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Interactive report

Why do we sleep?[1]

Terrence J. Sejnowski[a,b,*], Alain Destexhe[c]

[a]*Howard Hughes Medical Institute and the Salk Institute, 10010 North Torrey Pines Road, La Jolla, CA 92037, USA*
[b]*Department of Biology, University of California at San Diego, La Jolla, CA 92093, USA*
[c]*Unite de Neurosciences Integratives et Computationnelles, CNRS, UPR-2191, Avenue de la Terrasse, 91198 Gif-sur-Yvette, France*

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Abstract

Slow-wave sleep consists in slowly recurring waves that are associated with a large-scale spatio-temporal synchrony across neocortex. These slow-wave complexes alternate with brief episodes of fast oscillations, similar to the sustained fast oscillations that occur during the wake state. We propose that alternating fast and slow waves consolidate information acquired previously during wakefulness. Slow-wave sleep would thus begin with spindle oscillations that open molecular gates to plasticity, then proceed by iteratively 'recalling' and 'storing' information primed in neural assemblies. This scenario provides a biophysical mechanism consistent with the growing evidence that sleep serves to consolidate memories.

Keywords: Slow-wave sleep; Spindle oscillation; Spatio-temporal synchrony; Synaptic plasticity; Memory consolidation; Computational model; Rapid eye movement sleep

1. Introduction

On average, a third of our lives pass by in sleep. Although body movements are largely suppressed during sleep, resulting in reduced external behavior, the internal activity of the brain has a richness that defies explanation. At the onset of sleep, brief episodes of 7–14 Hz synchronized spindling occurs in the thalamus and cortex, producing large-scale spatio-temporal coherence throughout the forebrain. During sleep the low-amplitude, high-frequency activity in the neocortex characteristic of the awake state is replaced with high-amplitude, low-frequency rhythms [117]; the cortex alternates between periods of slow-wave sleep in the 2–4 Hz range and episodes of rapid eye movement (REM) sleep, characterized by sharp waves of activity in the pons, the thalamus and the occipital cortex.

The widespread activity that occurs in the brain during sleep has a purpose; however, there is still no consensus on what that might be. Activity in the sleeping brain is largely hidden from us because very little content of the brain activity that occurs during sleep directly enters consciousness.

New methods have, however, been developed to eavesdrop on this ongoing activity and computational models of sleep states have been mathematically analyzed and simulated with digital computers. This approach is still in its infancy, but it may someday allow us to better understand the purpose of the extensive activity that occurs in sleeping brains.

Before approaching the behavioral consequences of sleep, we must first understand the patterns of electrical activity and the biochemical states of neurons that occur in the brain during sleep. A phenomenological description of sleep states will provide a firm foundation for generating hypotheses for the functions of sleep that can be experimentally tested. This summary is based on two recent reviews, i.e. Refs. [100,117].

The next section focuses on the biophysical aspects of slow-wave sleep oscillations, including the influence of thalamic-generated oscillations on cortical cells and the analysis of the spatial and temporal distribution of neuronal activity during slow-wave sleep. A scenario is introduced for the steps that may occur leading to the consolidation of recent memories, including the conditions leading to the opening of calcium-mediated biochemical pathways triggering gene expression and a 'recall-store'

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*Corresponding author. The Salk Institute, Computational Neurobiology Laboratory, 10010 North Torrey Pines Road, La Jolla, CA 92037, USA. Tel.: +1-858-453-4100; fax: +1-858-587-0417.

E-mail address: terry@salk.edu (T.J. Sejnowski).

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iteration during slow-wave sleep. This summary is based on two recent articles, i.e. Refs. [30,42].

Recent behavioral and physiological experiments will be reviewed supporting the hypothesis that memory consolidation may occur during sleep. Finally, some computational issues are examined arising from recent attempts to scale up neural network learning algorithms to multilayered architectures.

Some concrete suggestions are made for how the different sleep rhythms could contribute to memory consolidation [39,105,106].

2. Brain rhythms during sleep

The thalamus and cerebral cortex are intimately linked by means of reciprocal projections [72]. The thalamus is the major gateway for the flow of information toward the cerebral cortex and is the first station at which incoming signals can be modulated during sleep. This modulation shifts the brain from an alert, aroused state, open to signals from the outside world, to the closed state of sleep. The electroencephalogram (EEG) during early stage of quiescent sleep is associated with spindle waves, which occur at a frequency of 7–14 Hz; as sleep deepens, delta waves with slower frequencies (1–4 Hz) appear on the EEG [117]. Even slower rhythms occur during slow-wave sleep that group delta waves and spindles [3,29,90].

2.1. Delta oscillations

Delta waves (1–4 Hz) were initially shown to arise between cortical layers II to III and V [116]. Intracellular recordings in vivo and in vitro indicate that the thalamus is also involved in the generation of this rhythm [117]. A delta-frequency rhythm can be generated in single cells by the interplay of two intrinsic currents of thalamocortical neurons: the hyperpolarization-activated cation current (I_h) and the transient low-threshold Ca^{2+} current (I_T). A wide variety of other ionic currents with different voltage dependencies and kinetics of activation and inactivation contribute to the shaping of the amplitude and time-course of each burst of action potentials, as revealed both through biological experiments and computational modeling [83,89].

The hyperpolarization of thalamocortical cells is a critical factor for the interplay between I_h and I_T that generates delta oscillation [117]. At the normal resting level in vivo, I_T is inactivated, but a hyperpolarization of 10 mV can lead to spontaneous, self-sustained delta oscillation. The dependence of delta oscillation upon membrane hyperpolarization can also be demonstrated in simulations of thalamic neurons based on Hodgkin–Huxley-like kinetic models of the ionic currents [89].

Corticothalamic volleys potentiate and synchronize the delta oscillation of simultaneously recorded thalamic cells. In simulations of thalamocortical cells oscillating in the bursting mode at delta frequency, depolarizing cortical inputs are easily able to reset the cell to a new phase of its rhythm [84].

Thalamic synchronization can also be induced by stimulating cortical foci that are not directly connected to the thalamic nuclei where the recordings are performed; this recruitment of thalamic cells may be achieved through the reticular thalamic nucleus, which receives collaterals of layer VI corticothalamic cells and thalamic neurons that project to the cortex [8]; the reticular cells are exclusively inhibitory and project back to the thalamus (but not to the cerebral cortex) and also innervate other cells of the reticular thalamic nucleus. The reticular nucleus is uniquely positioned to influence the flow of information between the thalamus and cerebral cortex.

Delta waves are not present throughout the entire brain. For example, during slow-wave sleep, the hippocampus undergoes brief, 50–100 ms sharp waves, which are highly synchronized events throughout the hippocampus [21]. Sharp waves, also called large irregular amplitude (LIA) activity, are often associated with brief periods of fast oscillations (100–200 Hz) called ‘ripples’ which synchronize action potentials among hippocampal neurons [133].

2.2. Spindle oscillations

EEG spindles are characteristic of brain electrical synchronization at sleep onset, an electrographic landmark for the transition from waking to sleep that is associated with loss of perceptual awareness. Spindle oscillations consist of 7–14 Hz waxing-and-waning field potentials, grouped in sequences that last for 1–3 s and recur once every 3–10 s. These oscillations are generated in the thalamus as the result of synaptic interactions and intrinsic membrane properties of inhibitory neurons of the reticular thalamic nucleus and excitatory thalamocortical, and their interaction with cortical pyramidal neurons [117].

In intracellular recordings from reticular and thalamocortical cells as well as from computational modeling, these two neuronal classes display a mirror image during spindles [117]. In reticular cells, rhythmic (7–14 Hz) bursts are generated by low-threshold Ca^{2+} spikes and are superimposed on a slowly rising and decaying depolarizing envelope. The bursts of reticular cells inhibit large numbers of the amocortical cells through their divergent GABAergic axons, leading to the appearance of rhythmic inhibitory postsynaptic potentials (IPSPs) in thalamocortical neurons. Some of these IPSPs result in enough removal of inactivation of the low-threshold Ca^{2+} current to be followed by a rebound Ca^{2+} spike and associated burst of action potentials. These periodic bursts in thalamocortical cells converge onto reticular neurons and close the loop for rhythmic oscillation. A simple model consisting of a thalamocortical cell reciprocally

interacting with a reticular cell already demonstrates the essential features of spindling [43].

The waxing and waning of the spindling in this two-neuron model is controlled by the intracellular calcium level in the thalamocortical neuron, which increases with each Ca^{2+} spike; calcium binding to the I_h channels change their voltage dependence and eventually terminate the spindle [40], a prediction verified experimentally [81].

Thalamic reticular neurons are involved in the genesis of synchronized thalamocortical oscillations, which depend in part on their complex bursting properties. A high density of low-threshold calcium current (I_T) has to be present in the dendrites of these cells compared to the soma to reproduce the firing pattern characteristics found experimentally in vitro and in vivo [47].

Isolation of the reticular nucleus from the rest of the thalamus and cerebral cortex abolishes spindle oscillations in thalamocortical systems, but the deafferented reticular thalamic nucleus can generate oscillations at spindle frequencies [118]. Axonal and, in some species dendrodendritic, interconnections between reticular cells may allow the coupling and interaction of these endogenous oscillators, thereby generating oscillations in an isolated nucleus. Models of simplified reticular thalamic neurons with full connectivity and slow mutual inhibition exhibit synchronous oscillatory activity, but the frequency is below the range of the spindling rhythm [45,128]. An array of model reticular neurons with fast inhibition between locally-connected neurons exhibits 8–10 Hz oscillations in the local field potential in the model (based on the average membrane potential for a cluster of nearby neurons) that wax and wane similar to experimental observations [45].

Spindling has been observed in thalamic slice preparations [127]. However, when the reticular cells were isolated from the thalamocortical cells, spindling was abolished. Models of the thalamus suggest that a larger and more intact collection of reticular thalamic cells may be needed to generate spindle waves autonomously. Another possible reason is that the presence of neuromodulators in vivo keep the resting levels of reticular cells more depolarized than in vitro; in the model, the oscillations in the reticular network are abolished at resting levels that are too hyperpolarized [46]. The spindling observed in thalamic slices exhibits traveling waves [76]. Many properties of these traveling waves can be modeled by a one-dimensional chain of thalamocortical and reticular neurons reciprocally connected within local neighborhoods [44,57].

In the cortex, synchrony between cortical cells separate by 1 cm was insensitive to cutting the horizontal intracortical connections between them, suggesting that corticothalamic projections have a powerful impact in synchronizing distant part of cortex and thalamus through corticothalamic loops. The overall spindle activity pattern in the thalamus is, in turn, organized by the cortex. The spatiotemporal properties of synchronized thalamic spindle oscillations became disorganized after removal of the cortex [31,32]. Modeling studies have shown how the corticothalamic projections organize the global coherence of thalamic oscillations [41].

