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Mechanisms of spontaneous active states in the neocortex

Intrinsic and synaptic mechanisms of cortical active states generation during slow wave sleep

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Abstract

Without any sensory input cortical networks may display spontaneous transitions between silent (hyperpolarized) and active (depolarized) states. These transitions may be periodic as observed during slow-wave sleep or irregular as spontaneous burst generation found in the isolated neocortical slabs. In this paper we will review intrinsic and synaptic mechanisms mediating properties of spontaneous active states. We will present different hypotheses regarding initiation and termination of active network states and we will discuss the possible role of transitions between silent and active network states in learning and memory.

1. Slow wave sleep oscillations and active network states in thalamocortical system

A signature of the slow-wave sleep in the electroencephalogram (EEG) are large-amplitude fluctuations of field potential [1], which reflect alternating periods of activity and silence in the thalamocortical networks [2-7]. Similar patterns were recorded in neostriatal neurons by Wilson and Kawaguchi [8] who introduced now widely used terms of "Up state" for the depolarizing phases of slow oscillation and "Down state" for the hyperpolarizing phases of slow oscillation. Similar to neocortical neurons [4, 6] Up and Down states in neostriatal neurons occurred only during slow wave sleep (SWS) [9]. Cortically generated slow oscillation was also found to entrain the thalamus [5, 10, 11]. Similar to neocortical and neostriatal neurons, both the thalamic reticular and thalamocortical neurons are hyperpolarized during depth-positive EEG waves due to disfacilitation, i.e. an absence of spontaneous synaptic activities [4, 12-14]. During depth-negative EEG waves, cortical, neostriatal and inhibitory thalamic reticular neurons are depolarized and fire spikes, while thalamocortical neurons are primarily hyperpolarized, reveal rhythmic IPSPs and occasionally fire rebound spike-bursts [5, 10]. Thus, in the dorsal thalamus, the intracellular activities occurring during depth-negative EEG waves cannot be characterized as either depolarizing or Up state. For the purposes of this article, we used the terms 'active states' for processes occurring during EEG depth-negative waves and 'silent states' for processes occurring during EEG depth-positive waves. We believe that such terminology better represents the functional state of the thalamocortical network during the slow oscillations.

Survival of slow oscillations after extensive thalamic lesions [3] and the absence of slow oscillations in the thalamus of decorticated cats [15] point to an intracortical origin for this rhythm. Recent studies show that following activation of the metabotropic glutamate receptor (mGluR), mGluR1a, cortical inputs can recruit cellular mechanisms that enable the generation of an intrinsic slow oscillation in thalamocortical neurons *in vitro* with frequencies similar to those observed *in vivo* [16, 17]. Intracellular studies on anesthetized and non-anesthetized cats have shown that the hyperpolarizing phase of the slow oscillation is associated with disfacilitation, a temporal absence of synaptic activity in all cortical, thalamocortical and reticular thalamic neurons [6, 14, 15]. Even a moderate spontaneous hyperpolarization of thalamocortical neurons during depth-positive EEG waves is sufficient to displace them from firing threshold, thereby affecting transmission of information toward the cerebral cortex and thus creating disfacilitation [15, 18]. Responses to peripheral sensory stimuli still may reach cerebral cortex during sleep or anesthesia [19-27], but the precision of cortical network to respond to peripheral volley during disfacilitation periods is lost [24, 26]. The spike timing is critical in cortical information processing [28] and a minimal time interval of stable thalamocortical activity is required to achieve conscious perceptions [29]. Thus, the conscious perception is impaired during sleep and anesthesia, likely, because the lost of precision in the sensory information transfer from periphery to the cerebral cortex and the presence of silent states.

During sleep in humans, each cycle of the slow oscillation is a traveling wave originating at a definite site and traveling over the scalp at an estimated speed of 1.2-7.0 m/sec [30]. In anesthetized cats the active states originated from the border of area 5-7 and propagated in anterior and posterior directions [31]. In vertical dimension, the active states start in lower cortical layers and progressively involve superficial layers [32] (see also chapter by Chauvette et al). This finding is congruent with previous in vitro study in which active states were found to start in lower or infragranular layers and to propagate *in vitro* [33]. The conditions under which active states can propagate *in vivo* and specific mechanisms of their synchronization still remain to be investigated.

2. Mechanisms underlying the generation of slow oscillation in neocortex

At least two distinct mechanisms for the origin of slow cortical oscillations were proposed based on what causes the transition to the active (Up) state of the slow-sleep oscillation: (a) spontaneous mediator release in a large population of neurons leading to occasional summation and firing [34]

and (b) spontaneous intrinsic activity in layer 5 intrinsically bursting neurons [33]. Below we will discuss these two mechanisms as well as some other processes contributing to the periodic transitions between silent and active states during slow sleep oscillations.

2.1. Spontaneous mediator release and transitions to active cortical states

Spontaneous miniature synaptic activities (minis) [35] are caused by spike-independent release of transmitter vesicles and are regulated at the level of single synapses [36, 37]. Such spike-independent synaptic release occurs during the silent state of the cortical network, for example in slices [37, 38], in the neocortical slabs [34, 39], or during the hyperpolarizing components of slow sleep oscillation (I.Timofeev, unpublished). According to the "minis"-dependent hypothesis of active states initiation, occasionally, summation of spike-independent minis may depolarize cortical neurons to the level of activation of the persistent Na^+ current [40, 41]. These minis dependent depolarization may then activate intrinsically bursting neurons that results in depolarization and spiking of a population of postsynaptic neurons; activity spreads thus triggering onset of an active state [34, 42]. Effect of minis produced in distally located synapses of large cortical pyramidal cells can be enhanced by a variety of intrinsic currents in cell dendrites [43]. The effect of the initial EPSPs at the onset of an active state is enhanced by progressive strengthening of the synaptic efficacy during silent state of slow oscillations [44]. Shunting inhibition [45, 46] and activity dependent increase of failures of synaptic transmission [44] during active states significantly reduce the effectiveness of single axon EPSPs, thus preventing the network from overexcitation.

