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Neuronal Synchronization and Thalamocortical Rhythms in Sleep, Wake and Epilepsy

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Abstract

Neuronal synchronization can be defined as a correlated appearance in time of two or more events associated with various aspects of neuronal activity. Neuronal synchronization depends on chemical and electrical synaptic as well as ephaptic and non-specific interactions. We consider two distinct types of neuronal synchronization: local synchronization that is responsible for the generation of local field potentials; and long-range synchronization, detected with distantly located electrodes and mediated primarily via chemical synaptic interactions, which contributes to the EEG synchronization. Neocortical synchronization during sleep and wakefulness is often associated with rhythmic oscillations of neuronal activity: slow oscillation, delta, spindle, beta, gamma and ripples. Normal thalamocortical oscillations [sleep or wake oscillations] are generated as a result of both local and long-range synchronization. During paroxysmal [seizure] activity, the role of chemical synaptic interactions decreases because of alterations in ionic composition that impairs synaptic transmission. Synchronized activities in large population of neurons (such as neocortex) may occur as nearly simultaneous patterns across an entire population or as propagating waves. Neocortical synchronization is controlled by the activities in ascending systems: cholinergic, norepinephrinergic and serotoninergic. The presence of cortico-thalamo-cortical feedback loops contribute to the synchronization of cortical activities. We propose that all the types of neuronal interactions contribute to the generation of synchronous oscillatory activities, but the ratio of their contribution is different for different types of oscillations.

Neuronal synchronization can be distinguished into long-range and local synchronization. The *long-range synchrony* is usually detected with two or more electrodes placed at some distance apart. It leads to brain activity that is correlated at long distances and may be seen using both local filed potential (LFP) and electroencephalogram (EEG) recordings. The first tool (i.e., the LFP) provides a microscopic measure of brain activity summarizing electrical activities of possibly thousands of neurons [1–4]. The second type of recording (i.e., the EEG) is a result of changes of electrical activity of multiple sources and ultimately represents activity patterns of large populations of neurons and glial cells in the brain. The *local or short-range synchrony*

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can be detected either with one relatively large field potential electrode or with two or more small, intracellular or extracellular unit (action potential) recording electrodes located at short (less than 1 mm) distances from each other. Synchronous activity of a few neurons not necessarily leads to measurable EEG signals, but can be seen using LFP recordings. Because of the low-pass filtering properties of the extracellular media [5], high frequency electric field associated with action potentials steeply attenuate and the large amplitude slow LFP and EEG potentials are mainly generated from nearly simultaneously occurring de- and hyperpolarizing events in a large number of neighboring cells with a major contribution of large pyramidal neurons [6].

In general, synchronization of electrical activity in the brain occurs as the result of interaction among sets of neurons. The following major types of interactions between brain cells (neurons and glia) are possible: (a) Chemical synaptic transmission, which takes place when an action potential that is fired by the presynaptic neuron, invades the nerve terminals, allowing Ca^{2+} entry, triggering neurotransmitter release, and finally causing de- or hyperpolarization of the postsynaptic neuron [7,8]; (b) Interactions between electrically coupled cells via *gap junctions* [9]; these interactions are bidirectional and work as a low-pass filter, i.e., fast processes (for example: action potentials) are filtered out, but slow processes (for example: slow synaptic potentials) are transmitted with minor attenuation [10]; (c) Ephaptic interactions, which are mediated by large extracellular currents and field potentials generated by cortical structures in the absence of specialized contacts [11,12] (it should be noted that some researchers separate ephaptic transmission from field effect interactions [13]); (d) Non-specific interactions, commonly achieved by alteration in the extracellular ionic balance caused by the activity of brain cells [14–17].

MECHANISMS OF NEURONAL SYNCHRONIZATION

Neuronal synchronization is defined as correlated appearance in time of two or more events associated with various aspects of neuronal activity at different levels, from single cell to the whole brain.

A common scenario involves adjustment or phase locking of rhythms of two or more neurons leading to a stable phase difference of membrane voltage oscillations (periodic or not), e.g., coincidence of action potentials. Such coincidence of electrical activities of many neurons would lead to coordinated changes of extracellular ionic currents in close proximity to these neurons, which can be then detected as changes of the LFP, which are reflected on the scalp EEG. If individual neurons fire action potentials periodically, and these events are synchronized among many cells, one would observe periodic LFP oscillations. Finally, if long-range synchronization takes place among distinct brain areas, it would lead to global changes of electrical activity usually associated with EEG rhythms.

Chemical Synaptic Mechanisms of Synchronization

Synaptic interaction is a common mechanism of communication between neurons. Transmitter release by presynaptic terminal leads to receptor activation on the postsynaptic cell and the generation of inward or outward currents, which depolarize or hyperpolarize the postsynaptic cell. Summation of activities from synchronized inputs enhances transmission of information more effectively than raising discharge rates [18]. Generally both excitatory and inhibitory synaptic interaction may contribute to synchronization of neuronal activity. For example, in a minimal circuit including synaptic connection from cell **A** to cell **B** the action potential in cell **A** would trigger excitatory postsynaptic potential (EPSP) in cell **B**. If this potential is ample enough, it can trigger an action potential in cell **B,** which may occur nearly simultaneously (after small delay) with action potential in cell **A**.

