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Are corticothalamic ‘up’ states fragments of wakefulness?

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The slow (<1 Hz) oscillation, with its alternating ‘up’ and ‘down’ states in individual neurons, is a defining feature of the electroencephalogram (EEG) during slow-wave sleep (SWS). Although this oscillation is well preserved across mammalian species, its physiological role is unclear. Electrophysiological and computational evidence from the cortex and thalamus now indicates that slow-oscillation ‘up’ states and the ‘activated’ state of wakefulness are remarkably similar dynamic entities. This is consistent with behavioural experiments suggesting that slow-oscillation ‘up’ states provide a context for the replay, and possible consolidation, of previous experience. In this scenario, the T-type Ca²⁺ channel-dependent bursts of action potentials that initiate each ‘up’ state in thalamo-cortical (TC) neurons might function as triggers for synaptic and cellular plasticity in corticothalamic networks. This review is part of the INMED/TINS special issue Physiogenetic and pathogenic oscillations: the beauty and the beast, based on presentations at the annual INMED/TINS symposium (http://inmednet.com).

Introduction
The function of sleep is a mystery that has long fascinated biologists and is still the matter of intense debate [1]. One of the most prominent features of sleep in mammals is the occurrence of the slow (<1 Hz) sleep oscillation that dominates slow-wave sleep (SWS; Box 1). This oscillation is extremely similar in different species [2–12], suggesting that it might have well-defined, conserved roles. Fairly recently, behavioural experiments have indicated that SWS might be related to memory consolidation [11–17] and the basis of such consolidation might be the slow sleep oscillation itself [12,14–18]. Here, we explore this issue from an electrophysiological and computational modelling perspective. Specifically, we reassess various electrophysiological measurements of the waking (or wake-like) state and compare them with those obtained for the ‘up’ state of the slow (<1 Hz) sleep oscillation in the specific brain structures involved in its generation. The extremely close similarity of both single-neuron and network dynamics during these different scenarios is compatible with the results of behavioural experiments indicating that during SWS selected epochs of prior experience are episodically replayed and consolidated.

The dynamics of single neurons during ‘activated’ states and slow-wave sleep
We start by reviewing the essential cellular correlates of the ‘activated’ brain state, which corresponds to attentive wakefulness, and examine how they qualitatively compare with those of SWS. Brain activation is invariably associated with a so-called ‘desynchronized’ electroencephalogram (EEG), which consists of low-amplitude fluctuations at relatively high frequencies (>15 Hz) [5,6] (Figure 1a). This state is associated with tonic and irregular firing of cortical neurons [19], the membrane potential of which has been shown in naturally waking animals to be persistently depolarized and to fluctuate around −60 mV [5,6] (Figure 1a).

During SWS, the overriding activity of the EEG is the so-called slow (<1 Hz) sleep rhythm or slow (<1 Hz) sleep oscillation [2,3,20] (Figure 1a). This slow oscillation comprises rhythmically repeating, large-amplitude biphasic waves (i.e. slow waves) and is responsible for temporally

Glossary

**In vitro models of the slow oscillation**: a slow oscillation can be reliably generated in isolated slices of the neocortex. This oscillation is an emergent property of networks of cortical neurons, with the ‘up’ state being generated by recurrent excitation that is balanced and regulated by inhibitory networks [24]. The ‘down’ state arises if these mechanisms fail but also seems to be shaped by activity-dependent (i.e. Ca²⁺, Na⁺ and ATP-dependent) K⁺ channels [24,42]. A recovery from this active disfacilitation can eventually lead to a new ‘up’ state. In thalamic slices, individual TC and TRN neurons can generate a slow oscillation intrinsically, without the need for any network input. This occurs if leak K⁺ currents are reduced below a certain threshold [43,44], a feat that can be easily achieved by tonically activating metabotropic glutamate receptors, as probably occurs in the whole brain. In both TC and TRN neurons, the ‘up’ and ‘down’ states are primarily generated by the ‘switching’ on and off, respectively, of the T-type Ca²⁺ ‘window’ current (reviewed in Refs. [9,43–47]).

**Local field potentials (LFPs)**: recordings of extracellular electrical activity using low-impedance electrodes. They provide a signal similar to the EEG but sample more local populations (of the order of 1 mm) in the cortex.