Since the number of neurons in slices is small, their interconnections are reduced and are also strongly affected by the thickness of the slice [47]; it is unlikely that minis-dependent spontaneous activity would lead to active periods in slices with typical bath concentrations of K^+, Ca^{2+} and Mg^+ (2 mM Ca^{2+}, 2 mM Mg^{2+} and 2.5 mM K^+). Only when the bath solution was changed to increase excitability (1.0 or 1.2 mM Ca^{2+}, 1 mM Mg^{2+} and 3.5 mM K^+), spontaneous rhythmic oscillations were described *in vitro* [33]. In isolated small (10 x 6 mm) cortical slabs relatively rare (3.2±0.3 periods per minute), non-periodic spontaneous active states were found (Fig. 1, see also [34]). The burst events found in slab were similar to the active states of SWS but frequency was low presumably because a relatively small amount of cells was interconnected. It was proposed that these events are initiated by minis-dependent depolarization (see Fig. 1, bottom) and that increasing the size of

the isolated cortical tissue should increase the number of sites where activity could arise [34, 42]. This would lead to an increased probability of occurrence of the active periods. The study suggested that cortical SWS oscillations could arise from the same mechanisms as spontaneous slab activity in the limit of a very large neuronal population. This is still an open question, however, why *in vivo*-alike oscillations are possible in very small (~2 mm) strips of cortex [33]. One likely possibility is that increased excitability in these slice preparations made possible relatively strong spontaneous activity triggering periodic transitions to the active states.

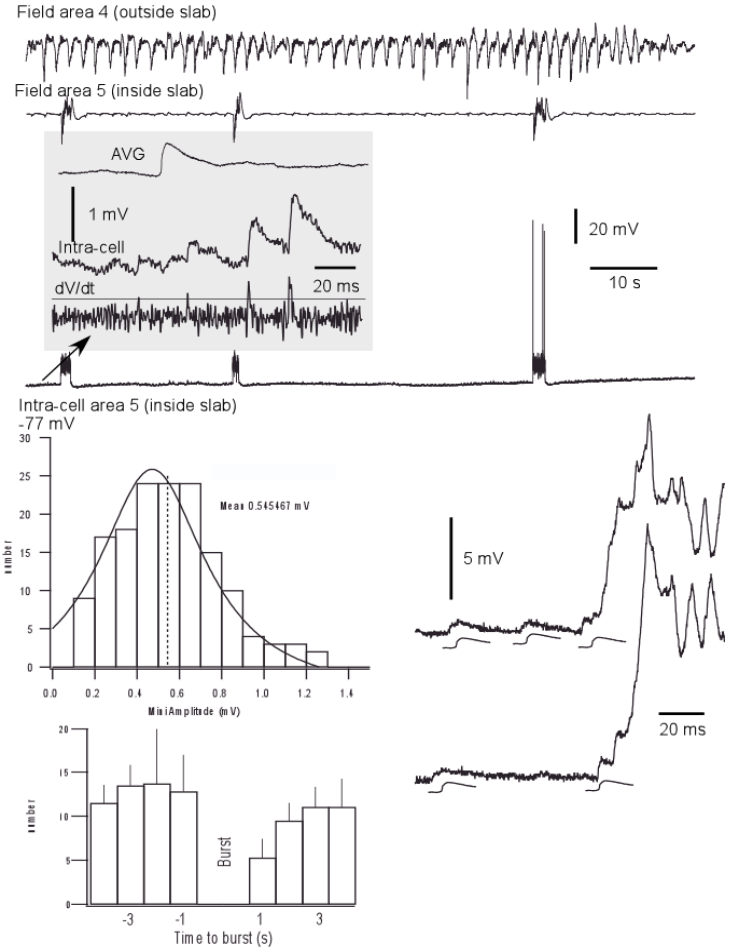

Figure 1. The background neuronal activity in a small slab consists of small

Figure 1. Legend continued

depolarizing potentials (SDPs) interrupted by bursts of high-amplitude depolarizing events. Upper panel, the three traces represent (from top to bottom) field potentials from area 4 (outside the slab), area 5 (in the slab) and intracellular recording of a neuron within the slab. Part indicated by an arrow at the extreme left of the intracellular trace is expanded above and shows the presence of SDPs. SDPs were identified from first derivative of intracellular trace (dV/dt). Average obtained from 100 SDPs, selected by the maximum of the first derivative of the voltage trace (>4.0 V/s). Below, histogram of amplitude distribution of slow amplitude depolarizing potentials (SDPs). Below, histogram of temporal distribution of SDPs before and after the high-amplitude bursts. The number of SDPs significantly decreased during 1 s after the high-amplitude bursts. Bottom right - superimposition of the onset of two bursts from the cellular trace in the top panel (frist and second bursts). The average SDP is shown close to individual SDPs (modified from Timofeev et al., 2001).

A Hodgkin-Huxley based network model was designed to study spontaneous active states in the isolated cortical slabs [34]. In this study the parameters of the pyramidal neurons were adjusted to mimic the spike bursting patterns as observed in recordings from the slabs. The synapses between the neurons were based on Markov models of synaptic conductance changes and were also matched to recordings from dual impalements. Poisson processes with time-dependent mean rate were used to model the arrival times for spontaneous miniature EPSPs at AMPA-mediated synapses between cortical pyramidal cells. In this model, starting from the last Na^+ spike during a preceding active period, the rate of minis at each synapse increased rapidly during first few seconds and then grew more slowly as observed experimentally [34].