During spindling and slow-wave sleep, the thalamus excites the cortex with patterns of activity that are more spatially and temporally coherent than would be normally encountered in the awake state. Depolarizing pulses of Ca^{2+} that enter thalamic and cortical neurons may influence enzyme cascades and regulate gene expression, homeostatically adjusting the balance of ionic currents and regulatory mechanisms. This widespread activity could be used to reorganize cortical networks following learning in the awake state [131], as discussed below.

2.3. Arousal

Electrical activation of certain brainstem and hypothalamic regions, including the so-called reticular activating system, causes a variety of neurotransmitters including acetylcholine (ACh), norepinephrine (NE), serotonin (5-HT), histamine (HA), and glutamate to be released though diffuse ascending axonal arborizations. These neuromodulators mimic arousal by suppressing sleep spindles, delta waves, and slow cellular rhythms, and by replacing these low-frequency oscillations to activity similar to that of the awake attentive animal. In cortical pyramidal neurons, ACh, NE, 5-HT, HA, and glutamate can reduce three distinct K^+ currents, thereby resulting in a markedly enhanced responsiveness to depolarizing inputs and changes in neuronal firing mode [88]. Adenosine, and GABA can reduce excitability by increasing membrane K^+ conductance.

These neurotransmitter systems abolish the low-frequency rhythms in thalamocortical systems during waking and REM sleep, as well as promote more tonic activity or the appearance of fast oscillations. The changes in firing between sleep and arousal in thalamic neurons are accomplished by depolarization of the membrane potential by 5 to 20 mV, which inactivates the low-threshold Ca^{2+} current and therefore inhibits burst firing. These results have been simulated in models of thalamocortical and reticular neurons [40,89].

2.4. Rapid eye movement (REM) sleep

REM sleep is characterized by an abolition of low-frequency oscillations and an increase in cellular excitability, although motor output is markedly inhibited [68]. In the thalamocortical system, REM sleep and wakefulness have equivalent electrophysiological signatures [80]. Dream reports are common upon arousal from REM sleep, but can also occur during slow-wave sleep. Despite great interest, there is no generally accepted function for dreams or, for that matter, for the sleep state itself. It is of interest that during REM sleep, the activity in the hippocampus, which forms reciprocal connections with the neocortex, displays a

strong, low-frequency rhythm in the theta range, 6–8 Hz, which is entrained by inhibitory inputs from the septal nuclei, which primarily project to the inhibitory interneurons in the hippocampus.

In the hippocampus there is a population of excitatory principal cells with recurrent connections that strongly interact with inhibitory interneurons. Paradoxically, increasing an external inhibitory drive onto the inhibitory interneurons, without directly affecting any other part of the network, can in some circumstances cause the interneurons to increase their firing rates [125]. For this to occur, recurrent connections among the excitatory cells have to be strong enough to make the excitatory network unstable when feedback inhibition is removed. When there is a periodically varying input, such as the input to the hippocampus from the septal nucleus, there should be a systematic relationship between the phase shift and depth of modulation for each interneuron. This prediction was tested and confirmed by recordings from interneurons in the CA1 region of the rat hippocampus in vivo [125].

The two major sleep phases, slow-wave and REM sleep, are mirrored by two awake states in the hippocampus of rats and probably in other mammals: the first is a state of low-frequency theta oscillation that occurs during active exploration, which resembles the state of the brain during REM sleep, and a second awake state consisting of sharp waves that occurs during rest, which resembles the activity in the hippocampus characteristic of slow-wave sleep.

2.5. Fast oscillations

Changes in the activity pattern generated by cortical neurons and circuits are less stereotyped than those of thalamic cells and circuits, although some common features exist. The low-frequency oscillations of the cortical EEG disappear upon arousal and are replaced by higher frequency rhythms in the 20–80 Hz frequency range, which includes beta and gamma frequency bands. As in the thalamus, these alterations in cortical activity take place, at least in part, by depolarization of pyramidal cells, presumably through the reduction of specialized K^+ conductances by ACh, NE and other neuromodulators [88,114].

The fast oscillations in the EEG occur during some behaviors such as immobility during hunting and focused attention to stimuli during complex sensory or motor tasks. Neurons throughout the nervous system (for example, retina, lateral geniculate thalamic nucleus, and cortex) have the ability to generate repetitive trains of action potentials in the frequency range 20–80 Hz, although the synchronization of this activity into behaviorally relevant subgroups of widely spaced neurons has only been demonstrated in the cerebral cortex [58].

Fast (30–40 Hz) spontaneous oscillations have been observed in intracortical, corticothalamic, and intrathalamic networks [42,115], demonstrating, first, that fast oscillations are in phase throughout the cortical depth, and second, that these oscillations are also present during sleep-like activity patterns; this goes beyond the conventional view that fast oscillations are present only during brain-activated states. Intracortical coherency of fast oscillations is coupled with synchronized fast rhythms in corticothalamic circuits. The coherence of the fast rhythms is short range whereas low-frequency sleep rhythms exhibit synchronization on a larger spatial scale (see below).

The diversity of cortical cells and their complex interactions make it difficult to model cortical networks with the same confidence that thalamic networks have been modeled. It is not, however, difficult to generate oscillatory activity in the 20–80 Hz range with networks of simplified neurons [100]. These models have revealed the need to regulate the tendency of recurrent networks to oscillate. The excitability of neurons can be controlled by inhibition; however, inhibition is also an efficient mechanism for synchronizing large populations of pyramidal neurons because of voltage-dependent mechanisms in their somata and the strategic location of inhibitory boutons on the somata and the initial segments of axons, where action potentials are initiated [82]. Networks of reciprocally interconnected interneurons can produce gamma oscillations when the interneurons fire doublets [124]. Realistic simulations of cortical neurons demonstrate that sparse excitatory connectivity between distant populations of neurons can produce synchronization within one or two cycles, but only if the long-range connections are made on inhibitory as well as excitatory neurons [20].

Thalamocortical oscillations are characterized by distinct spatiotemporal patterns of activity, which suggests that these oscillations may play distinct roles. We turn to the biophysical characterization of these oscillations in order to explore possible roles.

3. Biophysical aspects of sleep oscillations

To investigate the possible role of oscillations, we studied the effects of thalamic input on neocortical pyramidal neurons based on intracellular recordings in vivo and computational models [30]. The data and model suggest that spindle oscillations are highly effective at inducing Ca^{2+} entry in the dendrites of pyramidal neurons, which might prime the neuron for biochemical events that later could lead to permanent changes in the network. In the second part, we examine the spatiotemporal distribution of the patterns of activity associated with different events of wake and sleep states [42]. These results lead to a scenario in which slow-wave sleep oscillations serve to reorganize the cortical network (see details in Ref. [39]).

3.1. Characterization of the effect of thalamic inputs in neocortical pyramidal neurons

Highly synchronized spindle oscillations are generated

by intrathalamic and thalamocortical loops in which the rebound bursts of thalamocortical (TC) cells are central. EPSP/IPSP sequences often follow synchronized thalamic inputs in neocortical pyramidal neurons during sleep spindles (Fig. 1A1–A2). The dendrites of neocortical pyramidal cells therefore receive highly synchronized and powerful excitatory inputs from the thalamus. However, despite the potentially powerful nature of these synchronized thalamic inputs, pyramidal neurons have a relatively low rate of discharge during spindle oscillations [51,112], as shown in Fig. 1A. Could it be that although strong EPSPs do indeed occur in pyramidal cell dendrites, they are not apparent in somatic recordings because of strong feedforward inhibition?

The possibility was explored with computational models and intracellular recordings in vivo [30]. Intracellularly recorded pyramidal neurons in the suprasylvian gyrus of cats under barbiturate anesthesia showed that spindle oscillations in the EEG are paralleled with EPSP/IPSP sequences in cortical neurons (Fig. 1A1–A2). These sequences were indistinguishable from that obtained from thalamic stimulation, suggesting that spindle-related IPSPs