**θ rhythms**: EEG oscillations at ~10 Hz (range, 8–13 Hz) that primarily occur during relaxed wakefulness. In humans, they are most pronounced at occipital sites and most prominent when the eyes are closed.

**Sleep spindles**: brief bursts (typically lasting 0.5–1.5 s) of rhythmic EEG activity at ~7–14 Hz. Sleep spindles are characteristic of early sleep and commonly associated with individual slow-wave complexes (see above).
grouping all other types of sleep-related EEG patterns, such as spindle waves (7–14 Hz) and δ oscillations (1–4 Hz), into clearly demarcated, recurring sequences [3,20] (Box 1 and Figure 1a). Similar to the activated state, the intracellular correlate of the slow (<1 Hz) oscillation in individual cortical neurons is also characterized by periods of irregular tonic firing and a membrane potential that rapidly fluctuates around −60 mV [5,6] (Figure 1a). Unlike the activated state, however, such periods are regularly interrupted by large, stereotypical hyperpolarizations that occur in tandem with the depth-positive component of the EEG slow waves [5,6] (Box 1 and Figure 1a). These distinct depolarized and hyperpolarized periods are usually referred to as ‘up’ and ‘down’ states, respectively. Thus, even in this cursory evaluation of intracellular recordings, it is apparent that the ‘activated’ state of wakefulness and ‘up’ states of the slow (<1 Hz) sleep oscillation correspond to broadly similar membrane-potential dynamics.

Interestingly, several anaesthetic regimens, including urethane and ketamine–xylazine, can also lead to a slow oscillation in the EEG of various species [10,21–28], with

correlated ‘up’ and ‘down’ states in individual cortical neurons that are similar to those that occur during natural sleep [10,21–24,27,28] (Figure 1b). Indeed, although the slow oscillations induced by anaesthesia might not show all the dynamic variability of those present during normal sleep, they capture many important aspects of natural sleep oscillations and have, therefore, proven to be an indispensable tool [3]. During anaesthetic treatment, brain activation can be mimicked by stimulation of the ascending arousal system [29–32]. For example, under ketamine–xylazine anaesthesia, brief electrical stimulation of the pedunculopontine tegmentum (PPT) typically induces a prolonged period (~20 s) of desynchronized EEG activity that is paralleled by a continuous depolarized state of the membrane potential (Figure 1b), similar to that observed during natural waking [30–32] (Figure 1a). Again, broad qualitative similarities between this stimulation-induced ‘activated’ state and ‘up’ states of the slow oscillation are clearly evident, with the PPT stimulation seeming to ‘lock’ the membrane potential into an extended ‘up’ state.