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This process is more complex in real cortical networks. The amplitude of the single-axon EPSPs is small and variable. *In vitro*, it ranges from 0.1 to 2 mV (but sometimes up to 9 mV), with a mean of about 1 mV [19–23]. *In vivo*, due to multiple factors associated with network activities (e.g., shunting or frequency dependent attenuation), the amplitude of successful single axon EPSPs is about 0.5 mV [15]. Given the fact that the EPSP amplitude depends linearly on the number of synaptic contacts formed by all the presynaptic neurons [21,23], only 40 to 50 synaptic contacts are needed to bring the postsynaptic neuron membrane potential from resting level of −75 mV to −80 mV to firing threshold of around −55 mV *in vivo*. On the other hand, the actual rate of EPSPs received by a neocortical neuron *in vivo* may be much higher. Indeed, spontaneous firing rates in vivo are at the order of 10 Hz [24,25]. Large neocortical neurons possess between 10,000 and 50,000 synapses [26]. Assuming 25,000 synapses on average and considering that eighty percent of these synapses are excitatory [27], about 200,000 synapses may be activated each second, or 200 synapses each millisecond (80% from 25,000 synapses * 10 Hz = 200.000 per sec or 200 per msec). The half-width of EPSPs *in vivo* is about 10 ms and this time might be assumed as a period for efficient integration of presynaptic inputs. Thus, a neocortical neuron can receive up to 2000 inputs during 10 ms window for the efficient integration. Because the failure rates *in vivo* are very high (70–80%) [15] the neuron receives EPSPs in the order of 400–800 within integrating period. This is still 10–20 times more than the needed number of simultaneously firing presynaptic neurons to fire postsynaptic neuron (40–50 synapses [see above]). Therefore, the mechanisms of cortical synchronization based exclusively on excitatory intracortical connectivity would lead to over-excitation of the network and cannot be considered as an efficient mechanism of cortical synchronization.

Efficient way to synchronize population of excitatory cells involves inhibition. Imagine a group of excitatory neurons $\mathbf{A_1}$,…, $\mathbf{A_n}$ that generate action potentials, which are not synchronized across cells. Imagine now that all these neurons receive common inhibitory input from inhibitory cell **B**. Action potential in cell B would provide synchronous inhibitory postsynaptic potentials (IPSPs) in neurons $\mathbf{A_1}$,…, $\mathbf{A_n}$, so, when the IPSP terminates, all these neurons $\mathbf{A_1}$, …, $\mathbf{A_n}$ can spike synchronously. If now some of these excitatory cells project back to inhibitory neuron **B**, synchronous spiking between $\mathbf{A_1}$,…, $\mathbf{A_n}$ would trigger a new spike in cell **B** therefore starting a new cycle of oscillation (Figure 1). This mechanism of synchronization commonly referred to as "feedback inhibition" (see [28] for review of this topic), is involved in many brain rhythms in different brain systems including, e.g., some types of gamma oscillations [29,30], thalamic spindles [1,31] and others.

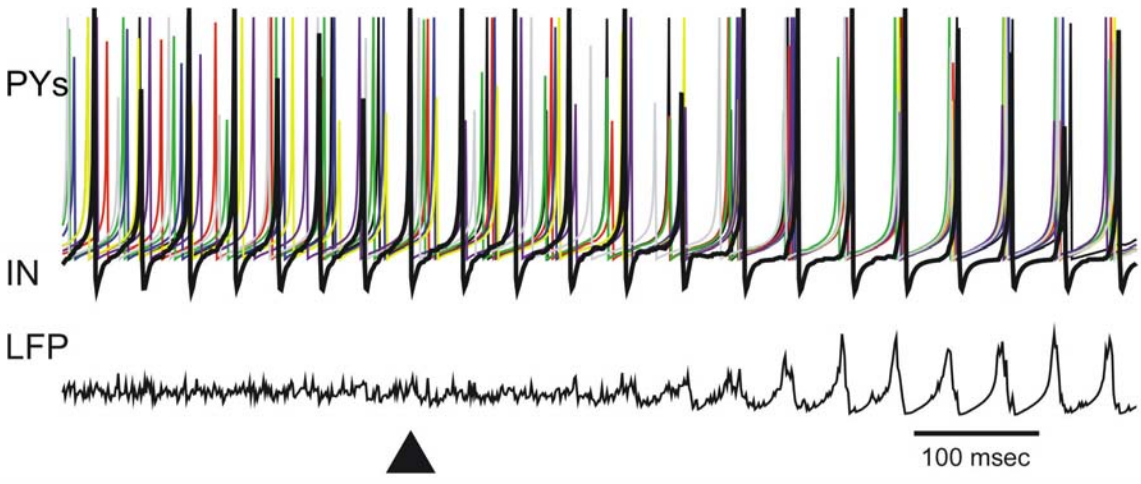

Figure 1. Effect of feedback inhibition in spike synchronization

Top, eight pyramidal neurons (PYs, thin lines of different color) oscillate asynchronously in 20–25 Hz frequency range with no inhibitory feedback. About 200 ms after inhibitory GABAergic synapse from the interneuron (IN, black thick line) to PYs was activated (arrowhead), spikes in the pyramidal neurons became synchronized by IN-mediated IPSPs. Bottom, increase of PYs synchronization was reflected in large amplitude LFP oscillations (Bazhenov, Timofeev, unpublished observation).