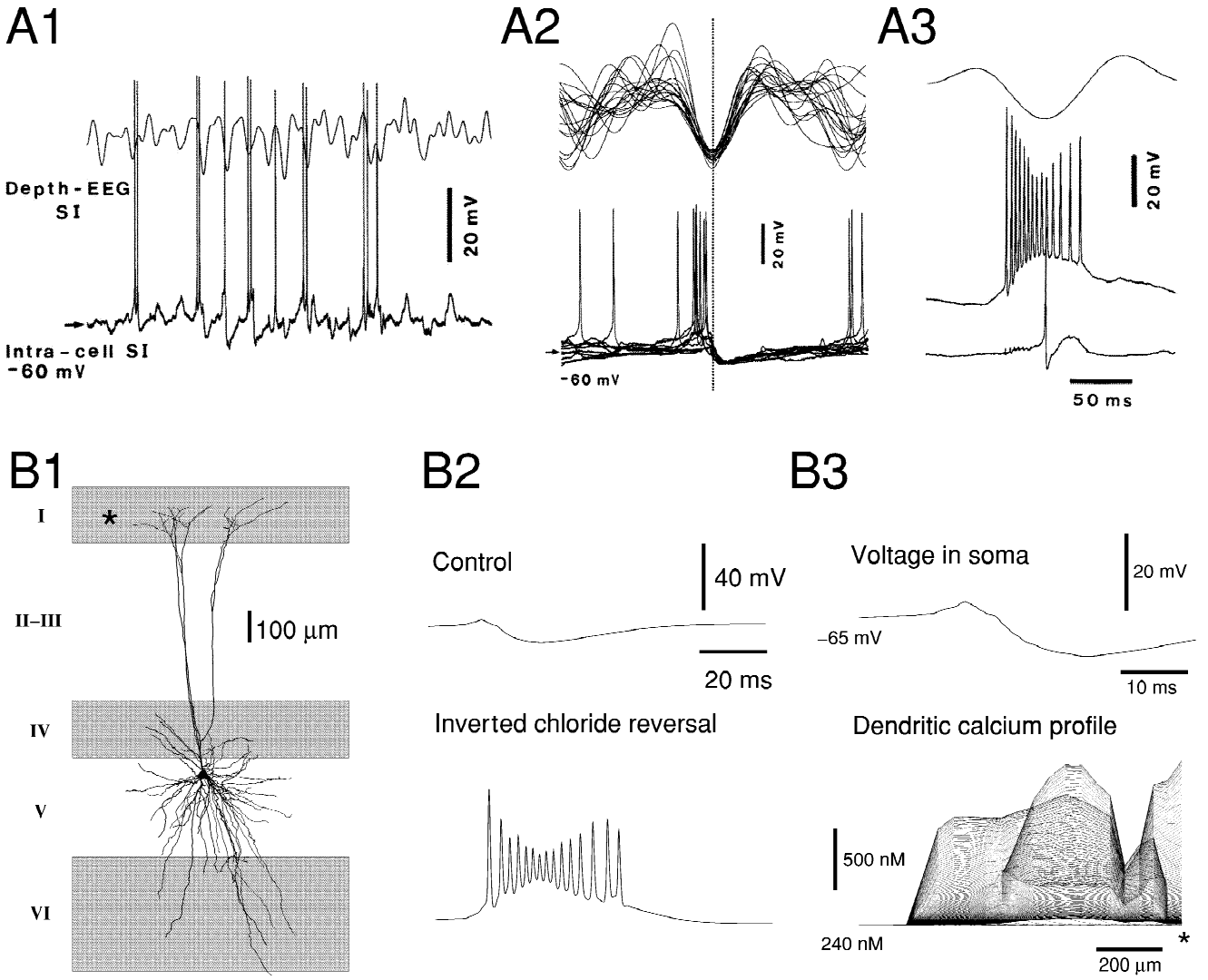

Fig. 1. Evidence that spindle oscillations evoke calcium entry in pyramidal neurons. (A) In vivo intracellular recordings in suprasylvian cortical neurons during spindle oscillations under barbiturate anesthesia. (A1) simultaneous recording of intracellular and extracellular activity. (A2) each cycle of the spindle oscillation corresponds to EPSP/IPSP sequences in the recorded pyramidal neuron. (A3) dual intracellular recording in which one of the neuron (middle trace) was recorded with chloride-filled pipettes. In this case, the EPSP/IPSP sequence transformed into a powerful burst of action potentials. (B) Computational models of thalamic inputs in pyramidal neurons. (B1) morphology used in the simulations. A layer V pyramidal neuron recorded intracellularly in A was filled and its morphology was integrated into simulations. Simulations of thalamic inputs in layers I, IV and VI (gray areas) were directly compared to the experimental recordings of thalamic inputs in that cell. (B2) simulated EPSP/IPSP sequences and bursts following inversion of the chloride reversal potential. The model could match experiments only if both excitatory and inhibitory conductances were strong. (B3) calcium transients in the dendrites of the model following thalamic inputs. The membrane potential at the soma (top trace) consisted in an EPSP/IPSP sequence. However, representing the profile of calcium concentration (bottom trace) along a path from soma (left) to distal apical dendrite (*) shows important calcium transients consequent to strong dendritic depolarization. Figure modified from Ref. [30] (see for details).

were triggered by thalamic inputs. To further characterize the IPSP component, dual intracellular recordings were performed in which one cell was recorded using a K–Cl filled pipette. Cells recorded with chloride pipettes fired bursts of 4–7 action potentials at 100 Hz with spike inactivation, in phase with spindle waves (Fig. 1A3).

Computational models were designed based on these experiments. Neurons were impaled for intracellular recording, stained with Neurobiotin and reconstructed using a computerized tracing system, as shown in Fig. 1B1. The model of thalamic EPSP/IPSP sequences was based on three sets of constraints: (a) The relative density of excitatory and inhibitory synapses in different regions of the cell; (b) The fraction of these synapses activated by a given stimulus; and (c) The kinetics of the different types of receptors involved (see details in Ref. [30]). Thalamic axons end preferentially in cortical layers I, IV and VI [64,72]. Based on these anatomical data, the thalamocortical synapses are distributed 15% in layer I (more than 800 μ above the soma), 60% in layer IV (from 50 to 200 μ above the soma), and 25% in layer VI (below 200 μ of the soma); there were no excitatory synapses in any other layers in the model. A schematic of this distribution is shown in Fig. 1B1.

This model was used to estimate the excitatory and inhibitory conductances underlying spindle-related EPSP/IPSP sequences. To reproduce the strong burst discharges observed with chloride-filled pipettes, it was necessary to include relatively strong $GABA_A$-mediated conductances. Under these conditions, the reversed IPSPs could explain the genesis of these strong bursts. However, to reproduce the relatively moderate discharge under normal conditions, it was also necessary to assume significant excitatory conductances. Only under these conditions was it possible to reproduce both moderate control discharges and bursts in the presence of chloride (Fig. 1A2). The exact values of the conductances, the kinetics of synaptic receptors and the distribution of synapses can be found in Ref. [30].

This combination of models with in vivo intracellular recordings strongly suggests that during spindling, the strength of thalamic input on neocortical pyramidal cells should be stronger than that indicated by the low firing rates of these cells. The model suggests that the thalamic inputs on neocortical pyramidal cells could evoke powerful glutamatergic conductances in parallel with strong GABAergic conductances. It is conceivable that this strong GABAergic component prevents the cell from firing by shunting the EPSPs to prevent avalanches of excitatory discharges. This conclusion is in agreement with direct measurements of conductances during visual inputs in cortical neurons that also revealed large GABAergic conductances [19].

The synaptic conductances evoked by thalamic inputs in cortical pyramidal neurons are more than a simple shunt of the EPSPs by IPSPs. Morphological data indicate that excitation and inhibition are not evenly distributed in pyramidal neurons: the dendrites are dominated by excitatory synapses while the soma essentially receives inhibitory synapses [37]. This imbalance necessarily implies that the dendrites of pyramidal neurons must experience strong depolarization, but this depolarization is not visible at the somatic level due to the proximal inhibition. Thus the model suggests that during spindling, cortical pyramidal cells receive strong dendritic excitation in parallel with strong inhibition around the soma, preventing the cell from firing.

It thus seems that, during sleep spindles, the synchronized bursts of high-frequency action potentials in thalamic neurons generate in the cortex ideal conditions for strongly depolarizing their dendrites but keeping the cell from firing. Simulations indicate that this type of input is well-suited to triggering calcium entry into dendrites (Fig. 1B3). This is consistent with in vitro studies showing that dendritic depolarization is accompanied by Ca^{2+} entry [134]. The proximal inhibition would allow a massive Ca^{2+} entry into the dendrites of pyramidal neurons without producing excessive firing in the cortical network.

Various calcium-dependent mechanisms are involved in synaptic plasticity (reviewed in Ref. [56]). Thus, calcium entry during sleep may serve to prime the synapses for permanent changes. In particular, CaMKII, an enzyme that is abundant at synapses and is implicated in synaptic plasticity of excitatory synapses in the cortex and elsewhere [108,129], is not only sensitive to Ca^{2+} but also to the frequency of Ca^{2+} spikes [38]. It is possible that sleep spindles provide a selective signal to efficiently activate CaMKII in the dendrites of cortical pyramidal neurons.

Another possible consequence of massive Ca^{2+} entry in pyramidal neurons is calcium-dependent gene expression, which is also frequency sensitive [60,79] in the delta range of frequencies (1–4 Hz). Calcium that enters dendrites during spindles may accumulate in the endoplasmic reticulum, which forms a continuous compartment within the neuron continuous with the nucleus. Calcium-stimulated calcium release from the endoplasmic reticulum during delta waves may then deliver the calcium signal to the nucleus [11].

The repeated Ca^{2+} entry may activate a molecular ‘gate’, opening the door to gene expression. This possibility is based on the observation that repeated high-frequency stimuli, but not isolated stimuli, activate protein kinase A (PKA), an enzyme implicated in long-lasting synaptic changes and long-term memory [2]. The proposed mechanism is that PKA acts like a ‘gate’ by inhibiting phosphoprotein phosphatases, which themselves exert a tonic inhibition over biochemical cascades leading to gene expression [2,15,16] (for a model, see Ref. [12]). The evidence for this hypothetical mechanism is supported by observations that activation of PKA alone does not induce synaptic changes, but blocking PKA suppresses long-term synaptic changes in the hippocampus [53].

All the necessary enzymes for this mechanism are

located at or near the active zone of the synapse [26,48,75,93].

Similar mechanisms could occur during spindling. It may be that the massive Ca^{2+} entry during spindles, repeated at approx. 10 Hz frequency, provides the conditions needed to open a molecular gate, for example mediated by PKA. Sleep spindles could therefore provide a physiological signal similar to the repeated tetanus used to induce long-term synaptic changes in slices. It could also provide a 'priming' signal, opening a gate that allows permanent changes to subsequent inputs following the sleep spindles (see below).

3.2. Spatiotemporal structure of slow-wave sleep oscillations

Spindles generally appear during the early phase of slow-wave sleep, which is later dominated by other types of oscillation, such as slow-waves (delta waves at 1–4 Hz or slow oscillations of <1 Hz). We analyzed the spatiotemporal coherence of these types of oscillations in the suprasylvian gyrus of cats during natural awake and sleep states [42]. We found that low-amplitude fast oscillations of wakefulness (Fig. 2A, left panel) are characterized by relatively low spatiotemporal coherence, in agreement with previous findings [49,59,113]. This is shown in the correlations, which fluctuated in both space and time, only reaching high values occasionally and only for neighboring sites (Fig. 2B, left panel).

Analyzing the correlations between extracellularly-recorded units and local EEG revealed that units fired tonically, and wave-triggered averages showed that unit firing was correlated with the depth-EEG negativity (Fig. 2C, left panel). Similar characteristics were found for fast oscillations during REM sleep (see details in Ref. [42]).

In contrast, slow oscillations are remarkably coherent across several millimeters in cortex (Fig. 2A, middle panel). Consistent with this, correlations during slow oscillations stay high across wide regions of the cortex (Fig. 2B, middle panel). Remarkably, slow-wave complexes are correlated with a concerted decreased/increased firing in single units (Fig. 2C, middle panel). This shows that these high-amplitude EEG waves reflect a remarkably synchronized network event consisting of a generalized silence followed by an increased firing, or network 'rebound'. Similar conclusions were drawn for delta waves in various preparations [7,25,54], for spontaneous slow oscillations under anesthesia [28,123] as well as in cortical slices [102].

Perhaps the most interesting observation was that slow-waves also contain a myriad of brief episodes of low-amplitude fast oscillations that are nested within slow-wave complexes (Fig. 2A, right panel). This corroborates previous observations in anesthetized animals [63,132] or during natural sleep [115]. Focusing specifically on these brief episodes showed that their spatial and temporal coherence are similar to the fast oscillations during wakefulness (Fig. 2B, right panel). This similarity applied to the relation between these fast oscillations with unit discharges, which showed that the depth-negative EEG components are correlated with an increased probability of unit firing (Fig. 2C, right panels).

Therefore, these brief episodes are electrophysiologically indistinguishable from the 'sustained' fast oscillations of awake and REM sleep.

The observation that highly coherent slow-wave patterns alternate with brief episodes of low-coherence fast oscillations can be interpreted in several ways. Slow waves and fast oscillations might represent different states of responsiveness of cortical neurons and different receptive field properties [34,50,63,132]. We favor another interpretation [42,39], in which slow-wave sleep is viewed as a cyclic, iterating process leading to memory consolidation. Brief episodes of processing similar to the awake state (episodes of fast oscillations) alternate with highly synchronized network events (slow-waves). As shown above, during the rebound of the network (depth negativity of the slow wave), cortical cells should receive strong EPSPs followed by IPSPs, which is likely to trigger a massive calcium entry in the dendrites. Slow-waves may therefore be part of a process for establishing permanent changes in the network through calcium-dependent mechanisms. Slow-wave sleep in this scenario could then be part of 'recall' and 'store' sequences, in which the fast oscillations could reflect recalled events experienced previously, which are stored in the network through the synchronized firing that occurs during the slow-wave complexes in the EEG.