Figure 2A shows one pyramidal (PY) neuron that was randomly selected from the network of 2 x N PY neurons and interneurons (INs), where N was varied from 50 to 2000. When the summation of the miniature EPSPs in one of the PY cells depolarized this cell sufficiently to activate the $I_{Na(p)}$ and to initiate a Na^+ action potential, the activity spread through the network and was maintained by lateral PY-PY excitation and $I_{Na(p)}$ (Fig. 2B). A similar mechanism for propagation has been previously described [48]; however, this network model only had excitatory neurons and only a single burst lasting around 50 ms was studied. A weak depression of the excitatory interconnections and activation of the Ca^{2+}-dependent K^+ current led to the termination of activity after a few hundred milliseconds. A similar effect could be achieved by slow inactivation of $I_{Na(p)}$ [49], which, however, was not taken into account in the model. Because any PY neuron could be an initiator of the spontaneous activity and because these events are independent, the total probability of initiation in the network increased with

N, the number of cells in the network (see below). As a consequence, there was a strong variability in the time intervals between patterns of activity in the small network of 2 x 50 PY-IN cells.

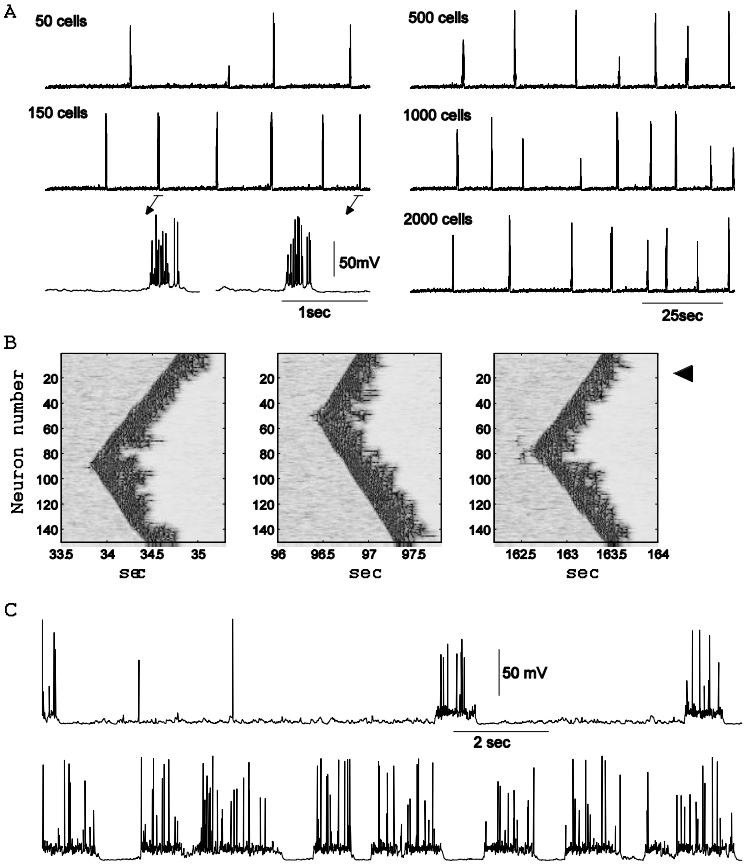

Figure 2. Patterns of spontaneous activity in cortical network model. (A) In a network with 50 PY-IN pairs, the probability of initiation was relatively low, so the time intervals between bursts varied between 10 sec and 30 sec. An increase of the total number of neurons (up to 2000 PY-IN pairs) raised the probability of initiation and increased and stabilized the frequency of the active periods. Expanded fragments (arrows) show that durations of the active periods are variable. The spike amplitudes varied because of the low sampling rate. **(B)** The activity was initiated at the different network foci and then propagated with a constant velocity of about 100 cell/sec. Black arrow indicates the PY cell shown in the upper panels. **(C)** Increase (from top to bottom) in the amplitude of miniature EPSPs transformed rare

Figure 2. Legend continued

depolarizing events to the quasi-periodic activity at the frequency about 0.5 Hz. The mean firing rate of spontaneous miniature EPSPs for the Hodgkin-Huxley model was approximated by either a logarithmic or sigmoid function:

$\mu_1(t) = \log((t+50)/50)/400$ or

$\mu_2(t) = (2/(1+e^{-t/5000}) - 1)/40$

where t=0 corresponds to the last successful burst event. (Modified from [34]).

In larger networks, the increased number of foci where the activity could be initiated resulted in an increase in the frequency of active periods and less variability in their occurrence (Fig. 2A). Note that the probability of spike initiation was smaller for the boundary PY cells, which received a reduced number of intact synapses, so that the active periods were usually initiated far from the network boundaries (see Fig. 2B). To test the effects of miniature EPSP size, their amplitude was increased by either 50% (top trace in Fig. 2C) or 100% (lower trace in Fig. 2C). These modifications significantly increased the frequency of spontaneous bursting and in the later case produced almost periodic oscillations at about 0.5 Hz. This activity is similar to the slow oscillations recorded *in vivo* during slow wave sleep [3].

2.2. Effect of the network size of the properties of cortical active states

In the network simulations based on Hodgkin-Huxley type neuron models, the parameters of spontaneous transmitter release were adjusted to permit spontaneous bursting in small (compared with *in vivo* preparations) models of the cortex [34]. Particularly, asymptotic value of the mean firing rate of minis was chosen much higher than that estimated from *in vivo* data. To predict, however, if the minis rate observed *in vivo* may be sufficient to explain properties of slow sleep oscillations, the mean T and standard deviation σ of interburst intervals should be estimated analytically for networks of different size using parameters of the miniature events found *in vivo*. This was done by fitting *in vivo* histogram similar to that shown in Fig. 1 (see also [34]). The main assumption used in these calculations was that n miniature EPSPs need to occur within a time window δt to depolarize the cell membrane sufficiently to activate persistent Na^+ current. Although this

assumption is a simplification, it permits the probability distribution function to be calculated analytically with reasonable accuracy.

