haven, CT 06510, United States

Corresponding author: McCormick, David A (david.mccormick@yale.edu)

Current Opinion in Neurobiology 2015, **31**:133–140

This review comes from a themed issue on **Brain rhythms and dynamic coordination**

Edited by **György Buzsáki** and **Walter Freeman**

For a complete overview see the Issue and the Editorial

Available online 22nd October 2014

http://dx.doi.org/10.1016/j.conb.2014.10.003

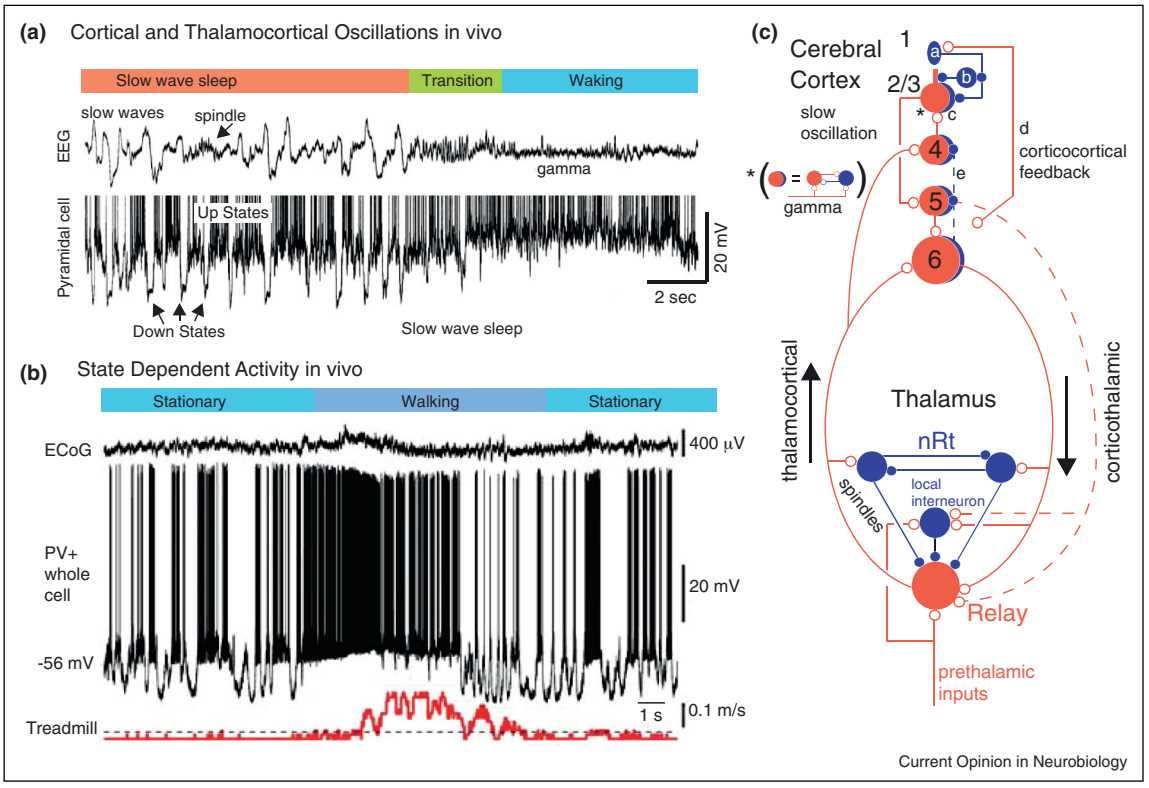
Introduction

The forebrain is a network of coupled oscillators — even repetitive action potential generation is a type of oscillation. The high degree of interconnectivity between cortical neurons and between the cortex and thalamus, together with intrinsic membrane and synaptic properties, gives rise to a number of state-dependent network oscillations [1–3]. Currently we understand well the mechanisms of generation of three of these oscillations: slow, spindle, and gamma waves. Slow and spindle waves occur largely during slow-wave sleep, while gamma waves are present throughout brain states, but are most prominent in the alert and attentive animal. Reviewing the cellular and network mechanisms of these rhythms is instructive, pointing us towards the possible basis for network activity that is not yet well understood. Interestingly, all of these rhythms depend upon an excitatory or activating component (e.g., recurrent excitation, inward currents) interacting with an inhibitory or refractory component (e.g., return inhibition or adaptation). The unique properties of these network oscillations arise in part from the time it takes to complete one cycle, to the subtypes of neuron involved and their density of involvement, to the pattern of propagation and synchronization.