3.3. A biophysically-based hypothesis for network reorganization during sleep

The global picture that emerges from the studies summarized above is that two types of sleep oscillation, spindles and slow waves, may have complementary roles in network reorganization. At sleep onset, the thalamus enters a burst mode and generates synchronized spindle oscillations. During these oscillations, the high-frequency bursts of thalamic relay cells occur synchronously in the thalamus and therefore provide unusually strong excitatory/inhibitory inputs in cortical pyramidal neurons. The repetition of these inputs at approx. 10 Hz is particularly efficient to trigger periodic calcium entry in cortical dendrites and activate intracellular mechanisms, such as CaMKII or molecular gates. This process could serve to open the door between synaptic activation and gene expression, so that pyramidal neurons are ready to produce permanent changes in response to some specific synaptic events that need to be consolidated.

As sleep deepens, slow-waves such as delta oscillations progressively dominate the EEG. A slow-wave complex is a remarkably synchronized network event, in which a concerted period of silence is seen across the network,

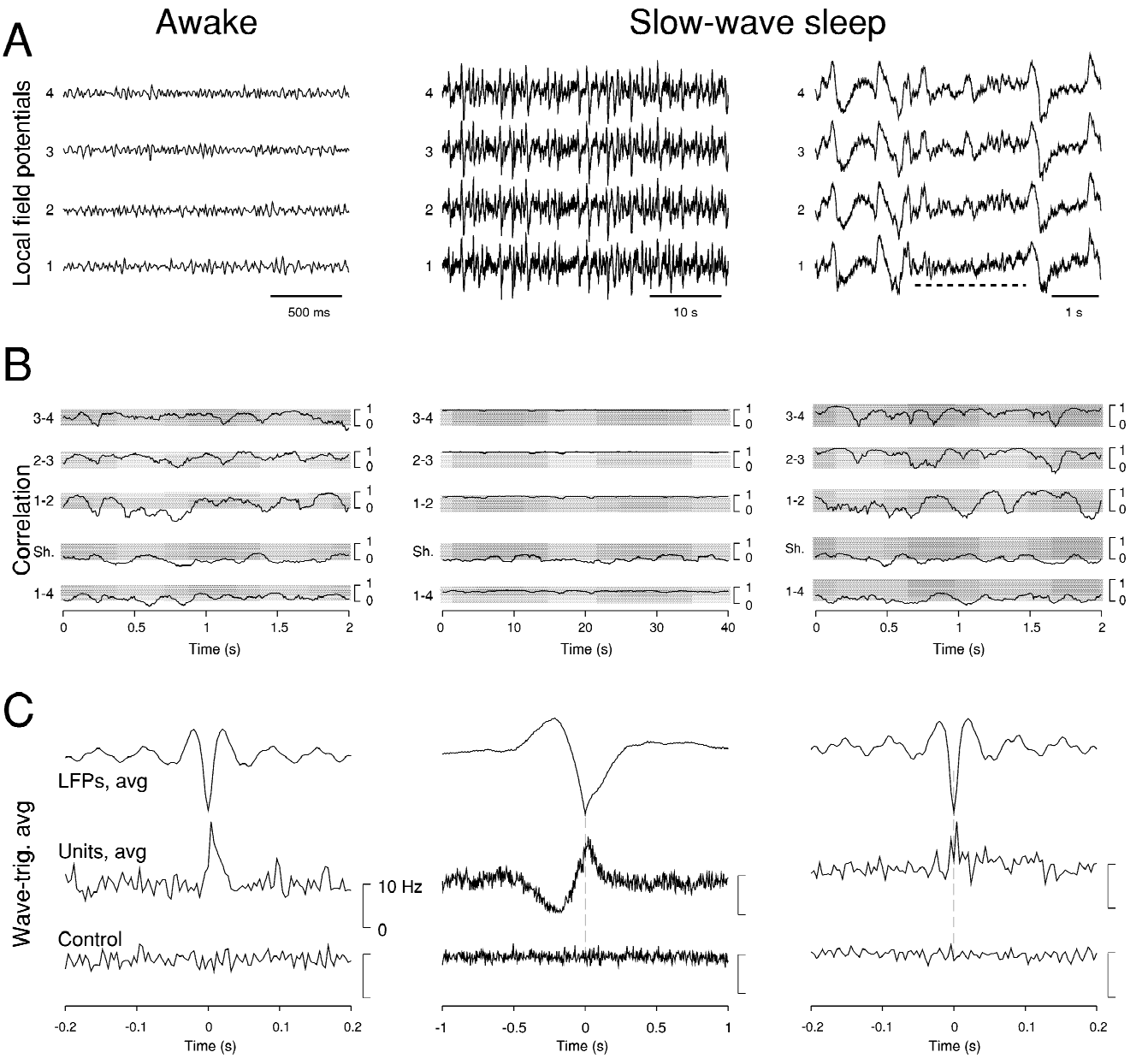

Fig. 2. Spatial and temporal coherence of wake and sleep oscillations. (A) Bipolar local field potentials (LFPs) recordings at four equidistant sites (1 mm interelectrode distance) in suprasylvian cortex of cats during natural awake (left) and slow-wave sleep states (middle; note different time scale). Awake periods consisted in low-amplitude fast (20–60 Hz) activity while slow-wave sleep was dominated by waves of slower frequency (0.5–4 Hz) and larger amplitude. The right column shows a period of slow-wave sleep with higher magnification, in which a brief episode of fast oscillations was apparent (dotted line). (B) Correlations between different sites, calculated in moving time windows. Correlations were fluctuating between high and low values between neighboring sites during fast oscillations (left), but rarely attained high values for distant sites (1–4; 'Sh.' indicates the control correlation obtained between electrode 1 and the same signal taken 20 s later). By contrast correlations always stayed high during slow-wave sleep (middle). Episodes of fast oscillations during slow-wave sleep (right) revealed similar correlation patterns as during the awake state. (C) Wave-triggered averages between extracellularly-recorded units and LFP activity. During the awake state, the negativity of fast oscillations was correlated with an increase of firing (left; 'Control' indicates randomly shuffled spikes). The negativity of slow wave complexes was correlated with an increased firing preceded by a silence in the units (middle; note different time scale). During the brief episodes of fast oscillations of slow-wave sleep (right), the correspondence between units and LFP was similar as in wakefulness. Figure modified from Ref. [42].

followed by a rebound firing in most of the cells. We suggest that some synapses could be 'tagged' by short-term potentiation during brief episodes of fast oscillations. During the subsequent slow-wave, these tagged synapses would then be selected by the synchronized pattern of firing, through a calcium-mediated signal evoked in pyramidal cells. This calcium signal could be routed to the nucleus (assuming the 'gate' has been opened by spindles) or to local protein synthesis in dendrites, leading to long-term modifications or even morphological changes. A brief

episode of fast oscillations that follows next would then potentiate or tag another subset of synapses; these tagged synapses would be selected by the next slow-wave for permanent changes, and the cycle repeats itself several hundred times during the slow-wave sleep episode.

Alternating slow-wave complexes with brief episodes of fast oscillations during slow-wave sleep could thus result in the permanent formation of small sets of strongly interacting neurons. This type of interactions might provide a biophysical mechanism for the consolidation of memory traces in cerebral cortex. This theme is explored in more detail in the next section.

4. Sleep and memory consolidation

There is growing evidence that memory consolidation occurs during sleep [22–24,120,119]. However, not much is known about how the different phases of sleep contribute to consolidation or what biophysical mechanisms are involved. Our emerging understanding of the events that take place in the thalamocortical system during sleep suggest that sleep spindle oscillations might have a prominent role in gating mechanisms for plasticity in pyramidal neurons, and in a subsequent phase of sleep the alternation of slow waves and fast oscillations could provide the substrate for consolidation. This mechanism might involve a interactions between the hippocampus and the neocortex. We review here evidence for this scenario and discuss some consequences that raise new issues and explore new hypotheses.

4.1. Hippocampus, neocortex and retrograde amnesia

Behavioral experiments on retrograde amnesia have shown that lesions limited to the hippocampus and surrounding regions produce memory impairment in monkeys; only recent memories are impaired while remote memories remain intact [6,136]. These experiments suggest that the hippocampal formation is required for memory storage for only a limited time period after learning. As time passes, its role in memory diminishes, and a more permanent memory gradually develops, probably in neocortex, that is independent of the hippocampal formation [18,73,87,110,136]. The hippocampus may not be the site of storage for the information before it is consolidated, but may instead facilitate the associative links between information stored in different parts of the cerebral cortex and other parts of the brain.

Until recently, the processes that may occur in the cortex during consolidation could only be inferred indirectly from lesion experiments, but recordings from freely moving rats during awake and sleep states corroborate the idea that the hippocampus and the neocortex exchange information during sleep states [131,107,120]. Neurons in the rat hippocampus respond to places in the environment [96].

Changes occur in the correlations between hippocampal place cells in freely moving rats as a consequence of learning a new environment [131]. In these experiments, neurons that had neighboring place fields and fired together during exploration of an environment became more highly correlated during subsequent sleep episodes in comparison with activity during preceding sleep episodes. The correlated firing of neurons in the hippocampus during sleep may be a ‘played back’ version of newly acquired experiences to the neocortex through feedback projections [22,27,86,87,107]. Thus, the neocortex during the wake state provides the hippocampal formation with a detailed description of the days events; during sleep, the inputs from the hippocampus recreates some version of these events in the neocortex, where permanent memory representations are gradually formed over repeated episodes of sleep.

Cortical representations of objects and events are widely distributed in cerebral cortex; for example, the representation of the shape of a violin might be stored in the visual cortex, the sounds made by a violin in the auditory cortex, how it is grasped in the parietal cortex, and how it is played in the motor cortex [35]. Problems arise when new experiences and objects must be integrated with existing information that is widely distributed. Learning algorithms designed for artificial neural networks that use such distributed representations can suffer from ‘catastrophic interference’ when new information is stored in the same neural circuits as previously stored information [87]. Therefore, the brain must solve two problems during learning: where to make the changes needed to create new links between existing memories, and how to make changes that are compatible with previously stored memories.

4.2. Computational models of sleep

During REM sleep the brain is as metabolically active as in the awake state. What is all this metabolic activity being used for? One intriguing possibility is that information acquired by the brain during the day is being recalled during sleep [68]. Neural network models of associative memory included such a ‘sleep phase’ to calibrate the storage of memories acquired by Hebbian mechanisms [4,33,70]. Another related idea is that sleep is used to consolidate memories of recent facts and events (reviewed in Ref. [106]).

In one computational explanation for memory consolidation, brain activity in the neocortex representing previous events during waking is reactivated through feedback from the hippocampal formation. Before consolidation, the lack of direct connections between distant brain areas prevent parts of the memory trace to reactivate other parts that represent a unique episode. During sleep, indirect connections are formed within the neocortex that allow the memory traces in different parts of the brain to become

re-excited without the need of the hippocampus [5,87]. After learning, activity in the hippocampus is no longer needed to reactive a memory, and in the process, the elements of the specific memory have been integrated into the general knowledge store by virtue of repeated reactivations. This type of model might be called the completion model for memory consolidation since the purpose of sleep in this model is to improve associative pattern completion in a sparsely connected system of networks in the neocortex.