Figure 1. (a) One cycle of the EEG slow (<1 Hz) oscillation at different cortical depths. Note the reversal in polarity between 0.25 and 0.5 mm. The bottom panel shows an enlarged slow wave from a depth recording with depth-positive and -negative components clearly indicated. Modified and reproduced, with permission, from [61]. (b) A simultaneous surface EEG, depth EEG and intracellular recording from a cortical pyramidal neuron during the slow oscillation. The depth-positive EEG component is associated with neuronal silence (‘down’ state), whereas the depth-negative component is related to neuronal depolarization (‘up’ state). Modified and reproduced, with permission, from [33]. (c,d) TC and TRN neurons also show ‘up’ and ‘down’ states in association with the EEG depth-negative and -positive components, respectively. Note the stereotypical nature of the ‘up’ and ‘down’ states and how each ‘up’ state commences with a T-type Ca2+ channel-mediated burst. Sleep spindles tend to be grouped by the slow oscillation and typically occur immediately following the depth-negative peak (d). They are closely associated with rhythmic firing during the early part of the ‘up’ state in TRN neurons. Although sleep spindles are primarily generated within the TRN, their widespread spatiotemporal coherence is brought about by corticothalamic feedback [65]. Modified and reproduced, with permission, from [33,66]. (e) Bursts of EEG δ (1–4 Hz) rhythms recur within the frequency of the slow oscillation. These rhythms can be traced back to the activity of several TC neurons, which can exhibit brief epochs of intrinsic rhythmic bursting rather than a silent ‘down’ state. Again, although δ-frequency activities originate primarily from intrinsic thalamic oscillators, these oscillators are synchronized by corticothalamic feedback [29]. In (c) and (d), EEG and intracellular recording were performed simultaneously, whereas the upper and lower traces in (e) are from separate recordings. Modified and reproduced, with permission, from [21,22]. All data are from the cat.
The increased stability of intracellular recordings during the anaesthetic-induced slow oscillation has proved vital for assessing the behaviour of neurons in key subcortical structures that are crucially involved in influencing the dynamics of sleeping and waking states [21,32,33]. Specifically, intracellular recordings from both thalamocortical (TC) and thalamic reticular nucleus (TRN) neurons have revealed a pattern of ‘up’ and ‘down’ states during the slow oscillation that are similar to, and synchronized with, those in cortical neurons [21,32,33] (Figure 1c) and correspond closely to the activity of thalamic neurons observed during natural sleep. Thus, the slow oscillation ‘up’ states in TC and TRN neurons are characterized by seemingly irregular tonic firing and/or a membrane potential that fluctuates around –60 mV, whereas the ‘down’ state is manifest as a rhythmically recurring, stereotypical hyperpolarizing event (Figure 1c). Also, in close similarity to cortical neurons, the activity of both types of thalamic neurons during brain activation...
becomes apparently ‘locked’ in a depolarized state (Box 1c), being characterized by continuous firing and/or fluctuations of the membrane potential that are superficially indistinguishable from those that occur during slow-oscillation ‘up’ states [21,32,33] (Figure 1c). The qualitative similarities between the cellular correlates of the ‘activated’ state and ‘up’ states of the slow (<1 Hz) sleep oscillation therefore seem to be a ubiquitous feature of neuronal dynamics in corticothalamic networks.

**Similarities in cortical network dynamics between the ‘activated’ state and ‘up’ states of the slow oscillation**

The similarity between activated states and the slow-oscillation ‘up’ state in the cortex is not only apparent at the rank of single cells, but can also be found at the level of the EEG and local field potentials (LFPs) (see Glossary). First, the typical desynchronized EEG pattern of arousal is evident locally in the EEG during ‘up’ states, both in the naturally sleeping animal (Figure 1a) and during anaesthesia (Figure 1b). A second, and stronger, indication of the similarities comes from studies using multiple bipolar electrodes in awake and naturally sleeping cats [34], whereby it was shown that the desynchronized EEG patterns that are present during wakefulness are not only irregular temporally, but, more generally, are also characterized by low and fluctuating spatiotemporal coherence in LFPs (Figure 2a). The LFP signals at neighbouring electrodes (at a distance of 1 mm) alternate between periods of high and periods of low coherence (HC and LC, respectively; Figure 2a), as quantified by the correlation excursions (Figure 2b). However, these fluctuations in coherence are local, because the excursions of correlations are greatly diminished between more distant pairs of electrodes [34–37] (Figure 2b). Extremely similar results are obtained for ‘up’ states of the slow oscillation during natural sleep (Figure 2a), indicating that the spatiotemporal dynamics of these ‘up’ states, as viewed through the EEG and LFPs, are essentially indistinguishable from those of wakefulness.

Extracellularly recorded cortical neurons also display similar dynamics during activated states and slow-oscillation ‘up’ states. It has been known for some time that the mean firing rate of cortical neurons during wakefulness and SWS is in the same range [19] (Figure 2c), a fact that is especially evident if the ‘up’ states of the slow oscillation are specifically analysed [5,34]. However, the dynamic similarity concerns not only the mean rate, but also the temporal patterns of discharge and the respective timing between different cells. Although such entities are more difficult to characterize, a convenient, albeit subjective, way to appreciate such information is by transforming the spike patterns into audio signals by assigning a specific note to each neuron. Allowing for the presence of ‘concerted silences’ during SWS, owing to the slow-oscillation ‘down’ states, the melodies produced by wakefulness and SWS are remarkably similar (such audio material can be downloaded from http://www.archive.org/details/NeuronalTones).

Importantly, the similarity between cortical ‘up’ states and activated states not only is evident in EEG and LFP dynamics and single-cell firing, but also extends to their relationship. Performing wave-triggered averages...
of spiking activity, by averaging the periods of neuronal firing around the negative peaks of the LFP (Figure 2c), reveals that the depth-negative EEG component is correlated to an increased probability of unit firing, both in the waking state and during slow-oscillation ‘up’ states (Figure 2c).