Slow wave sleep activity

A fundamental characteristic of slow wave sleep is the presence of slow (0.5–4 Hz) rhythms in the EEG [1]. Intracellular recordings from cortical neurons revealed that a major generator of these slow rhythms is the so-called cortical slow oscillation [3–5]. The slow oscillation is characterized by alternating sequences of Up and Down states, generated within the cortex, but which are influenced by, and distributed to, subcortical structures such as the thalamus, basal ganglia, brainstem, and cerebellum [2–4,6,7]. The Up state of the slow oscillation results from intracortical recurrent excitation that is roughly balanced with recurrent local inhibition [8,9]. The transition from the Down to Up state occurs when a strong enough (but not too strong) excitatory volley, either spontaneous or driven, enters into a local cortical network whose refractory mechanism has recovered sufficiently from the occurrence of the last Up state [8,10,11]. The subsequent activation of excitatory neurons results in an amplification that initiates even more excitatory neurons to discharge, in a positive feedback loop. This recurrent excitation not only activates excitatory cortical neurons, but also local inhibitory interneurons, particularly fast spiking cells [12••], subsequently dampening and controlling the amplitude and spatial spread of the recurrent excitation. Since both the degree to which cortical excitatory and inhibitory neurons are excited depends upon the amplitude of the recurrent excitatory signal, the two increase and decrease together, resulting in a proportionality or 'balance' [9,11]. This balance, however, is only on average and moment to moment fluctuations in the dominance of excitation or inhibition cause rapid fluctuations in the membrane potential, typically in the gamma frequency range (Figure 2d), and the initiation of action potentials (see Figures 1a and 2). During the generation of the Up state, refractory mechanisms build up, such as the activation of Ca^{2+} and Na^{+} dependent K^{+} conductances in pyramidal cells [8,10], synaptic depression [13], and perhaps even metabolic

Figure 1



State dependent activity in cortical and thalamocortical networks. **(a)** Slow wave sleep is associated with the generation of Up and Down states of the slow oscillation and spindle waves. The transition to waking is associated with an abolition of these network oscillations, the loss of the Down state of the slow oscillation, and the increased prevalence of rhythmic activity in the gamma frequency range. **(b)** Recent recordings in head-fixed mice differ from the recordings in cats (a), and demonstrate the presence of slow oscillatory activity during quiet resting without movement. Walking on a cylinder results in a suppression of the slow rhythmic activity. Cessation of walking results in the return of the slow rhythmic activity. Recording was obtained from a putative fast spiking (parvalbumin positive) interneuron in the primary visual cortex. **(c)** Schematic diagram of basic thalamocortical circuit for the generation of rhythmic activities. The slow oscillation is generated within the cortex as a relatively balanced recurrent interaction of excitatory (red) and inhibitory (blue) neurons. Gamma frequency oscillations are also generated within the cortex, as an interaction of excitatory and inhibitory neurons. Spindle waves are generated during sleep in the thalamus as an interaction of thalamic reticular GABAergic neurons and thalamocortical relay cells. These rhythms interact with one and another, owing to the interconnected nature of the forebrain. Networks of cortical inhibitory interneurons (cells a,b,c) and intracortical connections are important for dynamic control of cortical state and oscillations [69••,70••,71••].
(a) from [5]; (b) from [38].

changes [14]. Owing to the buildup of refractory mechanisms, the recurrent networks become less able to maintain activity, and the network eventually and suddenly fails, resulting in a rapid transition to the Down state (Figures 1a and 2).

Even very small (0.5 mm × 0.5 mm) regions of the neocortex can generate the slow oscillation, and layer 5 appears to have the lowest threshold in most cortical regions [8], although layers 2/3 may also initiate this rhythm in some cortical areas or circumstances [12••,15]. While the slow oscillation was once thought to be restricted to periods of slow wave sleep, animal studies now suggest that it may occur in the waking state, particularly during periods of inattentiveness or drowsiness (Figure 1b). Down states may occur in local cortical regions [16,17], and presumably represent brief periods of disrupted processing in that cortical area. Indeed, the density of Down states, or slow waves, in cortical activity increases with time awake, such that there is a peak of such activity at the beginning of slow wave sleep, and a subsequent slow dissipation of slow waves and Down states with sleep [18]. Since the slow oscillation can initiate anywhere in the cortex, it may occur either very locally, or rapidly propagate throughout the cortical network [8,10,16,19–21], depending in large part on state. During deep slow wave sleep, local cortical networks may exhibit broad synchrony through recurrent connections which allow the transitions between Up and Down states to occur rapidly and nearly synchronously in distributed cortical networks that are interconnected by long range axons [22]. In other circumstances, such as during drowsiness or less deep sleep, Down states may be more local, and lack broad synchrony across the cortex [16,17].