In another theoretical approach to memory consolidation, the cortex stores probability densities for sensory states in a hierarchy of layers; that is, the higher areas of the cortex encode higher-order statistical regularities in the sensory inputs and in the absence of sensory input can generate activity in earlier stages of processing with the same statistics using feedback connections. By generating ideal input patterns, the feedforward connections responsible for recognition can be accurately trained to improve processing at earlier stages [66]. Conversely, when the brain is awake, the sensory inputs drive the feedforward system, during which the weights on the feedback connections can be altered, thereby improving the generative model. This two-phase process produces an internal, hierarchical representation of experiences that are economical. The feedback connections in this model are used to generate prototypical input patterns. The learning mechanisms needed are biologically possible since, unlike previous learning algorithms for hierarchical networks that required a detailed teacher and error backpropagation, this awake–sleep model only depends on locally available signals and there is no teacher other than the sensory experience.

The awake–sleep learning algorithm attempts to capture the statistics of sensory inputs with an internal code that is capable of representing component features that are common to many objects. Because these statistical components are not apparent without comparing many sensory experiences, the training process is gradual, in the sense that only small changes are made during any one awake–sleep cycle. Although the feedback connections are not used during the awake or feed forward phase of the algorithm, it is possible to view them as representing a prior probability distribution on complex brain states. Thus, if sensory input is locally ambiguous, it may be possible for the feedback connections from higher levels in the hierarchy help disambiguate them [65,78].

The awake–sleep model is limited to a passive, unsupervised form of learning that is entirely driven by the statistics of sensory states. Not all sensory inputs are equally important, and some tasks might require special representations. It would be easy to add attentional mechanisms that would modulate the learning rate with significance of the stimulus. There may also be biases in cortical representations at birth that are specified during development, which could incorporate a prior probability distribution for the world. There is also a goal-directed reinforcement learning system in the brain that involves subcortical as well as cortical structures [95]. Unsupervised awake–sleep learning and other forms of learning could work together, biasing, shifting and adapting cortical representations to insure survival in complex and uncertain environments.

The two computational explanations offered above for memory consolidation during sleep are neither mutually exclusive nor exhaustive. They nonetheless have the virtue of allowing specific predictions to be made for some of the puzzling physiological phenomenon summarized above. For the completion hypothesis, feedback projections from higher cortical areas to lower ones are used during sleep for the purpose of reactivating assemblies of neurons that had previously been used to represent specific episodic memories. In this case, plasticity should occur to strengthen connections that encourage the same patterns to reoccur in the future. In the case of the generative hypothesis, ideal patterns of activity are instantiated in lower cortical areas for the purpose of altering the feedforward connections.

4.3. Interactions between the hippocampus and the neocortex

During the transition from wakefulness to sleep, the cerebral cortex becomes less responsive to external sensory inputs and less concerned with actively gathering information. The thalamus, which during the wake state relays sensory information from the periphery to the cortex, becomes less of a relay and more of a mirror, as feedback connection from the cortex to the thalamus become capable of entraining thalamic neurons through synchronous bursting. In a sense, during sleep, the cortex no longer listens to the outside world, but rather to itself. Feedback connections from the cortex to the thalamus become as important as thalamocortical ones and information can flow in both directions.

Theta oscillations occur in the hippocampus when an animal explores its environment and also during REM sleep, when the cortex is in a state that resembles active exploration. During this state the hippocampus is primed for receiving and retaining information from the neocortex: the inputs to the hippocampus report on the detailed state of the cortex while the animal is actively exploring the world and the synapses in the hippocampus are particularly susceptible to changes in efficacy [71]. In contrast, during slow-wave sleep, the hippocampus bombards the cortex with activity rather than the sensory world. Recently stored information in the hippocampus may be played back to the neocortex during slow-wave sleep, but in combinations that may not have occurred simultaneous during the day and at a rate that is much faster [98]. This information is a distillation of recent sensory impressions and cortical states that are activated during REM sleep. The information

stored in the hippocampus is probably not a literal copy of information stored in the neocortex, which has a much larger capacity, but rather is an abstraction of that information, a pointer that is capable of reactivating that information in the neocortex through feedback connection from the hippocampus.

Feedback from the hippocampus to the neocortex takes the form of sharp waves, brief bursts of activity that occur at intervals of 0.3 to 3 Hz [21]. Not much is known about the mechanisms that initiate sharp waves in the hippocampus or elsewhere (see Ref. [97]). It is thought that spontaneous activity in hippocampal neurons and associated neurons in the hippocampal formation ignites an assembly of reciprocally connected neurons to discharge in less than 100 ms. The temporary associations between neurons formed during the day, perhaps at different times, may be recapitulated during the brief bursts of activity that then can imprint traces of these associations on the neocortex, which is in a receptive state during slow-wave activity.

When the neocortex switches from slow-wave sleep to REM sleep, characterized by high-frequency activity, the hippocampus switches from sharp wave activity to a theta rhythm. During REM, the cortex may activate recently formed associations between neurons, which may lead to changes in the connection strengths of neuron in the hippocampus, while it is in a theta state. This cycle of reciprocal activation and reactivation occurs repeatedly during sleep.

In addition to the prominent slow-wave activity in the cortex during sleep, there is also a high-frequency oscillation of 40 Hz during REM in the neocortex, similar to that which occurs during attentive waking states. At even higher frequencies, 'ripples' of action potentials in the 100–200 Hz range fire in synchrony during sharp waves in the hippocampus. The extent of synchrony between the firing of neurons in these high-frequency states is more spatially localized than during the low-frequency oscillations. Inhibitory neurons in the thalamus and the cortex are of particular important in producing synchrony and in controlling the spatial extent of the coherent populations.

Synchrony and other network properties could be exploited for controlling the flow of information between brain areas and for deciding where to store important information. Synchronization can enhance the signal-to-noise ratio of a message [67,101] but it can also reduce the amount of information that can be encoded [100] since perfectly synchronous firing in a pool of neurons signals a single event. Thus, perfectly synchronous oscillation would correspond to a carrier wave upon which deviations can be used to code information [122].

4.4. Temporally asymmetric hebbian plasticity

The discussion so far has focused on global states of thalamocortical assemblies, but long-term memory may be based on mechanisms for synaptic plasticity that are synapse specific and driven by local signals. In particular, Donald Hebb in 1949 [62] proposed a Neurophysiological Postulate for how synaptic strengths could be adjusted by an activity-dependent mechanism:

> *''When an axon of cell A is near enough to excite cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased.''* (*Hebb*, 1949, *p*. 62)

The traditional interpretation of this postulate is that synaptic plasticity is based on coincidences between the release of neurotransmitter from a presynaptic terminal and the depolarization of the postsynaptic dendrite. Evidence for a coincidence detection mechanism has been found in the hippocampus, where long-term potentiation (LTP), discovered there in 1973 by Tim Bliss and Terje Lomo, was shown to be Hebbian in the sense of temporal coincidence [14,74]. LTP of synapses on hippocampal neurons can be elicited by pairing synaptic input with strongly depolarizing current [130], when neither alone produces a long lasting change, consistent with this interpretation. Furthermore, the induction of LTP at some synapses is controlled by the NMDA receptor, which requires both binding of glutamate and depolarization to allow entry of calcium into the cell. Another issue is that increases in the strength of a synapse from random coincidences will end inexorably in saturation [104]. Hebb suggested that unused synapses might decay, and a form of long-term depression (LTD) induced by low frequency activity might provide such decay from spontaneous activity in the cortex, and a long train of 1 Hz does in fact induce LTD in hippocampal neurons [9]. However, if synaptic strengths are to encode long-term memories it is important to have a mechanism for LTD as specific as that for LTP.

Synapses between pairs of cells can be directly examined with dual intracellular recordings in cortical slices. In an experiment designed to test the importance of relative timing of the presynaptic release of neurotransmitter and the postsynaptic activity to LTP, Markram et al. [85] paired stimulation of cell A either 10 ms before or after spike initiation in cell B. They found reliable LTP when the presynaptic stimulus preceded the postsynaptic spike, but, remarkably, there was LTD when the presynaptic stimulus immediately followed the postsynaptic spike. Similar results have been found for hippocampal neurons grown in culture [13,36], between retinal axons and neurons in the optic tectum of frogs [135], and in the electrical line organ of weakly electric fish [10] — this is different from the others in that it is of opposite polarity (presynaptic release before the postsynaptic spike causes LTD). Thus, this temporally asymmetry in synaptic plasticity is widespread in cerebellar as well as cortical

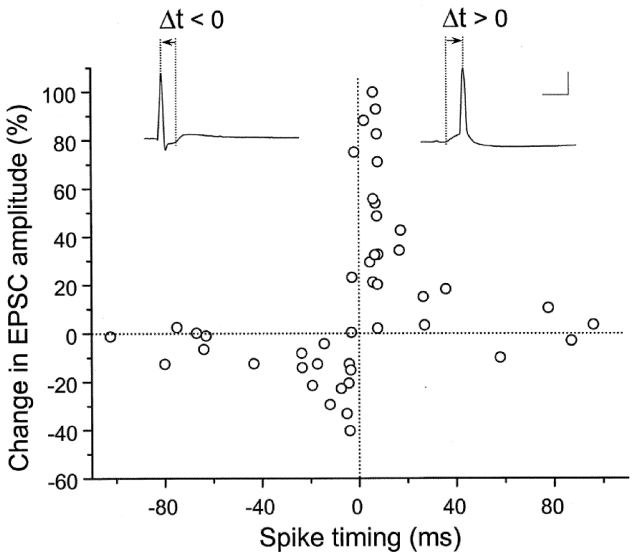

Fig. 3. Synaptic modification in cultured hippocampal neurons. The relative timing of the paired postsynaptic spike and excitatory synaptic inputs (inset) determines whether the subsequent change in the excitatory postsynaptic current (EPSC) increases (when the spike follows the synaptic input) or decreases (when the spike precedes the synaptic input). This is a temporally asymmetric form of Hebbian synaptic plasticity. Figure reproduced from Ref. [13]. Calibration: 50 mV, 10 ms.

structures. In Fig. 3, where the time delay between the synaptic stimulus and the postsynaptic spike was varied over a wide range, the window for plasticity is around 20 ms and the transition between LTP and LTD occurs within a time difference of a few milliseconds.