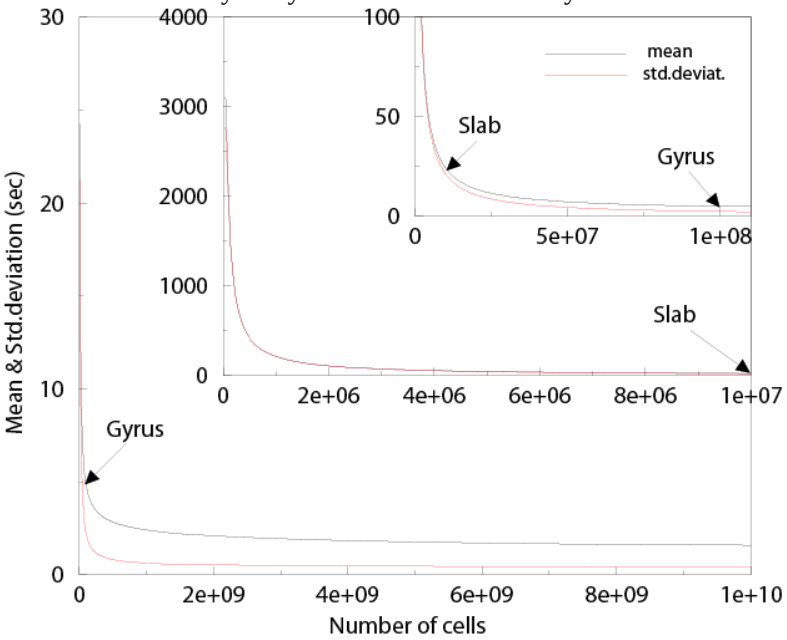

Figure 3. Properties of slow oscillation in the cortical populations of different size. Mean T and standard deviation σ of interburst intervals are plotted as a function of number of cortical neurons. Calculations are based on *in vivo* data: δt=22ms, n=9. Estimated mean of interburst intervals for slab (about 10^7 neurons) is 24 sec (standard deviation is 21 sec) and for gyrus (about 10^8 neurons) mean is 4.9 sec (standard deviation 2.3 sec.) (Modified from [34]).

The total number of cells was estimated to be 10^7 in the cortical slab and ~10^8 in the isolated gyrus. The number of cells in the isolated slab was close to the minimal number that the model predicted should be needed to generate activity. The mean interburst interval for the slab was 24 sec and CV = 0.87 (Fig. 3). Further reduction of the slab size led to a dramatic decrease of the average frequency of burst initiation and increase in the variability of the interburst intervals. As the number of neurons and synapses in the network increased, the frequency of active periods increased toward an asymptotic value. For an isolated gyrus the mean period of bursting was predicted to be 4.9 sec with CV = 0.47. For 10^9 neurons in a 100 cm^2 region of cortex, the predicted frequency of spontaneous bursting was ~0.5 Hz and the CV < 0.3

(see Fig. 3), in good agreement with *in vivo* recordings. The frequency was nearly independent of size for larger cortical regions because there is a minimum recovery time following a depolarizing event.

2.3. Slow-wave sleep oscillations in the thalamocortical network model

To study synchronization properties of slow-wave sleep oscillations a one-dimensional four-layer array of N PY, M=N/4 IN, L=N/2 reticular thalamic (RE) and L=N/2 thalamocortical (TC) cells was studied [42]. N was varied between 20 and 200. While thalamic RE and TC cells were not necessary to maintain SWS oscillations in the model, their presence changed spatio-temporal patterns of SWS activity.

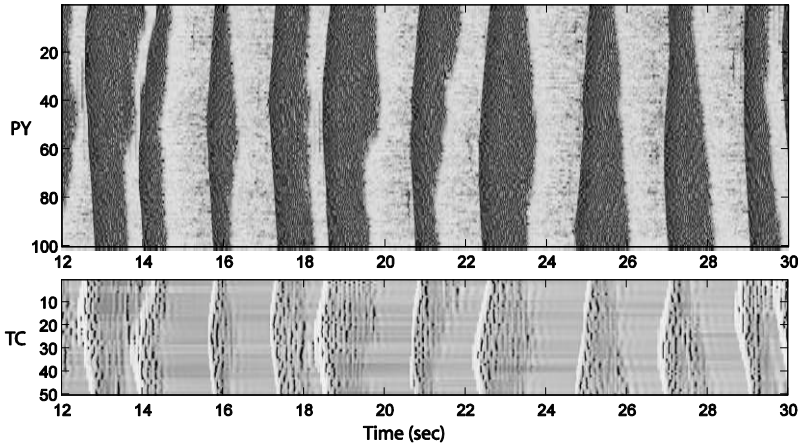

Figure 4. Two dimensional plots of spontaneous activity in thalamocortical network. 100 PY - 25 IN - 50 RE - 50 TC cells were simulated. Each pattern of activity was randomly initiated at different foci of the network. Both thalamic and cortical network displayed transitions between active and silent states. The connection fan out was ±5 cells for AMPA and NMDA mediated PY-PY synapses; ±1 cell for AMPA and NMDA mediated PY-IN synapses; ±5 cells for $GABA_A$ mediated IN-PY synapses; ±10 cells for AMPA mediated TC-PY synapses; ±2 cells for AMPA mediated TC-IN synapses; ±5 cells for AMPA mediated PY-TC and PY-RE synapses; ±5 cells for AMPA, $GABA_A$ and $GABA_B$ mediated synapses between RE and TC cells. (Modified from [42]).