From the recent intracellular investigation of SWS [5], the membrane-potential dynamics of cortical neurons were decomposed into excitatory and inhibitory conductance components [38]. Such an analysis demonstrates that, in the majority of cortical cells, inhibition is stronger than excitation, at the level of both mean conductance and conductance variation, as quantified by the standard deviation (σ) of the conductance (Figure 2d). This pattern is reported for both wakefulness and the ‘up’ states of SWS. However, there is a significant difference between the absolute values measured during the two states, with SWS generally showing higher conductance (Figure 2d). Nevertheless, both states have a qualitatively similar ratio of excitatory-to-inhibitory conductance, in which both the mean inhibitory conductance and its associated fluctuations are larger, on average, compared with excitatory contributions (Figure 2d). This resemblance also extends to the spike-triggered average conductance patterns in the two states [38].

Finally, additional indirect evidence that cortical slow-oscillation ‘up’ states and wakefulness stem from similar network dynamics comes from modelling studies. Biophysical models with realistic cellular properties and synaptic interactions have simulated cortical slow-oscillation patterns of ‘up’ and ‘down’ states that are owing to recurrent interactions between networks of excitatory and inhibitory neurons [39–41]. These models have established that minimal parameter changes enable the transition from ‘up’ and ‘down’ states of the slow oscillation to a sustained ‘up’ state, with electrophysiological features consistent with experimental measurements. Thus, several independent lines of experimental and modelling evidence indicate that cortical network dynamics during slow-oscillation ‘up’ states are extremely similar to those present during wakefulness or brain activation.

Similarities between a persistently depolarized state and the ‘up’ state of the slow oscillation in thalamocortical and thalamic reticular nucleus neurons

Both cortical and thalamic slow (<1 Hz) oscillations can be reproduced using in vitro models. In cortical slices, the slow oscillation is reliant on a modified, artificial cerebrospinal fluid, containing a reduced Ca^{2+} concentration, and is generated primarily by network-dependent mechanisms [24,42] (see Glossary). In thalamic slices, by contrast, the slow oscillation in both TC and TRN neurons is generated mainly by intrinsic mechanisms [9,43–46] (see Glossary). These oscillations have extremely similar properties to those observed in thalamic cells during natural sleep [45,47] and become apparent if activation of modulatory cortical input is mimicked through either electrical stimulation of corticofugal afferents or the persistent pharmacological activation of metabotropic glutamate receptors that are postsynaptic to these afferents [9,43–46]. The intrinsic nature of the slow oscillation in thalamic neurons offers a unique opportunity to examine the similarities between slow-oscillation ‘up’ states and a continuously depolarized state (as occurs in natural wakefulness and brain activation; Figure 1c), because these two scenarios can be invoked at will by simply varying the amount of steady, injected current during an intracellular recording (Figure 3a,b). For example, the distribution of interspike intervals (ISIs) in a condition in which thalamic neurons fire continuously in the absence of injected current (Figure 3) and a condition in which they are hyperpolarized to produce intermittent epochs of firing during slow-oscillation ‘up’ states (Figure 3c) can be compared. Such a comparison reveals that the mode and essential form of the distribution of ISIs are extremely similar, although their coefficient of variation (CV) is always larger for ‘up’-state-generated firing episodes than the ‘activated’ state. Interestingly, the typical rate of firing of TRN neurons (~40 Hz; Figure 3b) under both these conditions is always much higher than that of TC neurons (~10 Hz; Figure 3a) [9,43,45]. This, in turn, suggests a dominance of inhibitory over excitatory activity in the thalamus during both brain activation and the slow-oscillation ‘up’ state, in a similar manner to that revealed for cortical neurons (see above and Figure 2d).

In most TC neurons, continuous firing during sustained depolarization consists solely of tonic firing of single action potentials (Figure 3a) and, correspondingly, the slow-oscillation ‘up’ state also shows straightforward firing of single action potentials [9,43] (Figure 2a). In a small number of TC neurons, however, firing during sustained depolarization comprises rhythmic (~3–15 Hz) high-threshold (HT) bursting [9,43] (Figure 3a) and, correspondingly, the slow-oscillation ‘up’ state also produces epochs of HT bursting (Figure 3a). Because these HT burst-generating neurons might function as pacemakers for wake-related α (8–13 Hz) rhythms [47–49], a distinct possibility is that they also function to generate brief epochs of α-frequency activity during the ‘up’ state of the slow oscillation in SWS [50,51].