This temporally asymmetric form of synaptic plasticity has many nice features. First, it solves the problem of balancing LTD and LTP in a particularly elegant way since chance coincidences should occur about equally with positive and negative relative time delays. Second, when sequences of inputs are repeated in a network of neurons with recurrent excitatory connections, this form of synaptic plasticity will learn the sequence and the pattern of activity in the network will tend to predict future input. This may occur in the visual cortex where simulations of cortical neurons can become directionally selective when exposed to moving visual stimuli [99]. Similar models have been proposed for neurons in other brain regions, although the temporal window for synaptic plasticity was taken to be 100 ms in the hippocampus [17], where there is evidence that the locations of place cells shift to earlier locations in rats running repetitively through a maze [91], and less than 1 ms in a model for learning auditory localization by the relative timing of spikes from two ears [55].

The rapid transition between LTP and LTD at the moment of temporal coincidence does not conform to the traditional view of a Hebbian synapse. Notice that in Hebb's formulation the synapse increases in strength when an axon of cell A is near enough to excite cell B and repeatedly or persistently takes part in firing it. For cell A to take part in firing cell B implies causality, not simple coincidence. Thus, the importance of temporal order is implicit in Hebb's formulation. If cell A produces an excitatory event just before cell B fires a spike then it is likely to have contributed. Hebb did not specify what should happen if cell A fires just after cell B, but weakening is consistent with causality since it is then unlikely for cell A to have caused cell B to fire. The temporally asymmetric learning rule may be more 'Hebbian' than the earlier coincidence version (see also Refs. [77,111]).

For the spike at the soma to influence synapses on distal dendrites, there must be a flow of information from the soma toward the dendrites, which violates the principle of dynamic polarization. This reverse flow of information could not occur without active currents in dendrites, which we now know support exactly the sort of backpropagating action potentials in pyramidal neurons required by the strict form of Hebb's postulate. Detailed simulations of calcium entry during the backpropagating spike and during activation of the NMDA receptor show a knife-edge switch from LTP to LTD might be implemented in the postsynaptic spine [52].

The temporally asymmetric Hebbian learning rule is equivalent to the temporal difference learning algorithm in reinforcement learning [99] and can be used to make predictions and implement classical conditioning [94]. There is evidence in primates that the transient output from dopamine neurons in the ventral tegmental area carry information about the reward predicted from a sensory stimulus [103] and in bees, an octopaminergic neuron has a similar role [61]. The temporal window for classical conditioning is several seconds, much longer than the window for LTP/LTD observed at cortical and hippocampal synapses. The temporal order of input stimuli is a useful source of information about causal dependence in many different learning contexts and over a range of time scales.

4.5. Thalamocortical assemblies

Local inhibitory interneurons, such as basket cells that can induce synchronized rebound spiking in many cortical pyramidal cells, may have an important function in regulating the timing of spikes within a column of neurons [100]. The relative order of spikes in a population of neurons could also be used to encode information about objects in the world [69]. In particular, the first neuron in a population to spike in response to a sensory stimulus will have an advantage since its synapses will be the first to activated and more likely to be strengthened compared to synapses from other neurons that spike later [1,126]. Such cell assemblies in primary visual cortex could account for our ability to distinguish Vernier offset of visual stimuli with arc second resolution, an order of magnitude smaller than the diameter of a photoreceptor [92]. The plasticity might also serve to stabilize cell assemblies [109].

We can now be more specific about what a cell assembly might be and how it might provide insight into the role of sleep oscillations in the consolidation of cortical memory traces. Consider first the recruitment of neurons in visual cortex in response to a flashed visual stimulus in the awake state. Stimulus specificity of single neurons is already present in the first few spikes of a response [121]. If the most selective neurons came to threshold first, they could recruit neurons through local connectivity within a column. Inhibitory neurons would also be recruited, which would limit the total size of the assembly that represents the stimulus in the column. At the same time, temporally asymmetric Hebbian plasticity would strengthen the sequence of neurons responding to the stimulus. Noise in the system would produce a different order of firing each presentation, which would result in reciprocal connection among the neurons most selective for the repeated stimulus. This defines a cortical assembly by construction.

Sensory experience may not produce a sufficiently strong tetanization of cortical synapses to produce LTP, particularly in a primary sensory areas where the threshold for plasticity is set high, but it may be sufficient to prime the synapses in the assembly that are later consolidated during slow-wave sleep. It would be dangerous to change the strengths of synapses in a feedforward system during the processing itself. It is safer to statistically sample the inputs over a long time interval and wait until the cortex is in no longer processing sensory information before irreversible changes are made to the network. This may be the reason why the relay of sensory information through the thalamus is reduced during sleep.

LTP through temporally asymmetric Hebbian plasticity depends on the relative timing of the presynaptic and postsynaptic spikes, the frequency of pairing, and the total number of paired spikes. Thalamocortical sleep oscillations provide conditions that allow the relative phase of neurons in an assembly to be consistently maintained over many pairing. This is a consequence of the spatio-temporal coherence observed during spindling and slow-wave sleep. This mechanism could be used to strengthen connections between neurons in an assembly if the neurons in an assembly could be identified. If too many neurons are activated then assemblies that share neurons will interfere with each other and lose their identity.

One way to select a neural assembly in the cortex during sleep is a bottom up approach that depends on identifying assemblies of neurons interconnected by recently primed synapses. This takes advantage of the hyperpolarized periods in slow wave complexes during which the frequency of minis can be used to selecting neurons that have the highest density of synapses that were recently primed by short-term potentiation [123]. A second way to select a neural assembly, a top down approach, is appropriate for the highest levels of cortical representation that receive inputs from the hippocampal formation. Here, inputs arising from sharp waves in the hippocampus select cortical assemblies through feedback connections. The synapses between these assemblies could then become primed through thalamocortical spindles [107]. The assemblies identified from both bottom up and the top down sources can be further strengthened through the molecular mechanisms outlined earlier.

5. Conclusions

Spindle oscillations appear in the EEG during the early stages of slow-wave sleep. We have shown that during these oscillations, cortical pyramidal neurons are bombarded by unusually powerful excitatory inputs in the dendrites in parallel with strong inhibitory inputs around the soma [30]. We suggest here that this pattern of excitation–inhibition provokes a massive Ca^{2+} entry that specifically activates Ca^{2+}-dependent molecular gates in the spindling cells. Spindle oscillations could therefore open the door to subsequent long-term changes in cortical networks.

As sleep deepens, slow waves progressively dominate the EEG. These slow-wave complexes alternate with brief episodes of fast oscillations having similar properties as the sustained fast oscillations that occur during wakefulness [42]. We propose that these brief periods represent a recall of information acquired previously during wakefulness, which are subsequently stored by highly synchronized events that appear as slow waves in the EEG. Slow-wave sleep would thus begin by spindle oscillations that open molecular gates to plasticity, then proceed by iteratively ‘recalling’ and ‘storing’ information primed in neural assemblies.

Although speculative, this scenario is consistent with what is currently known about the biophysical mechanisms of sleep oscillations (see details in Ref. [39]). It is also consistent with the growing evidence that sleep serves to consolidate memories, as well as with models that require a ‘sleep’ phase for the long-term learning of generative representations [66]. The key insight is that slow-wave sleep is a specific state in which information is consolidated by activating Ca^{2+}-mediated intracellular cascades in pyramidal neurons. Implementing such a massive Ca^{2+} entry and network reorganization must necessarily take time and be performed during a state in which normal processing such as sensory processing — should not occur; this may ultimately be the primary reason why we need to sleep.

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References

[1] L.F. Abbott, S. Song, Temporally asymmetric Hebbian learning, spike timing and neuronal response variability, Adv. Neural Informat. Processing Syst. 11 (1999) 69–75.

[2] T. Abel, P.V. Nguyen, M. Barad, T.A.S. Deuel, E.R. Kandel, R. Bourtchouladze, Genetic demonstration of a role for PKA in the late phase of LTP and in hippocampus-based long-term memory, Cell 88 (1997) 615–626.

[3] P. Achermann, A. Borbely, Low-frequency (<1 Hz) oscillations in the human sleep EEG, Neuroscience 81 (1997) 213–222.

[4] D.H. Ackley, G.E. Hinton, T.J. Sejnowski, A learning algorithm for Boltzmann Machines, Cognit. Sci. 9 (1985) 147–169.

[5] P. Alvarez, L.R. Squire, Memory consolidation and the medial temporal lobe: a simple network model, Proc. Natl. Acad. Sci. USA 91 (1994) 7041–7045.

[6] P. Alvarez, S. Zola-Morgan, L.R. Squire, Damage limited to the hippocampal region produces long-lasting memory impairment in monkeys, J. Neurosci. 15 (1995) 3796–3807.

[7] C.J. Ball, P. Gloor, N. Schaul, The cortical electromicrophysiology of pathological delta waves in the electroencephalogram of cats, Electroencephalogr. Clin. Neurophysiol. 43 (1977) 346–361.

[8] M. Bazhenov, I. Timofeev, M. Steriade, T.J. Sejnowski, Computational models of thalamocortical augmenting responses, J. Neurosci. 18 (1998) 6444–6465.

[9] M.F. Bear, W.C. Abraham, Long-term depression in hippocampus, Annu. Rev. Neurosci. 19 (1996) 437–462.

[10] C.C. Bell, V.Z. Han, Y. Sugawara, K. Grant, Synaptic plasticity in a cerebellum-like structure depends on temporal order, Nature 387 (1997) 278–281.

[11] M.J. Berridge, Neuronal calcium signaling, Neuron 21 (1998) 13–26.

[12] U.S. Bhalla, R. Iyengar, Emergent properties of networks of biological signaling pathways, Science 283 (1999) 381–387.

[13] G. Bi, M. Poo, Activity-induced synaptic modifications in hippocampal culture: dependence on spike timing, synaptic strength and cell type, J. Neurosci. 18 (1998) 10464–10472.

[14] T.V. Bliss, G.L. Collingridge, A synaptic model of memory: long-term potentiation in the hippocampus, Nature 361 (1993) 31–39.

[15] R.D. Blitzer, T. Wong, R. Nouranifar, R. Iyengar, E.M. Landau, Postsynaptic cAMP pathway gates early LTP in hippocampal CA1 region, Neuron 15 (1995) 1403–1414.

[16] R.D. Blitzer, J.H. Connor, G.P. Brown, T. Wong, S. Shenolikar, R. Iyengar, E.M. Landau, Gating of CaMKII by cAMP-regulated protein phosphatase activity during LTP, Science 280 (1998) 1940–1942.

[17] K.I. Blum, L.F. Abbott, A model of spatial map formation in the hippocampus of the rat, Neural Comput. 8 (1996) 85–93.

[18] B. Bontempi, C. Laurent-Demir, C. Destrade, R. Jaffard, Time-dependent reorganization of brain circuitry underlying long-term memory storage, Nature 400 (1999) 671–675.

[19] L.J. Borg-Graham, C. Monier, Y. Fregnac, Visual input evokes transient and strong shunting inhibition in visual cortical neurons, Nature 393 (1998) 369–373.

[20] P. Bush, T.J. Sejnowski, Inhibition synchronizes sparsely connected cortical neurons within and between columns in realistic network models, J. Comput. Neurosci. 3 (1996) 91–110.