Figure 4 shows 2D spatio-temporal plots of PY and TC networks during SWS oscillations. Each active phase was initiated in one of the cortical PY cells and then spread over thalamocortical network. Isolated spikes

occurred in many PY cells during silent phases of SWS oscillations. However, these spikes were not able to induce postsynaptic response unless the postsynaptic cell itself was sufficiently depolarized by random minis summation. PY cells fired at a higher frequency during the initial phase of the depolarized state and at a reduced firing rate after 200-300 msec. In TC cells, activity patterns always started from hyperpolarization since the immediate effect of PY spiking was a burst of spikes in RE cells. This hyperpolarization was followed by de-inactivation of low-threshold Ca^{2+} current, I_T, and rebound low-threshold spike. Only a few TC cells fired Na^+ spikes in the second cycle; in many cases TC cells showed few cycles of subthreshold ~10 Hz oscillations followed by few cycles with low-threshold spikes crowned by action potentials. This pattern is a signature of waning spindle oscillations usually observed during active phases of SWS [10]. The main factor contributing to spindle termination in this model was powerful and nonsynchronous AMPA-mediated PY $\rightarrow$ RE input depolarizing RE cells that inactivated I_T and terminated rebound oscillations in the RE-TC circuit (see also [50]).

AMPA-mediated input from TC to PY cells induced additional depolarization, increasing the duration of cortical active phases up to 1-1.5 sec. In some cases, thalamic spindles outlasted cortical activity, which also reduced the duration of corresponding down states in the cortical network; TC-mediated EPSPs arriving at the top of mini-induced depolarization in PY cells could initiate new active patterns after about 0.5 sec or less. Thus, compared with isolated cortical network, slow sleep oscillations in the full thalamocortical model were characterized by prolonged active states and reduced silent tates. This prediction is consistent with recordings from cortical slice preparations where slow oscillations are characterized by prolonged silent and relatively short active states [33].

2.4 Spontaneous activity of layer V neurons and initiation of active cortical states

Another possible mechanism for recovery of active states during slow sleep oscillations could be the dynamics of some intrinsic currents in cortical neurons including the hyperpolarization-activated cation current, I_h, similar to the way that dynamics of the low-threshold Ca^{2+} current and I_h in thalamic relay cells can organize their oscillations in the delta frequency range [51-54]. Recently, it was shown that in bath solution with ionic concentrations that mimic those reported in situ (3.5 mM of K^+, 1.0 mM of Mg^+ and 1.0 or 1.2 mM of Ca^{2+}) cortical slices can oscillate in the frequency range of slow sleep oscillations [33]. This activity was usually initiated in layer 5 and

propagated over the whole slice. An increase in $[K^+]_o$ may depolarize neurons close to the firing threshold (see Fig. 2-3 in [33]. *In vivo* the I_h was efficient in induction of action potentials during seizures, when $[K^+]_o$ was high, which shifted all K^+ currents to more depolarized values [55] (see also [56, 57] for the modeling study of the effects of elevated $[K^+]_o$). Low Ca^{2+} will increase intrinsic excitability of neurons [58]. In these conditions the relatively large amplitude EPSPs, but not minis, might recruit postsynaptic neurons into active states. Only 5 to 20 synchronized presynaptic action potentials are needed to fire a postsynaptic neuron *in vitro*, assuming linear summation [59, 60]. Thus, spontaneous active periods might be obtained in slices that are exposed to a slightly increased $[K^+]_o$ and decreased $[Ca^{2+}]_o$ or any other factor leading to the depolarization of relatively large population of neurons *in vitro*. A computer model was proposed where transitions from down (silent) to the up (active) state were initiated by spontaneous spike discharges in a small random group of neurons [61]. *In vitro* studies indicate that a group of neurons, which could initiate active periods, could be either layer 5 intrinsically bursting neurons [33] or spatially structured neuronal ensembles [62]. A recent *in vivo* study demonstrated that fast-spiking and intrinsically-bursting neurons were the first to be activated during the onset of active states [31]. Layer 5 pyramidal neurons (many of them are intrinsically-bursting) are among the largest neurons in neocortex with the total number of synapses on them reaching 50,000 [63]. Thus, it is possible that more minis are found on these neurons. Bursts of action potentials generated by these cells may facilitate successful activation of further cells and thus switching of the entering of the whole network into the active state. Earlier onset of activity in FS cells, which are inhibitory interneurons, is more difficult to interpret. Possible factors, contributing to the earlier onset of active states in FS cells could be larger amplitude and faster onset dynamics of excitatory postsynaptic potentials in the FS cells than in pyramidal neurons [64]. Occasional spontaneous release, which can be one of the mechanisms for initiation of the active states [34], may depolarize the FS cells more effectively than neurons of other types. An additional factor could be the presence of electrical coupling among FS neurons [65, 66], which may facilitate detection of activity in electrically coupled neurons. The model of slow sleep oscillations that depends on spontaneous network activity was capable to capture many properties of this rhythm [61]. However, decrease of the network size in this model would not necessarily lead to the changes in frequency and regularity of transitions between active and silent states as observed in cortical slab preparations *in vivo*.