Gap Junctions and Synchronization

Gap junctions (i.e., electrical synapses) allow direct flux of ions between connected cells therefore providing a mechanism of communication that is action potential independent [32,33]. If few cells are connected through electrical synapses, any change of membrane voltage in one neuron would trigger current flow between coupled neurons leading to corresponding changes of membrane voltage in the latter cells, therefore, providing synchronizing effect. Because of the relatively high resistance of electrical synapses, they act as low pass filters [10]. In cortical networks, groups of GABA-releasing interneurons [34,35] and glial cells [36] are interconnected via gap junctions. There is a set of indirect evidences suggesting that electrical coupling may occur between axons of pyramidal neurons [37,38]. The role of axonal gap junctions in the generation of electrical activities is unclear. Intra-axonal recordings did not reveal the presence of afterhyperpolarizing potentials (AHP) in axons [39,40]. Low-pass filter properties of gap junctions prevent efficient transmitting of fast spikes to coupled neurons and absence of AHP prevents slower synchronization. Because of this and because of extreme short-range of electrical coupling, while axo-axonal gap junctions may enhance already existing synchronization manifested by slow membrane voltage oscillations, it is unlikely that they play a primary role in establishing neocortical synchronization.

Ephaptic Interactions

Extracellular currents produced by electrical activity of neurons and constituting local field potentials may directly influence electrical properties of neurons [13]. This effect may include depolarization or hyperpolarization of cell membrane, and therefore a change in excitability. While being relatively weak, these effects have a global influence and may provide significant impact when neuronal activity is already synchronized by means of other mechanisms. Examples include slow-wave sleep oscillations or epileptic activity when a certain degree of synchrony of electrical activity between neurons is already achieved through chemical or electrical interactions. In that case, weak but global effect of ephaptic interaction further enhances the synchrony. Not only internally generated fields can affect neuronal excitability. The application of external electric field with an amplitude within the range of *in vivo* endogenous fields modulates cortical slow oscillation [12,41] and potentiates memory [41].

Changes of the Extracellular Ionic Concentrations

Electrical activity of neurons is associated with opening and closing of different ionic channels and therefore may lead to changes of extracellular ion concentrations. These effects include primarily ions whose extracellular concentrations are low, such as K^+ and Ca^{2+}. Opening of K^+ channels (such as delayed rectifier voltage gated channels mediating hyperpolariziung phase of action potential) or Ca^{2+} channels increase extracellular K^+ concentration and decrease extracellular Ca^{2+} concentration. While these local changes are normally compensated by ionic pumps and interaction with glia, significant alternations of extracellular ion concentrations triggered by electrical activity in one cell may diffuse to neighbor neurons leading to changes of their excitability and, therefore, contribution to synchronization of electrical activity between neighbor cells. Experimental evidences suggest that indeed a variety of ions undergo activity-dependent changes in concentration [14,16]. During active states of cortical slow oscillation, due to activation of synaptic currents (primarily NMDA receptor-mediated) and Ca^{2+} gated intrinsic channels, the extracellular concentration of Ca^{2+} decreases from 1.2 mM to 1.0 mM [15,42]. This leads to a dramatic increase in synaptic failure rates (up to 80 %) [15]. Therefore, chemical synaptic interactions contributing to synchronization become

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largely impaired. On the other hand, lower concentrations of extracellular Ca^{2+} promote opening of hemichannels [43] that increases effectiveness of gap junctions and therefore, electrical coupling. The most dramatic changes in extracellular concentration of K^+ and Ca^{2+} occur during paroxysmal discharges. Extracellular K^+ concentration reaches 7–18 mM during spontaneous electrographic seizures in neocortex [44–46] and the extracellular Ca^{2+} concentration decreases to 0.4–0.7 mM [44,47,48]. These changes dramatically reduce synaptic excitability basically abolishing synaptic responses [49]. Changes in ionic concentrations affect reversal potential of a variety of intrinsic currents that contribute to neuronal excitability, synchronization and generation of oscillatory activities, potentially promoting synchronized oscillations during epileptic seizures [17,50]. For example, hyperpolarization activated depolarizing current (I_h) in neocortical neurons is relatively weak and in normal conditions it is unlikely to play any significant role in the generation of cortical oscillations. However, during seizure activity, when extracellular K^+ concentration increases, the I_h reversal potential shifts to a more depolarized value, allowing for this current to depolarize a set of cortical neurons to the firing threshold, thus leading to the generation of spikes and onset of next cycles of spike-wave discharges [51].

THALAMOCORTICAL OSCILLATIONS

Periodic oscillatory activity is a common result of neuronal synchronization and it is an emerging property of the thalamocortical system. Neuronal oscillations enable selective and dynamic control of distributed functional cell assemblies [52]. The patterns and the dominant frequencies of these oscillations are defined by the specific mechanisms involved and depend on the functional state of the brain. Normal oscillatory activities include slow (0.1–15 Hz, present mainly during slow-wave sleep or anesthesia), and fast (20–600 Hz) activities. The fast activities may be present in various states of vigilance and frequently coexist with slower rhythms. Each type of oscillation is generated by a particular set of intrinsic neuronal currents, synaptic interactions and extracellular factors. Spontaneous brain rhythms during different states of vigilance may lead to increased responsiveness and plastic changes in the strength of connections among neurons, thus affecting information flow in the thalamocortical system.