[21] G. Buzsaki, Hippocampal sharp waves: their origin and significance, Brain Res. 398 (1986) 242–252.

[22] G. Buzsaki, Two-stage model of memory trace formation, a role for 'noisy' brain states, Neuroscience 31 (1989) 551–570.

[23] G. Buzsaki, The hippocampo–neocortical dialogue, Cerebral Cortex 6 (1996) 81–92.

[24] G. Buzsaki, Memory consolidation during sleep: a neurophysiological perspective, J. Sleep Res. 7 (Suppl. 1) (1998) 17–23.

[25] G. Buzsaki, R.G. Bickford, G. Ponomareff, L.J. Thal, R. Mandel, F.H. Gage, Nucleus basalis and thalamic control of neocortical activity in the freely moving rat, J. Neurosci. 8 (1988) 4007–4026.

[26] D.W. Carr, R.E. Stofko-Hahn, I.D. Fraser, R.D. Cone, J.D. Scott, Localization of the cAMP-dependent protein kinase to the postsynaptic densities by A-kinase anchoring proteins. Characterization of AKAP 79, J. Biol. Chem. 267 (1992) 16816–16823.

[27] J.J. Chrobak, G. Buzsaki, Selective activation of deep layer (V–VI) retrohippocampal cortical neurons during hippocampal sharp waves in the behaving rat, J. Neurosci. 14 (1994) 6160–6170.

[28] D. Contreras, M. Steriade, Cellular bases of EEG slow rhythms: a study of dynamic corticothalamic relationships, J. Neurosci. 15 (1995) 604–622.

[29] D. Contreras, M. Steriade, Synchronization of low-frequency rhythms in corticothalamic networks, Neuroscience 76 (1997) 11–24.

[30] D. Contreras, A. Destexhe, M. Steriade, Intracellular and computational characterization of the intracortical inhibitory control of synchronized thalamic inputs in vivo, J. Neuro-physiol. 78 (1997) 335–350.

[31] D. Contreras, A. Destexhe, T.J. Sejnowski, M. Steriade, Control of spatiotemporal coherence of a thalamic oscillation by corticothalamic feedback, Science 274 (1996) 771–774.

[32] D. Contreras, A. Destexhe, T.J. Sejnowski, M. Steriade, Spatiotemporal patterns of spindle oscillations in cortex and thalamus, J. Neurosci. 17 (1997) 1179–1196.

[33] F. Crick, G. Mitchison, The function of dream sleep, Nature 304 (1983) 111–114.

[34] S.J. Cruikshank, N.M. Weinberger, Receptive-field plasticity in the adult auditory cortex induced by Hebbian covariance, J. Neurosci. 16 (1996) 861–875.

[35] A.R. Damasio, D. Tranel, Nouns and verbs are retrieved with differently distributed neural systems, Proc. Natl. Acad. Sci. USA 90 (1993) 4957–4960.

[36] D. Debanne, B.H. Gahwiler, S.M. Thompson, Long-term synaptic plasticity between pairs of individual CA3 pyramidal cells in rat hippocampal slice cultures, J. Physiol. 507 (1998) 237–247.

[37] J. DeFelipe, I. Fariñas, The pyramidal neuron of the cerebral cortex: morphological and chemical characteristics of the synaptic inputs, Prog. Neurobiol. 39 (1992) 563–607.

[38] P. De Koninck, H. Schulman, Sensitivity of CaM kinase II to the frequency of Ca^{2+} oscillations, Science 279 (1998) 227–230.

[39] A. Destexhe, T.J. Sejnowski, The Thalamocortical Assembly, Oxford University Press, Oxford, UK, 2001, in press.

[40] A. Destexhe, A. Babloyantz, T.J. Sejnowski, Ionic mechanisms for intrinsic slow oscillations in thalamic relay neurons, Biophys. J. 65 (1993) 1538–1552.

[41] A. Destexhe, D. Contreras, M. Steriade, Mechanisms underlying the synchronizing action of corticothalamic feedback through inhibition of thalamic relay cells, J. Neurophysiol. 79 (1998) 999–1016.

[42] A. Destexhe, D. Contreras, M. Steriade, Spatiotemporal analysis of local field potentials and unit discharges in cat cerebral cortex during natural wake and sleep states, J. Neurosci. 19 (1999) 4595–4608.

[43] A. Destexhe, D.A. McCormick, T.J. Sejnowski, A model for 8–10 Hz spindling in interconnected thalamic relay and reticularis neurons, Biophys. J. 65 (1993) 2474–2478.

[44] A. Destexhe, T. Bal, D.A. McCormick, T.J. Sejnowski, Ionic mechanisms underlying synchronized oscillations and propagating waves in a model of ferret thalamic slices, J. Neurophysiol. 76 (1996) 2049–2070.

[45] A. Destexhe, D. Contreras, T.J. Sejnowski, M. Steriade, A model of spindle rhythmicity in the isolated thalamic reticular nucleus, J. Neurophysiol. 72 (1994) 803–818.

[46] A. Destexhe, D. Contreras, T.J. Sejnowski, M. Steriade, Modeling the control of reticular thalamic oscillations by neuromodulators, NeuroReport 5 (1994) 2217–2220.

[47] A. Destexhe, D. Contreras, M. Steriade, T.J. Sejnowski, J.R.

Huguenard, In vivo, in vitro and computational analysis of dendritic calcium currents in thalamic reticular neurons, J. Neurosci. 16 (1996) 169–185.
[48] A. Dosemeci, T.S. Reese, Inhibition of endogenous phosphatase in a postsynaptic density fraction allows extensive phosphorylation of the major postsynaptic density protein, J. Neurochem. 61 (1993) 550–555.
[49] R. Eckhorn, R. Bauer, W. Jordan, M. Brosch, W. Kruse, M. Munk, H.J. Reitboek, Coherent oscillations: a mechanism of feature linking in the visual cortex? Multiple electrode and correlation analyses in the cat, Biol. Cybernetics 60 (1988) 121–130.
[50] J.M. Edeline, Y. Manunta, E. Hennevin, Auditory thalamus neurons during sleep: changes in frequency selectivity, threshold, and receptive field size, J. Neurophysiol. 84 (2000) 934–952.
[51] E.V. Evarts, Temporal patterns of discharge of pyramidal tract neurons during sleep and waking in the monkey, J. Neurophysiol. 27 (1964) 152–171.
[52] K.M. Franks, T.M. Bartol, M. Poo, T.J. Sejnowski, High spatial and temporal resolution estimates of calcium dynamics in dendritic spines using MCELL simulations, Soc. Neurosci. Abstracts 26 (2000) 1122.
[53] U. Frey, Y.Y. Huang, E.R. Kandel, Effects of cAMP simulate a late phase of LTP in hippocampal CA1 neurons, Science 260 (1993) 1661–1664.
[54] J.D. Frost, P.R. Kellaway, A. Gol, Single-unit discharges in isolated cerebral cortex, Exp. Neurol. 14 (1966) 305–316.
[55] W. Gerstner, R. Kempter, J.L. van Hemmen, H. Wagner, A neural learning rule for sub-millisecond temporal coding, Nature 383 (1996) 76–78.
[56] A. Ghosh, M.E. Greenberg, Calcium signaling in neurons: molecular mechanisms and cellular consequences, Science 268 (1995) 239–247.
[57] D. Golomb, X.J. Wang, J. Rinzel, Propagation of spindle waves in a thalamic slice model, J. Neurophysiol. 75 (1996) 750–769.
[58] C. Gray, Synchronous oscillations in neuronal systems: Mechanisms and functions, J. Comput. Neurosci. 1 (1994) 11–38.
[59] C.M. Gray, W. Singer, Stimulus-specific neuronal oscillations in orientation columns of cat visual cortex, Proc. Natl. Acad. Sci. USA 86 (1989) 1698–1702.
[60] X. Gu, N.C. Spitzer, Distinct aspects of neuronal differentiation encoded by frequency of spontaneous Ca^{2+} transients, Nature 375 (1995) 784–787.
[61] M. Hammer, R. Menzel, Learning and memory in the honeybee, J. Neurosci. 15 (1995) 1617–1630.
[62] D.O. Hebb, Organization of Behavior: A Neuropsychological Theory, Wiley, New York, 1949.
[63] S. Herculano-Houzel, M.H. Munk, S. Neuenschwander, W. Singer, Precisely synchronized oscillatory firing patterns require electroencephalographic activation, J. Neurosci. 19 (1999) 3992–4010.
[64] M. Herkenham, Laminar organization of thalamic projections to the rat neocortex, Science 207 (1980) 532–535.
[65] G.E. Hinton, Z. Ghahramani, Generative models for discovering sparse distributed representations, Philos. Trans. R. Soc. Lond. Ser. B 352 (1997) 1177–1190.
[66] G.E. Hinton, P. Dayan, B.J. Frey, R.M. Neal, The 'wake–sleep' algorithm for unsupervised neural networks, Science 268 (1995) 1158–1161.
[67] N. Hô, A. Destexhe, Synaptic background activity enhances the responsiveness of neocortical pyramidal neurons, J. Neurophysiol. 84 (2000) 1488–1496.
[68] J.A. Hobson, The Dreaming Brain, Basic Books, New York, 1988.
[69] J.J. Hopfield, Pattern recognition computation using action potential timing for stimulus representation, Nature 376 (1995) 33–36.
[70] J.J. Hopfield, D.I. Feinstein, R.G. Palmer, 'Unlearning' has a stabilizing effect in collective memories, Nature 304 (1983) 158–159.
[71] P.T. Huerta, J.E. Lisman, Synaptic plasticity during the cholinergic theta-frequency oscillation in vitro, Hippocampus 6 (1996) 58–61.
[72] E.G. Jones, The Thalamus, Plenum Press, New York, 1985.
[73] N. Kapur, D.J. Brooks, Temporally-specific retrograde amnesia in two cases of discrete bilateral hippocampal pathology, Hippocampus 9 (1999) 247–254.
[74] S.R. Kelso, A.H. Ganong, T.H. Brown, Hebbian synapses in hippocampus, Proc. Natl. Acad. Sci. USA 83 (1986) 5326–5330.
[75] M.B. Kennedy, M.K. Bennett, N.E. Erondu, Biochemical and immunochemical evidence that the 'major postsynaptic density protein' is a subunit of a calmodulin-dependent protein kinase, Proc. Natl. Acad. Sci. USA 80 (1983) 7357–7361.
[76] U. Kim, T. Bal, D.A. McCormick, Spindle waves are propagating synchronized oscillations in the ferret LGNd in vitro, J. Neurophysiol. 74 (1995) 1301–1323.
[77] W.B. Levy, O. Stewart, Temporal contiguity requirements for long-term associative potentiation/depression in the hippocampus, Neuroscience 8 (1983) 791–797.
[78] M.S. Lewicki, T.J. Sejnowski, Bayesian unsupervised learning of higher order structure, Adv. Neural Informat. Processing Syst. 9 (1997) 529–535.
[79] W. Li, J. Llopis, M. Whitney, G. Zlokarnik, R.Y. Tsien, Cell-permanent caged InsP3 ester shows that Ca^{2+} spike frequency can optimize gene expression, Nature 392 (1998) 936–941.
[80] R.R. Llinas, D. Pare, Of dreaming and wakefulness, Neuroscience 44 (1991) 521–535.
[81] A. Luthi, D.A. McCormick, Periodicity of thalamic synchronized oscillations: the role of Ca^{2+}-mediated upregulation of Ih, Neuron 20 (1998) 553–563.
[82] W.W. Lytton, T.J. Sejnowski, Simulations of cortical pyramidal neurons synchronized by inhibitory interneurons, J. Neurophysiol. 66 (1991) 1059–1079.
[83] W.W. Lytton, T.J. Sejnowski, Computer model of ethosuximide's effect on a thalamic cell, Ann. Neurol. 32 (1992) 131–139.
[84] W.W. Lytton, A. Destexhe, T.J. Sejnowski, Control of slow oscillations in the thalamo-cortical neuron: a computer model, Neuroscience 70 (1996) 673–684.
[85] H. Markram, J. Lubke, M. Frotscher, B. Sakmann, Regulation of synaptic efficacy by coincidence of postsynaptic APs and EPSPs, Science 275 (1997) 213–215.
[86] D. Marr, Simple memory: A theory for the archicortex, Philos. Trans. R. Soc. (Lond.) 262 (1971) 23–81.
[87] J.L. McClelland, B.L. McNaughton, R.C. O'Reilly, Why there are complementary learning systems in the hippocampus and neocortex: insights from the successes and failures of connectionist models of learning and memory, Psychol. Rev. 102 (1995) 419–457.
[88] D.A. McCormick, Neurotransmitter actions in the thalamus and cerebral cortex and their role in neuromodulation of thalamocortical activity, Prog. Neurobiol. 39 (1992) 337–388.
[89] D.A. McCormick, J.R. Huguenard, A model of the electrophysiological properties of thalamocortical relay neurons, J. Neurophysiol. 68 (1992) 1384–1400.
[90] M. McKeown, C. Humphries, P. Acherman, A. Borbely, T.J. Sejnowski, Low frequency interactions in the human sleep EEG, Sleep Res. 7 (Suppl. 1) (1998) 48–56.
[91] M.R. Mehta, C.A. Barnes, B.L. McNaughton, Experience-dependent, asymmetric expansion of hippocampal place fields, Proc. Natl. Acad. Sci. USA 94 (1997) 8918–8921.
[92] D.A. Miller, S.W. Zucker, Computing with self-excitatory cliques: A model and an application to hyperacuity-scale computation in visual cortex, Neural Comput. 11 (1999) 21–66.
[93] N. Mons, A. Harry, P. Dubourg, R.T. Premont, R. Iyengar, D.M. Cooper, Immunohisto-chemical localization of adenylyl cyclase in rat brain indicates a highly selective concentration at synapses, Proc. Natl. Acad. Sci. USA 92 (1995) 8473–8477.
[94] P.R. Montague, T.J. Sejnowski, The predictive brain: temporal coincidence and temporal order in synaptic learning mechanisms, Learning Memory 1 (1994) 1–33.
[95] P.R. Montague, P. Dayan, T.J. Sejnowski, A framework for