2.5. Homeostatic plasticity and active cortical states

During slow-wave sleep the neocortex is functionally deafferented due to the hyperpolarization of thalamocortical cells [67] and the reduction in cholinergic inputs. This deafferentation is similar to deafferentation observed after brain trauma when a population of neurons becomes partially disconnected from the rest of the network. Chronically isolated slabs of neocortex, produced by gray and white matter lesions, develop chronic hyperexcitability and focal epileptogenesis [68-70]. A few days after isolation spontaneous bursts of activity appear, which occur more frequently during subsequent days and weeks [69, 71, 72] while field potentials display slow waves at frequencies around 1 Hz [68]. At the same time the isolated cortex develops an increased susceptibility to experimentally induced epileptiform activity [68, 69, 71], similar to the phenomenon of disuse supersensitivity encountered in peripheral structures after deprivation of afferent inputs [73]. In slices of chronically (>1-2 weeks) isolated cortex electrical stimulation may evoke "epileptiform" burst discharges [74] that are initiated in layer 5 [75] and resemble in some ways the up-states of the slow (<1 Hz) oscillation in cortical slices [33] and naturally sleeping cats [4]. Similar burst discharges are observed in lesioned organotypic hippocampal slice cultures [76] and cell cultures subjected to chronic blockade of activity [77-80]. The mechanisms underlying epileptogenesis in chronically isolated neocortex are unclear. Previous hypotheses suggest that the sprouting of new excitatory connections [76, 81, 82], decreases in synaptic inhibition [83] and increases of NMDA currents and pyramidal cell excitability [84].

Neuronal activity of acutely isolated cortex is strongly reduced [34, 69, 85]. Evidence from *in vitro* and *in vivo* studies suggests that chronic blockade of activity may modify synaptic strengths and intrinsic neuronal excitability by activating homeostatic plasticity processes [86, 87] that upregulate depolarizing influences on excitatory neurons (such as inward ionic currents and glutamatergic synaptic conductances) and downregulate hyperpolarizing influences (such as outward ionic currents and GABAergic synaptic conductances). Homeostatic plasticity, which is thought to maintain a set-point level of activity in the cortex, may fail to control "normal" excitability in heterogeneous networks consisting of subpopulations of neurons with different levels of activity – conditions found in traumatized cortex [88]. This may create an unstable balance of excitation and inhibition and lead to paroxysmal seizures.

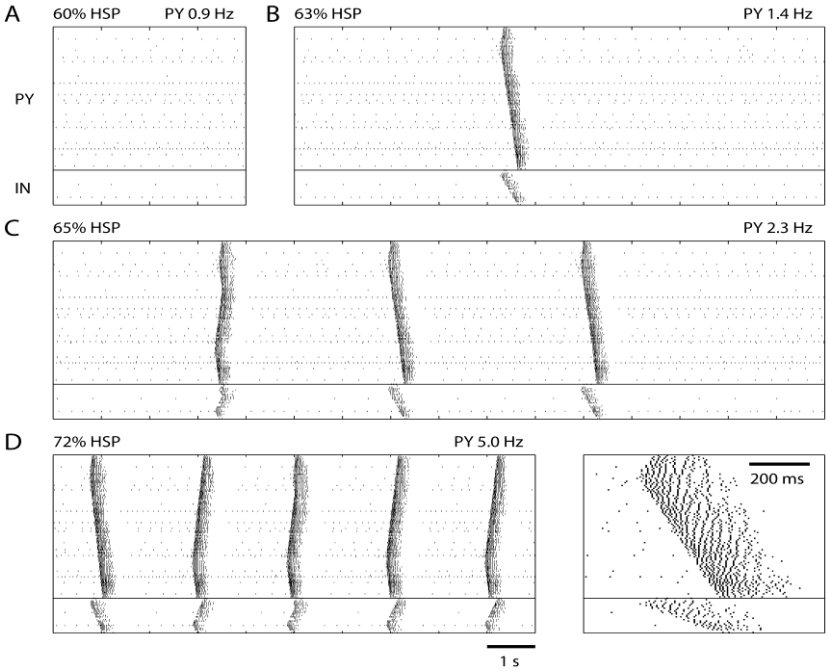

Figure 5. Computer model of propagating burst discharges in deafferented cortex after homeostatic synaptic plasticity. Each dot represents the spike from a single model neuron. Each line in the raster plot is from a single neuron. The PY cells are in the top part of the diagram and the IN cells are shown in the bottom part. These spike rasterplots show network activity after (A) 60% HSP, (B) 63% HSP, (C) 65% HSP and (D) 72% HSP. After 72% HSP a steady state was reached for which PY cells fired on average 5.0 Hz. The inset shows an expanded spontaneous burst at 72% HSP. (Modified from [89]).

This mechanism was explored in the network model of cortical population including activity dependent control of excitatory and inhibitory conductances [89]. The plasticity rule involved the upregulation of synaptic coupling between pyramidal neuron and downregulation of connections from inhibitory interneurons to pyramidal cells as long as the average firing rate of pyramidal cells was below a target firing rate, which was set at the average firing rate of pyramidal cells before deafferentation (5 Hz). In the deafferented cortex, homeostatic synaptic plasticity (HSP) had initially little effect on network activity [89]. Up to 60% HSP, firing rates were similar to those in the acutely deafferented network (Fig. 5A). PY cells fired at an average rate of 0.9

Hz and IN cells at 0.3 Hz. After 63% HSP, the spontaneous activity of the network changed in a qualitative manner (Fig. 5B). Occasionally, locally generated spike bursts propagated through the network. These burst discharges were approximately 200-400 ms in duration and involved multiple spikes in PY and IN cells (see Fig. 5B). Bursts were generated by network interactions because none of the cells possessed intrinsic bursting mechanisms (all PY cells were of the regular-spiking type). As the average number of spikes per PY cell measured over long periods of time (1.4 Hz) was still below the homeostasis target frequency of 5 Hz, further HSP increased the occurrence of network bursts (Fig. 5C, 65% HSP). Eventually a steady state was reached where bursts repeated at frequencies of about 0.5 Hz and the average PY cell firing rate (5.0 Hz) equaled the homeostasis target firing rate (Fig. 5D, 72% HSP). Transitions to active states (bursts) in this model depend on small fraction of cortical neurons which remain spontaneously active after deafferentation.