The various oscillatory rhythms generated in the thalamocortical system may be divided in two main classes: intrinsic, generated by a single neuron as a result of an interplay between specific intrinsic currents [e.g. thalamic delta oscillation], and extrinsic, or network oscillations, which require the interaction of excitatory and inhibitory cells within a neuronal population (e.g. spindle oscillation, reviewed in [53]). Intrinsic neuronal currents contribute to the generation of network oscillations. Oscillations may also be generated in a population of non-pacemaker neurons coupled through gap junctions.

a Near Steady or Infra-Slow Oscillation (<0.1 Hz)

This type of oscillatory activity has a period within the range of tens of seconds to a minute [54]. Prolonged metabolic disturbance, irritation of brain structures or afferent stimulation intensify these activities, and phenobarbital or diethyl ether anesthesia as well as strong electrical stimulation of cerebral cortex dramatically decrease or abolish this brain activity [54]. Very little is known about the underlying mechanisms of these oscillations. Hypercapnia induced negative scalp DC shifts (~ −0.3 mV/CO_2%) and hypocapnia induced positive scalp DC shifts (~0.3 mV/CO_2%) [55]. Infra-slow activities likely have a cortical origin given that they can be recorded from neocortical slabs [56]. Indirect evidence suggests that infra-slow oscillations (0.02–0.2 Hz) synchronize faster activities, modulate cortical excitability and contribute to the aggravation of epileptic activity during sleep [57].

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b Slow oscillation

During slow-wave sleep (SWS) and some types of anesthesia the dominant activity pattern is a slow oscillation occurring with a low frequency (0.3 – 1 Hz) [1,25,58–60]. During slow oscillation the entire cortical network alternates between silent (Hyperpolarizing, or Down) and active (Depolarizing, or Up) states, each lasting 0.2–1 s (Figure 2). Silent periods are periods of disfacilitation, i.e. periods of absence of synaptic activity, while active periods are periods of intensive synaptic activity leading to the generation of fast oscillations within the thalamocortical system [25,59,61–64]. The survival of slow oscillations after extensive thalamic lesions *in vivo* [65] and in cortical *in vitro* preparations [66], and the absence of slow oscillation in the thalamus of decorticated cats [67] point to an intracortical origin of this rhythm.

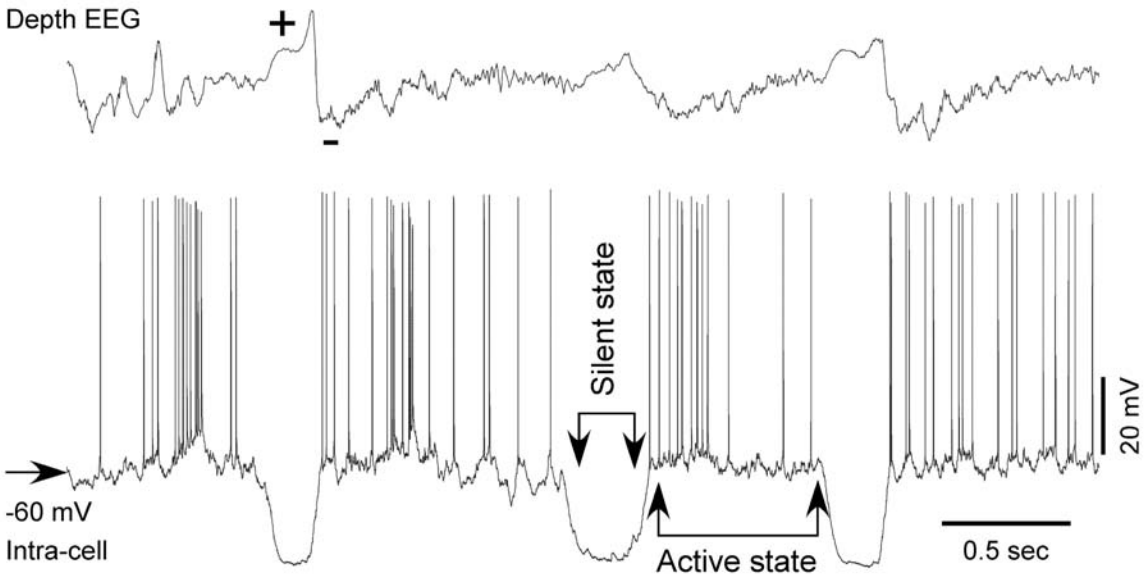

Figure 2. Cortical sleep slow oscillation

At EEG level the slow oscillation appears as periodic alterations of positive and negative waves (indicated by + and − signs). During EEG depth-positivity cortical neurons remain in hyperpolarized, silent state. During EEG depth-negativity cortical neurons move to active states, reveal barrages of synaptic events and fire action potentials. (Modified from [53]).

A particular feature of slow oscillation is that each cortical slow wave originates in a particular location and propagates to involve other cortical regions. According to Massimini et al. [68], in young adult humans (20–25 years old males) the preferential sites of origin of slow waves are in frontal cortical regions. However, in this high density EEG study, it was unclear whether it was active or silent states that propagated. Multisite intracellular experiments on cats demonstrated that it was the onset of active state that propagated, but the onset of silent states occurred more synchronously [69]. Distinct from the above mentioned study [68], the active states in cats more commonly start at the border between area 5 and 7 of parietal cortex [69]. A very recent study [70] demonstrates that propagation of slow activity in the human brain undergoes progressive age-dependent changes. In preschool children (2–3 years old), the propagating waves start from the occipital cortex. From early childhood to late adolescence, the location on the scalp showing maximal slow wave activity undergoes a shift from posterior to anterior regions. This suggests a progressive change in excitability of various cortical areas and that slow oscillation in the brain of adult cat is generated in areas homotypical to human adolescent brain. A propagation of activity suggests: (a) the presence of cortical regions with different levels of excitability that start the active states and (b) the presence of active synaptic chains.