Slow-oscillation ‘up’ states as micro-wake ‘fragments’

An assortment of data from the corticothalamic system has been presented that converges to establish that, at both single-cell and neuronal-network levels, the fully activated brain state and slow-oscillation ‘up’ states are dynamically similar. An attractive interpretation of this is that individual corticothalamic ‘up’ states provide micro-wake-like contexts that facilitate specific types of neuronal inter-action. In particular, they might provide brief epochs of network dynamics that aid the transfer of memory traces between short-term storage sites in the hippocampus and long-term memory space in the neocortex. Within this framework, the subtle differences that exist between the dynamics of continuous waking and slow-oscillation ‘up’ states might function to alter the direction of information flow between cortical areas while maintaining individual neurons in a depolarized and active state that is conducive to information processing. This modified information streaming might also be aided by the sleep-related changes that occur in various neuromodulator levels, particularly...
acetylcholine (Ach) [52]. These hypotheses are certainly consistent with the results of recent behavioural studies showing that firing sequences from cell assemblies in both the neocortex and the hippocampus are compressed and reactivated concurrently with generation of the cortical slow-oscillation ‘up’ state [12,13,53–56]. They also link well with human studies showing the following: first, local increases in the average power density of slow oscillations follow specific learning tasks and are related to a subsequent improvement in task performance [14]; and second, artificially boosting slow oscillations through the transcranial application of oscillating fields enhances the retention of hippocampus-dependent declarative memories [16].

Because the dynamics of slow-oscillation ‘up’ states are so similar to those of continuous wakefulness, why do they not lead to conscious experience during SWS? One possibility is that current methods and approaches overlook several vital variables and are simply too coarse to detect the essential differences between what constitutes conscious and unconscious dynamics. Alternatively, it could be that the differences in dynamics between the activated state and ‘up’ states (e.g. discrepancies in neuronal conductance and CVs, and compression of firing sequences) are sufficient to determine whether full awareness takes place or not. In this sense, perhaps the most obvious and intuitive candidate to explain the behavioural disparity between wakefulness and sleep is the increased level of

![Figure 3](https://example.com/figure3.png)

*Figure 3.* Close quantitative similarities between the ‘up’ state of the slow oscillation and a persistently depolarized state in TC and TRN neurons. (a) Left column: intrinsic slow (<1 Hz) oscillations, as recorded intracellularly from tonically hyperpolarized TC neurons in the cat lateral geniculate nucleus in vitro, exhibiting either simple tonic firing (i, −60 pA) or HT bursting (ii, −50 pA) during the ‘up’ state (see expanded sections, lower left). The corresponding histogram of the distribution of ISIs (lower right) is computed from several consecutive ‘up’ states. Right column: spontaneous activity of the neurons depicted in the left column; however, in the absence of hyperpolarizing current, the activity consists of continuous tonic firing (i) and HT bursting (ii; see expanded sections, lower left). The corresponding histogram of the distribution of ISIs (lower right) reveals an extremely similar pattern to that observed during slow-oscillation ‘up’ states. Adapted, with permission, from [9,43]. (b) Left column: intrinsic slow oscillation, recorded intracellularly from a tonically hyperpolarized (~50 pA) cat TRN neuron in vitro, exhibiting high-frequency tonic firing during the ‘up’ state (see expanded section, lower left). The corresponding histogram of the distribution of ISIs (lower right) is computed from several consecutive ‘up’ states. Right column: spontaneous activity of the same neuron in the absence of hyperpolarizing current consists of continuous tonic firing (see expanded sections, lower left). Again, the corresponding histogram of the distribution of ISIs (lower right) reveals an extremely similar pattern to that observed during slow-oscillation ‘up’ states. Adapted, with permission, from [45].
inhibition present during the ‘up’ state compared with the waking state (Figure 2d). Another possibility is that conscious awareness might require an uninterrupted stream of ‘activated’ neuronal dynamics lasting more than the few seconds of an ‘up’ state, perhaps so that certain types of long-range neuronal interactions during high-frequency (20–80 Hz) activity, which have been suggested to break down during sleep [57], can be fully established and maintained [58]. This is partly backed up by noting that during sleep the most lucid experiences occur during the rapid eye movement (REM) phase, during which the intermittent hyperpolarizations (i.e. ‘down’ states) of the slow oscillation are absent [5]. However, it should also be noted here that not all studies support the hypothesis that long-range interactions are diminished during sleep [15].