2.6. Termination of active cortical states during slow sleep oscillations

The synaptic depression of active synaptic connections [90, 91], the slow inactivation of the persistent Na^+ current [49, 92], the activation of Ca^{2+}-dependent K^+ current [93], and the activation of Na^+-dependent K^+ current [94], were proposed as potential mechanisms capable to displace the membrane potential of cortical neurons from the firing level and initiate transition to the hyperpolarized or silent state thus starting new cycle of SWS oscillations [42, 61, 95]. Recent *in vivo* study revealed surprisingly high synchrony of active states termination [31] that implies the existence of a network mechanism which switches population activity to silence.

It was shown that during slow-wave sleep neocortical and thalamic neurons display phase relations that are restricted to narrow time windows [5]. The onsets of silent states are synchronized even better than the onsets of activity, and showed no latency bias for any location or cell type [31]. These data indicate that termination of active states cannot relay exclusively on mechanisms taking into account intrinsic membrane properties or synaptic palsticity of individual cells or synapses, because intrinsic properties are extremely non-uniform in different cells and synapses. Thus a hypothetical network mechanism could be responsible for the termination of active network states.

2.7. Transient and self-sustained dynamics in large-scale 2D network.

Only transient waves or persistent activities are possible in one-dimensional (1D) network models. Therefore, in a 1D network each transition to the active network state should necessarily involve a specific mechanism that is independent on the mechanisms mediating active state propagation. Increasing the network dimensionality may lead to new dynamics that include self-sustained rotating spiral waves. A two-dimensional (2D) network of sufficiently large size may be required to maintain this activity. The need of a large network for the onset of spiral wave activity was previously demonstrated in a Hodgkin-Huxley based model of isolated thalamic reticular nuclei [96]. Later this statement was confirmed using two-layer large-scale model of the cortex [97]. In a small 2D network an external stimulation triggered a quasi-plane wave which propagated through the network similar to the wave of excitation in the 1D network (Fig. 6A, left). As the size of the 2D network grew, the transient plane waves bifurcated into self-sustained spiral waves (Fig. 6A, middle and right). In these simulations the critical network size (the number of neurons) that was required for the onset of self-sustained activity depended on the footprint size of synaptic interconnections. Near the transition point the network dynamics was usually dominated by a single spiral wave moving randomly around the network. Since the open (flow) boundary conditions were used, the spiral wave disappeared when the spiral core reached one of the boundaries, and the network switched to the silent state. However, further increase of the network size resulted in the onset of more stable multi-spiral regimes (Fig. 6A, right). Thus, increasing the network size increases the likelihood that self-sustained activity exists in the network infinitely. Increase of network dimensionality to 3D can further shape network activity patterns, however, qualitative changes (similar to those during transition from 1D to 2D) are less likely to be found. Furthermore, the thickness of the neocortex is relatively small (compare with other spatial dimensions) which makes 2D model to be a good approximation of the biological system.