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At least three distinct mechanisms for the origin of slow cortical oscillations were proposed. The first depends on spontaneous miniature synaptic activities (mPSP) [71] caused by the action potential-independent release of transmitter vesicles and regulated at the level of single synapses [72,73]. Occasional summation of the miniature EPSPs during the hyperpolarized (silent) phase of slow-sleep oscillations activates the persistent sodium current and depolarizes the membrane of cortical pyramidal cells, which is sufficient for spike generation [74–76]. This triggers the active phase of the slow oscillation, which is maintained by synaptic activities and the persistent sodium current. Modeling experiments suggest that short-term synaptic depression and the activation of Ca^{2+}-dependent K^+ current were sufficient to terminate the active state [75]. More recent electrophysiological experiments demonstrated that the active states terminate with high levels of synchrony [69]. Because the short-term synaptic plasticity and activity of intrinsic currents are very specific for each synapse or neuron, the occurrence of nearly simultaneous termination of the active states over large distances suggests the presence of active widespread (inhibitory) mechanism for the termination of active states. Indeed, about 40% of inhibitory fast-spiking interneurons increase their firing rates at the end of spontaneous active states during slow oscillation [77]. These cells can contribute to the synchronous termination of active states.

Another possible mechanism accounting for the generation of active states during slow-sleep oscillation may be the generation of spontaneous activity by layer V cortical neurons [66,78]. Using a cortical slice preparation, it was shown that oscillatory activity in the frequency range of slow sleep oscillation could be generated at a concentration of extracellular K^+ of 3.5 mM, which is slightly higher than *in vivo* (i.e., 3.2 mM) [66]. This activity was usually initiated in layer V and propagated over the whole slice.

The third hypothesis attributes transitions from silent to active states to the selective synchronization of spatially structured neuronal ensembles involving a small number of cells [79]. The ‘‘selective synchronization’’ hypothesis predicts that even during the silent states, some neurons of the network still generate irregular spontaneous firing.

A group of recent *in vitro* studies suggests that thalamocortical neurons encompass an intrinsic mechanism that may act as secondary oscillator supporting slow rhythm [80]. Cortical activity can recruit, through cortico-thalamic synapses, intrinsic oscillatory mechanisms in thalamocortical neurons [81], which could then increase synchrony among cortical inhibitory interneurons. Our current studies indicate that thalamic mechanisms may be responsible for the maintenance of active states with properties observed *in vivo* [82,83].

A recent *in vivo* study on anesthetized or sleeping cats demonstrated that spontaneous active states could originate from any cortical layer, but most often they start from deep layers and propagate toward more superficial layers [76]. It was shown indeed that numerous spontaneous, spike-independent synaptic events detected during network silent states summate prior to the onset of active states in all recorded neurons. The pyramidal layer V neurons are the biggest cortical neurons [26]; they possess the biggest number of synapses that contribute to the highest likelihood of these neurons to summate spontaneous synaptic events to a threshold level for action potential generation and initiate the active network states. During silent network states, the levels of extracellular Ca^{2+} are increased and contribute to the increase in synaptic release of neurotransmitter [15], facilitating the onset of the active network states.

Regardless of the specific mechanisms involved in sleep slow oscillation generation, long-range excitatory and inhibitory synaptic connectivity likely plays a major role in synchronization of transitions between active and silent states of slow oscillation leading to periodic LFP and EEG oscillations observed in animals and humans during deep sleep.

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c Delta oscillation

Field potential recordings from neocortex in human and animal models during sleep reveal the presence of delta oscillations (1–4 Hz). The delta oscillation likely has two different components, one of which originates in the neocortex and the other in the thalamus. Neocortical delta activity was significantly enhanced after surgical removal of thalamus [84] and chronically isolated neocortical slabs [85]. Little is known about the cellular mechanisms mediating cortical delta oscillation. One of the hypotheses suggests that cortical delta activity could be driven by the discharge of intrinsically bursting neurons [86]. On the other hand, thalamic delta rhythm is a well known example of rhythmic activity generated intrinsically by thalamic relay neurons as a result of an interplay between their low-threshold Ca^{2+} current (I_T) and hyperpolarization activated cation current (I_h) [86b]. As such, the delta oscillation may be observed during deep sleep when thalamic relay neurons are hyperpolarized sufficiently to deinactivate I_T [87–90]. It was also shown that at a certain level of leak current (I_{leak}), the 'window' component of I_T in thalamocortical neurons, may create oscillations similar in frequency to the intrinsic thalamic delta oscillation [91]. While specific intrinsic mechanisms are responsible for the generation of oscillatory activity in individual thalamic neurons, these oscillations would not be synchronized and would not lead to the observed LFP and EEG rhythms unless spiking/bursting activity of individual neurons become synchronized by chemical and electrical synapses as described earlier in this chapter.