T-type Ca2+ channel-mediated bursts in thalamocortical neurons as a trigger for ‘up’ states and synaptic plasticity

If individual ‘up’ states contain segments of prior wake-related dynamics, an attractive hypothesis is that these segments are determined and selected during wakefulness through ongoing remodelling of cortical [59] or corticothalamic attractors by sensory input [18]. Such attractors might then be preferentially activated in sleep during the slow-oscillation ‘up’ state [18], particularly in response to a strong thalamic signal, which is a highly effective way to trigger internally defined cortical ensemble dynamics [60,61]. This is noteworthy because a conspicuous property of the slow oscillation in TC neurons is the presence of a robust T-type Ca2+ channel-mediated burst at the commencement of each ‘up’ state [9,21,32,33,43] (Box 1 and Figure 4). Because these highly prominent TC neuron bursts invariably precede the ‘up’ state transitions in cortical neurons in vivo [33], they might be the key network triggers that are ultimately responsible for initiating a new epoch of reactivated corticothalamic dynamics. Supporting evidence for this comes from the finding that in cortical networks that lack thalamic input, i.e. cortical slabs [62] or slices [24], the slow-oscillation ‘down’ state is considerably longer than that if thalamic input is present. In addition, recordings in the intact brain demonstrate that the firing rate of a large proportion of cortical neurons is transiently elevated at the start of each ‘up’ state [27,34] (Figure 4), which is consistent with a robust, stereotypical excitatory input. Thus, although spontaneous ‘up’ and ‘down’ states can emerge in isolated cortical networks [24,42] (Box 1), there is strong evidence that in the intact brain cortical ‘up’ states might be triggered by thalamic input.

In addition to functioning as network triggers, T-type Ca2+ channel-mediated bursts might also have an important role in facilitating plasticity. The Ca2+ entry associated with these bursts, both directly (i.e. in thalamic neurons) and indirectly (i.e. in cortical neurons), could open the gate to subsequent modifications of synaptic strength and/or intrinsic excitability (Figure 4), as previously proposed for sleep spindle oscillations (Box 1) in the cortex [63,64]. Moreover, the large increase of firing that occurs at the start of the ‘up’ state in cortical neurons and its associated LFPs are synchronous over distances of several millimetres [34]. This highly synchronous nature of neuronal activity during the early part of the ‘up’ state might further contribute to bringing about cellular and synaptic plasticity. These suggestions are consistent with the demonstrations that the slow-oscillation ‘up’ state is crucially related to memory consolidation in humans [15] and cell-assembly reactivation in rats [13,53–56].

Concluding remarks

Electrophysiological and modelling data show that ‘up’ states of the slow (<1 Hz) sleep oscillation are dynamically equivalent to the activated state of wakefulness. This is in agreement with several behavioural investigations, which indicate that waking activities are replayed, and possibly consolidated, during SWS. The prominent T-type Ca2+ channel-mediated bursts in TC neurons might function as key network triggers that ensure the synchronous start of slow-oscillation ‘up’ states across related cortical territories. The highly synchronized and increased firing that is present in the initial portion of the ‘up’ state in different neuronal components of corticothalamic networks might represent an important element in bringing about cellular and synaptic plasticity.

Clearly, several outstanding questions remain. First, why are the corticothalamic dynamics of slow-oscillation ‘up’ states so similar to those of continuous wakefulness?
and why, considering this similarity, is the slow oscillation associated with a lack of consciousness? Second, what are the precise neuronal rudiments that define a lack of consciousness during sleep? Are our techniques too coarse to determine this or is it simply that ‘up’ states are too short to sustain conscious experience? Third, what are the basic cellular mechanisms underlying SWS-specific learning and memory consolidation?

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