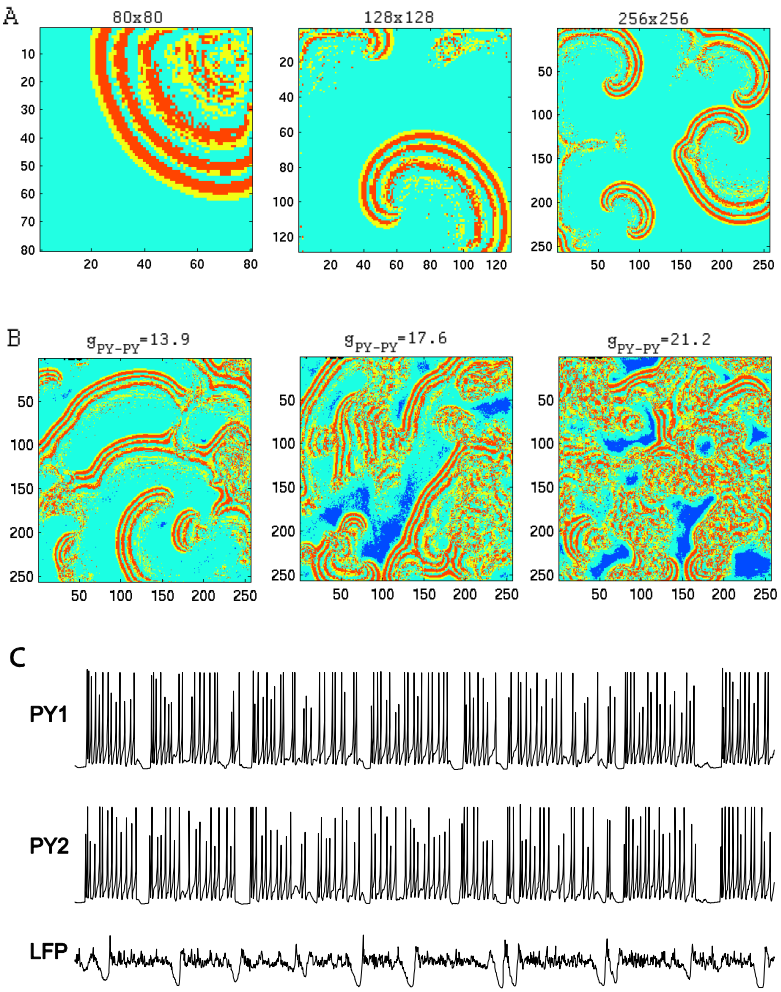

Figure 6. Waves in 2D cortical networks of pyramidal cells (PY) and inhibitory interneurons (INs) ($N_{IN}=N_{PY}/4$) coupled through excitatory and inhibitory synapses with short-term depression. (A) Only transient waves were found in a relatively small (N_{PY}=6400) network (left); as the network size increased (N_{PY}=25600, N_{PY}=65536) the bursting activity persisted in a form of rotating spiral waves (middle, right). (B) An increase of the strength of excitatory coupling between PY neurons transformed the patterns of activity with well separated spirals (left) into the regime dominated by spiking neurons (right). (C) Two representative traces of pyramidal cells and averaged network activity (10×10 group in the middle) from the network shown in panel B, right. In all simulations the radius of connection fan out was 8 neurons (~ 200 presynaptic neurons) for AMPA mediated

Figure 6. Legend continued

PY-PY synapses; 8 neurons (~ 200 presynaptic neurons) for AMPA mediated PY-IN synapses; 2 neurons (~ 12 presynaptic neurons) for $GABA_A$ mediated IN-PY synapses. (Modified from [97]).

The properties of the waves in the 2D network were affected by the coupling parameters. An increase of the AMPA mediated coupling between PY neurons extended duration of the bursts and eventually lead to a regime where prolonged active states were interrupted by relatively short silent states. This is illustrated in the Fig. 6B, 6C. Figure 6B shows snapshots of the PY cells activity in the network for 3 different values of the excitatory coupling; Fig. 6C displays voltage traces from 2 nearby PY cells and the average activity of 100 (10×10) cells in the center of the network for the regime shown in Fig. 6B (right panel). In this model transitions between silent and active states have not been initiated by any external stimuli. These transitions are the result of intrinsic network dynamics and are reminiscent of slow sleep oscillations. Duration of the silent states revealed in these simulations was, however, short compare with *in vivo* data. Even if this mechanism does not play a primary role in generating slow sleep rhythm, it can contribute to maintaining long active states in presence of strong synaptic depression and intrinsic firing adaptation.

3. Functional role of slow oscillation in neocortex

Active cortical states during slow-wave sleep (SWS) have many similarities with the wake state of the brain. Similar to the wake state, EEG shows low amplitude fast activity during active cortical states; this activity can be synchronized in beta-gamma frequency range [98, 99]. Extracellular recordings showed that local unit correlations and firing dynamics during active states of SWS are similar to those found during wakefulness [100]. Both during active states of SWS and wake the inhibition dominates over excitation in cortical circuits [101]. There was a significant difference, however, in the input resistances between active states of SWS oscillations and during wake state. During waking state in a fully activated cortical network the input resistance reached the level measured during silent states of SWS oscillations and significantly exceeded input resistance found during active states of SWS [4]. It was proposed that both reduction of K^+ leak and AMPA-mediated synaptic conductances in cortical neurons contributed to this shift in the passive properties of neurons during waking [42]. Decrease of input resistance during active states of SWS reduces the membrane time constant, therefore, allowing the membrane to repolarize more quickly and

reducing post synaptic potential integration window of cortical neurons. The reduced time constant allows the membrane voltage to fluctuate more rapidly, enhancing its ability to track high frequency inputs with precision, while degrading response precision for low frequency stimuli [102].

Similarities between active states during SWS and wake state of the brain are consistent with idea that the active brain states represent "replayed" events that have occurred previously during the wake state [100]. It was proposed that in slow-wave sleep, during the brief periods of wake-like activities (active states), the hippocampal formation would activate latent memories stored in the neocortex ("replay") and induce permanent changes in intrinsic or synaptic conductances [103]. The hypothesis about role of SWS for memory consolidation is consistent with minis-dependent mechanism of SWS oscillations. In this scenario, slow wave activity is driven by the spontaneously occurring coincidence of minis. Spontaneous miniature synaptic activity is caused by action-potential independent release of transmitter vesicles and is regulated at the level of single synapses [36, 37]. The frequency of spontaneous miniature synaptic events increases with the probability of evoked release in cortical neurons [104]. Thus, the synapses with the highest probability of release [105] should make the largest contribution to initiating an action potential in a neuron. Glutamate application at synapses between hippocampal neurons produces long-term potentiation of the frequency of spontaneous miniature synaptic currents [106], which suggests that the synapses with the highest rates of spontaneous miniature synaptic currents are the most likely to have been recently potentiated.

During SWS the initiation of spikes could occur in neurons having the largest number of recently potentiated synapses and, therefore, the highest rate of spontaneous synaptic activity. If these spontaneously occurring minis are amplified by the intrinsic currents in dendrites it may not take a large number of coincident events to initiate a spike. These neurons will represent a subset of cortical population that "drives" transitions from silent to active states of SWS. The spiking neuron would further need to recruit additional neurons connected to it; the ones nearest to threshold would be those depolarized as a consequence of minis, so that the recruited network would preferentially include cells that had been recently potentiated. Thus, the minis dependent mechanism of active states initiation will imply that the same sequences of cortical neurons will spike in precise order during slow sleep oscillations. Transition between silent and active network states can start in different network sites; however, if the number of initiation sites is small, each of the spike sequences will be replayed many times during slow wave sleep. Such propagation of correlated activity along connected pathways may play a role in spike timing-dependent synaptic plasticity during sleep. Other factors

that would influence recruitment of neurons during active states initiation include multiple synaptic boutons [107], spike bursting, which may itself further potentiate recently activated afferent synapses by virtue of the burst in the postsynaptic cell [108], and efferent synapses that were recently potentiated. This interpretation is consistent with the observations that SWS may be essential for memory consolidation and memory formation [109-113].

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