Slow wave sleep may be essential for memory consolidation and memory formation [92–95]. It has been proposed that synaptic plasticity associated with slow and delta oscillations could contribute to the consolidation of memory traces acquired during wakefulness [96].

d Sleep spindle oscillations

Sleep spindle oscillations consist of waxing-and-waning field potentials at 7–14 Hz, which last 1–3 seconds and recur every 5–15 seconds. *In vivo*, spindle oscillations are typically observed during the early stages of sleep or during active phases of sleep slow oscillation. *In vivo*, *in vitro* and *in silico* studies suggest that the minimal substrate accounting for spindle oscillations consists in the interaction between thalamic reticular and relay cells (Figure 3) [31,97–100]. Burst firing of reticular thalamic neurons induces inhibitory postsynaptic potentials in thalamocortical neurons. This deinactivates I_T, inducing rebound burst firing in thalamocortical neurons, which, in turn, excite reticular thalamic neurons allowing the cycle to start again. During the early phase of spindles, the reticular nucleus single-handedly drives the spindle oscillation via intrinsic mechanisms [100–103]. The second component of spindles, on the other hand, primarily develops as a result of interactions between reticular and relay neurons [104,105]. Additionally, cortical firing contributes to spindle synchronization through cortico-thalamic feedback connections, thereby imposing simultaneous excitation of reticular and relay neurons [106,107]. The waning phase of spindles occurs as a result of network desychronization [103,107a] and of Ca^{2+}-induced cAMP-dependent up-regulation of the hyperpolarization activated cation current, I_h, in relay cells 108–110. It is important to mention that reticular thalamic neurons are interconnected via gap junctions, which aid in synchronizing spindles [111,112].

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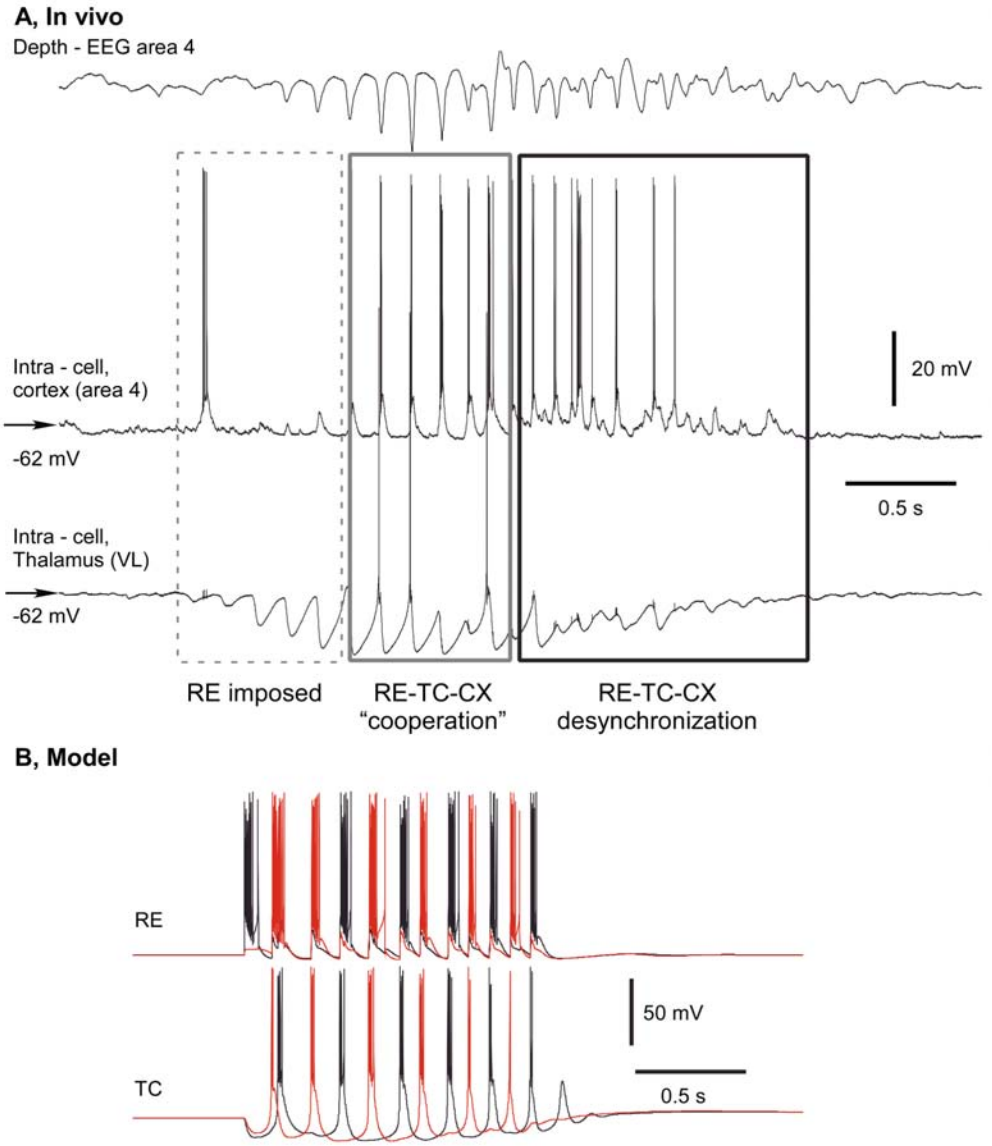

Figure 3. Cellular basis of spindle activity

A, *In vivo* recordings. Three phases of a spindle sequence. Dual intracellular recording of cortical (area 4) and thalamocortical (TC) neurons from ventro-lateral (VL) nucleus of the thalamus. B, Computational model. Spindle oscillations in the circuit of 2 reticular thalamic (RE) and 2 TC cells. RE cells fire every cycle of oscillations while TC cells skip every other cycle. Black and red colors are used to distinguish two different neurons. (Modified from [53]).