mesencephalic dopamine systems based on predictive Hebbian learning, J. Neurosci. 16 (1996) 1936–1947.
[96] J. O'Keefe, L. Nadel, The Hippocampus as a Cognitive Map, Clarendon Press, Oxford, UK, 1978.
[97] D. Pare, J. Dong, H. Gaudreau, Amygdalo-entorhinal relations and their reflection in the hippocampal formation: generation of sharp sleep potentials, J. Neurosci. 15 (1995) 2482–2503.
[98] Y.L. Qin, B.L. McNaughton, W.E. Skaggs, C.A. Barnes, Memory reprocessing in cortico–cortical and hippocampocortical neuronal ensembles, Philos. Trans. R. Soc. Lond. Ser. B 352 (1997) 1525–1533.
[99] R.P.N. Rao, T.J. Sejnowski, Predictive sequence learning in recurrent neocortical circuits, Adv. Neural Informat. Processing Syst. 12 (2000) 164–170.
[100] R. Ritz, T.J. Sejnowski, Synchronous oscillatory activity in sensory systems: New vistas on mechanisms, Curr. Opin. Neurobiol. 7 (1997) 536–546.
[101] E. Salinas, T.J. Sejnowski, Impact of correlated synaptic input on output firing rate and variability in simple neuronal models, J. Neurosci. 20 (2000) 6193–6209.
[102] M.V. Sanchez Vives, D.A. McCormick, Cellular and network mechanisms of rhythmic recurrent activity in neocortex, Nat. Neurosci. 3 (2000) 1027–1034.
[103] W. Schultz, P. Dayan, P.R. Montague, A neural substrate of prediction and reward, Science 275 (1997) 1593–1599.
[104] T.J. Sejnowski, Storing covariance with nonlinearly interacting neurons, J. Math. Biol. 4 (1977) 203–211.
[105] T.J. Sejnowski, Sleep and memory, Curr. Biol. 5 (1995) 832–834.
[106] T.J. Sejnowski, The computational neuroethology of sleep, in: N. Elsner, R. Wehner (Eds.), New Neuroethology on the Move, Vol. 1, Georg Theime Verlag, Stuttgart, Germany, 1998, pp. 127–144.
[107] A.G. Siapas, M.A. Wilson, Coordinated interactions between hippocampal ripples and cortical spindles during slow-wave sleep, Neuron 21 (1998) 1123–1128.
[108] T.R. Soderling, Calcium/calmodulin-dependent protein kinase II: role in learning and memory, Mol. Cell. Biochem. 127–128 (1993) 93–101.
[109] S. Song, K.D. Miller, L.F. Abbott, Competitive Hebbian learning through spike-timing-dependent synaptic plasticity, Nat. Neurosci. 3 (2000) 919–926.
[110] L.R. Squire, S. Zola-Morgan, The medial temporal lobe memory system, Science 253 (1991) 1380–1386.
[111] G. Stent, A physiological mechanism for Hebb's postulate of learning, Proc. Natl. Acad. Sci. USA 70 (1973) 997–1001.
[112] M. Steriade, Cortical long-axoned cells and putative interneurons during the sleep–waking cycle, Behav. Brain Sci. 3 (1978) 465–514.
[113] M. Steriade, F. Amzica, Intracortical and corticothalamic coherency of fast spontaneous oscillations, Proc. Natl. Acad. Sci. USA 93 (1996) 2533–2538.
[114] M. Steriade, R.W. McCarley, Brainstem Control of Wakefulness and Sleep, Plenum Press, New York, 1990.
[115] M. Steriade, F. Amzica, D. Contreras, Synchronization of fast (30–40 Hz) spontaneous cortical rhythms during brain arousal, J. Neurosci. 16 (1996) 392–417.
[116] M. Steriade, E.G. Jones, R.R. Llinas, Thalamic Oscillations and Signalling, Wiley, New York, 1990.
[117] M. Steriade, D.A. McCormick, T.J. Sejnowski, Thalamocortical oscillations in the sleeping and aroused brain, Science 262 (1993) 679–685.
[118] M. Steriade, L. Domich, G. Oakson, M. Deschênes, The deafferented reticular thalamic nucleus generates spindle rhythmicity, J. Neurophysiol. 57 (1987) 260–273.
[119] R. Stickgold, D. Whidbee, B. Schirmer, V. Patel, J.A. Hobson, Visual discrimination task improvement: A multi-step process occurring during sleep, J. Cognit. Neurosci. 12 (2000) 246–254.
[120] G.R. Sutherland, B. McNaughton, Memory trace reactivation in hippocampal and neo-cortical neuronal ensembles, Curr. Opin. Neurobiol. 10 (2000) 180–186.
[121] S.J. Thorpe, J. Gautrais, Rapid visual processing using spike asynchrony, Adv. Neural Informat. Processing Syst. 9 (1997) 901–907.
[122] P.H.E. Tiesinga, J.-M. Fellous, J.G. Jose, T.J. Sejnowski, Optical information transfer in synchronized neocortical neurons, Neurocomputing, in press.
[123] I. Timofeev, F. Grenier, M. Bazhenov, T.J. Sejnowski, M. Steriade, Origin of slow cortical oscillations in deafferented cortical slabs. Cerebral Cortex 10 (2000) in press.
[124] R.D. Traub, M.A. Whittington, I.M. Stanford, J.G. Jefferys, A mechanism for generation of long-range synchronous fast oscillations in the cortex, Nature 383 (1996) 621–624.
[125] M.V. Tsodyks, W.E. Skaggs, T.J. Sejnowski, B.L. McNaughton, Paradoxical effects of external modulation of inhibitory interneurons, J. Neurosci. 17 (1997) 4382–4388.
[126] R. Van Rullen, J. Gautrais, A. Delorme, S. Thorpe, Face processing using one spike per neurone, Biosystems 48 (1998) 229–239.
[127] M. von Krosigk, T. Bal, D.A. McCormick, Cellular mechanisms of a synchronized oscillation in the thalamus, Science 261 (1993) 361–364.
[128] X.J. Wang, J. Rinzel, Spindle rhythmicity in the reticularis thalami nucleus — synchronization among inhibitory neurons, Neuroscience 53 (1993) 899–904.
[129] G.Y. Wu, H.T. Cline, Stabilization of dendritic arbor structure in vivo by CaMKII, Science 279 (1998) 222–226.
[130] H. Wigstrom, B. Gustafsson, Y.Y. Huang, W.C. Abraham, Hippocampal long-term potentiation is induced by pairing single afferent volleys with intracellularly injected depolarizing current pulses, Acta Physiol. Scand. 126 (1986) 317–319.
[131] M.A. Wilson, B.L. McNaughton, Reactivation of hippocampal ensemble memories during sleep, Science 265 (1994) 676–679.
[132] F. Worgotter, K. Suder, Y. Zhao, N. Kerscher, U.T. Eysel, K. Funke, State-dependent receptive-field restructuring in the visual cortex, Nature 396 (1998) 165–168.
[133] A. Ylinen, A. Bragin, Z. Nadasdy, G. Jando, I. Szabo, A. Sik, G. Buzsaki, Sharp wave-associated high-frequency oscillation (200 Hz) in the intact hippocampus: network and intracellular mechanisms, J. Neurosci. 15 (1995) 30–46.
[134] R. Yuste, D.W. Tank, Dendritic integration in mammalian neurons, a century after Cajal, Neuron 16 (1996) 701–716.
[135] L.I. Zhang, H.W. Tao, C.E. Holt, W.A. Harris, M. Poo, A critical window for cooperation and competition among developing retinotectal synapses, Nature 395 (1998) 37–44.
[136] S.M. Zola-Morgan, L.R. Squire, The primate hippocampal formation: evidence for a time-limited role in memory storage, Science 250 (1990) 288–290.