While spindle oscillations propagate in thalamic slices [113], thalamocortical synaptic interactions promote large-scale synchrony of spindle oscillations *in vivo* [114]. Human sleep spindles are highly synchronous across the scalp when measured by EEG, but not when measured simultaneously with magnitoencephalogram (MEG) [115]. MEG signals show low correlation and low coherence with each other or with EEG signals. Principle Components Analysis shows that the MEG field pattern is more complex than the EEG pattern implying that MEG signals are produced from multiple partially independent cortical generators, whereas EEG may instead be dominated by a weak, but widespread spindle generator. It was proposed that the differential activity patterns in the core (thalamocortical neurons forming specific, focused projections to cortical layers IV and VI) and matrix (thalamocortical neurons

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forming diffuse projections to layer I) subsystems may explain discrepancies between the temporal patterns of spindles simultaneously observed in EEG and MEG recordings [116].

Recent studies show that sleep related spindle oscillations are essential for memory formation [92] and demonstrate short- and middle term synaptic plasticity (reviewed in [96]). Spindling may activate the protein kinase A molecular "gate", thus opening the door for gene expression [117] and allowing long-term changes to take place following subsequent inputs.

e Beta-gamma oscillation

The waking state of the brain is characterized by the predominance of frequencies in the beta (15–30 Hz) and gamma (30–80 Hz) ranges [118,119]. These fast rhythms are also synchronized between neighboring cortical sites during some forms of anesthesia, natural slow-wave sleep, and REM sleep [62,120,120a] when consciousness is suspended and thoughts are either absent or bizarre. During slow-wave sleep the fast rhythms follow the onset of depth-negative EEG wave (Figure 4). *In vitro* experiments and computational models demonstrated that gamma activity generation depends on the activity of inhibitory interneurons [121–126]. Gamma activity can exist in transient and persistent forms. Experimentally, transient (hundreds of milliseconds) gamma oscillations can be induced by tetanic stimulation of the hippocampus [124,127]. Persistent gamma activity is found in CA3 [128] and neocortex [129]; this form of gamma oscillation can be induced by bath-application of carbachol or kainate and it can last for minutes to hours. During persistent gamma activity, the interneurons fire on every cycle or every two cycles and pyramidal cells fire at much lower frequencies suggesting that active inhibition is involved in the generation of this particular rhythm. Finally, it was found that GABAergic interaction in isolated interneuron networks may lead to network oscillation in the gamma frequency range [130,131]. In both computational models and *in vitro* experiments, it was shown that the frequency of these oscillations depends on the conductance and decay time of $GABA_A$ currents [130]. Large-scale network simulations revealed that coherent gamma range oscillations may appear through occasional increases in spiking synchrony within local groups of cortical neurons [132]. It was shown that even local synaptic connectivity may explain long-range synchrony of gamma oscillations [133].

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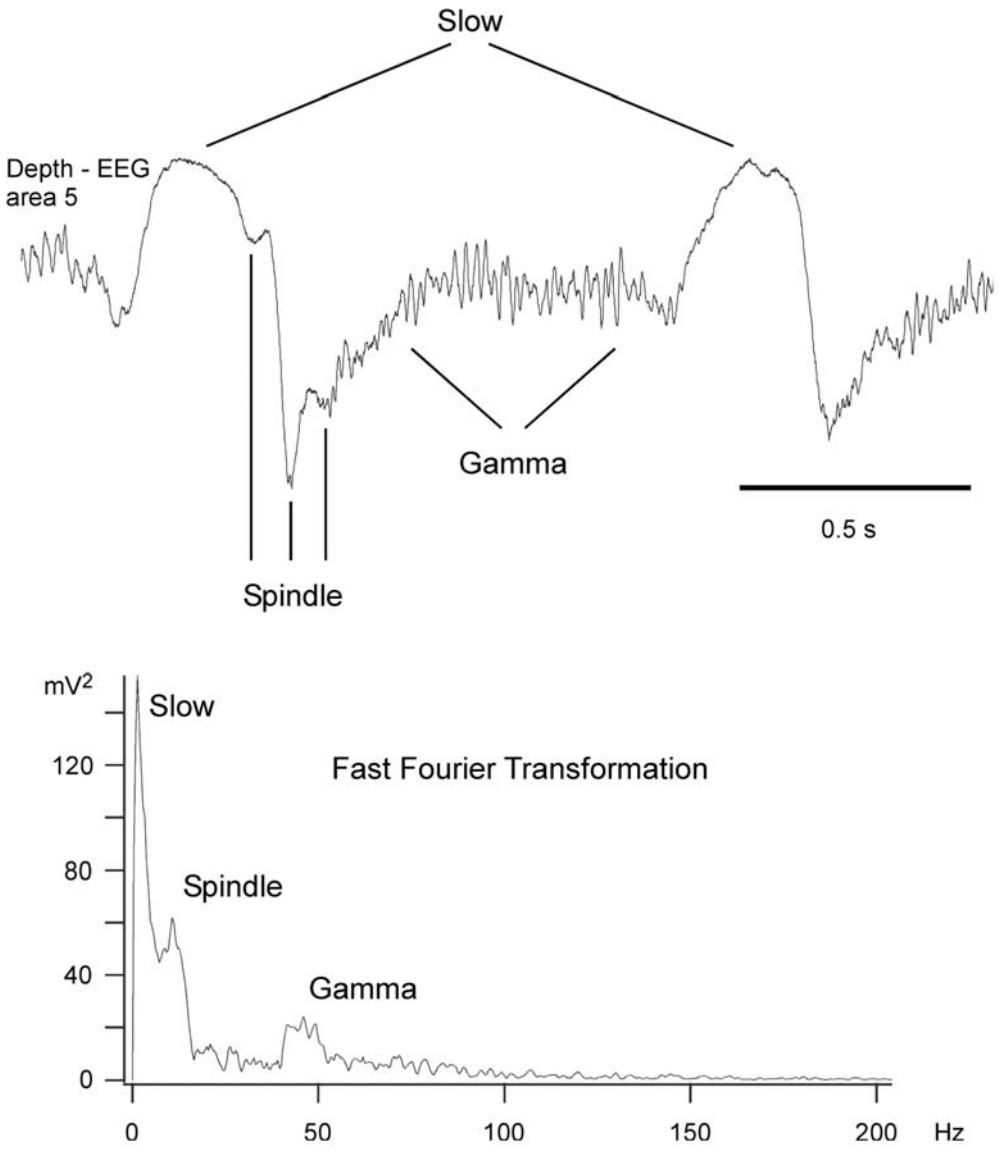

Figure 4. Gamma oscillation is an important component of slow oscillation of sleep

Depth- EEG recoding from area 5. Slow oscillation, spindles and gamma activities are indicated. Below, Fast Fourier Transformation of the recoding shown above. (Modified from [53]).

During waking, gamma activity is associated with attentiveness [134,135], focused arousal [136], sensory perception [137], movement [138,139] and prediction [140]. It has been proposed that synchronization in the gamma frequency range is related to cognitive processing and is important for temporal binding of sensory stimuli [18,141,142]. Gamma activity with low levels of coherence is present within active phases of slow-wave sleep [62,64,143,144]. However, the role of this activity is unknown. During REM sleep, highly coherent gamma activity [143] may contribute to the generation of dreams.

f Ripples

Fast oscillations (>100 Hz), termed ripples, were initially described in CA1 hippocampal area and perirhinal cortex, where they were associated with bursts of sharp potentials during anesthesia, behavioral immobility, and natural sleep [145–149]. In the neocortex, fast oscillations

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(>200 Hz, up to 600 Hz) have been found in sensory-evoked potentials in the rat barrel cortex [150,151], during high-voltage spike-and-wave patterns [152]. The neocortical network seems to be sufficient for the generation of ripples, as demonstrated using isolated cortical slab preparations [153]. In addition to active inhibition [149,153], the electrical coupling mediated by gap junctions contributes to ripple synchronization [154–156]. The electrical coupling may occur between axons of principal cells [157] as well as via a network of inhibitory interneurons [10,34,35,158,159]. Since ripples are also recorded in glial cells, the electrical coupling between gial cells could also play a role in the synchronization of ripples [155]. The field potentials increase neuronal excitability, and by a positive feedback loop they could also be involved in the generation of neocortical ripples [160]. In non-anesthetized brain the highest amplitude of ripples in neocortex occurs during active phases of slow-wave sleep, it is lower during both REM sleep and waking state, and it reaches lowest values during silent phases of slow-wave sleep [153].

Neocortical ripples are generated during large amplitude spontaneous or evoked field potential deflections. These ample changes in the field potential are associated with synchronous activity of many neurons. This suggests that ripples may "alarm" the brain network about the presence of a large firing neuronal constellation. The danger of such a focal synchronous excitation of a neuronal pool is that it may overcome a certain threshold of excitability, leading to the onset of seizures [155,160].

Short- and Long-Range Synchrony during Experimental Epilepsy

Cortically generated electrographic seizures arise without discontinuity from sleep oscillations [161]. These seizures are accompanied by the generation of large amplitude field potentials, suggesting the presence of enhanced local synchrony [161] and are characterized by spike-wave (SW) or spike-wave/polyspike-wave (SW/PSW) complexes at 1–2.5 Hz, intermingled with episodes of fast runs at ~7–16 Hz [162–165]. The evolvement of these seizures from the cortically generated slow oscillations may be shaped by the thalamus [81,163,166–169]. The electrographic pattern of SW/PSW seizures as well as their occurrence during slow-wave sleep resembles the seizures accompanying the Lennox-Gastaut syndrome in humans [170–173].

These seizures could be classified as primarily focal and secondarily generalized (see Figure 3 in [174]); visual inspection suggests that on most occasions they start and stop almost simultaneously in all recorded areas. Precise measurements of synchrony during SW/PSW seizures suggest that long-range synchrony recorded on a wave-by-wave basis is rather loose [161,168,174,175]. The coefficient of correlation of field potentials recorded during SW complexes fluctuates between 0.3 and 0.8 [176]. However, the field potentials recorded during these seizures are of large amplitude, often exceeding the amplitude of slow waves recorded during natural slow-wave sleep [176] or during anesthesia-induced slow oscillation [161,163], suggesting existence of high local synchrony. Within the fast runs, the patterns of synchronization recorded in different electrodes are as follows: (i) synchronous, in phase, (ii) synchronous, with phase shift, (iii) patchy, repeated in phase/phase shift transitions and (iv) non-synchronous, with slightly different frequencies in different recording sites or absence of oscillatory activity in one of the recording sites; the synchronous patterns (in phase or with phase shifts) were most common [174]. All these patterns could be recorded in the same pair of electrodes during different seizures or even during different periods of fast runs within the same seizure. An example of such recording is shown in the figure 5. Here, during the first period of fast runs, which started and terminated almost simultaneously at both the intracellular and the EEG levels, the field potential and the neuron recorded 2 mm apart oscillated with different frequencies, and thus there was no synchronization. During the next period of fast

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run, both the neuron and the field potential signal oscillated in perfect synchrony, and the neuron fired constantly during the descending phase of the field potential deflection.

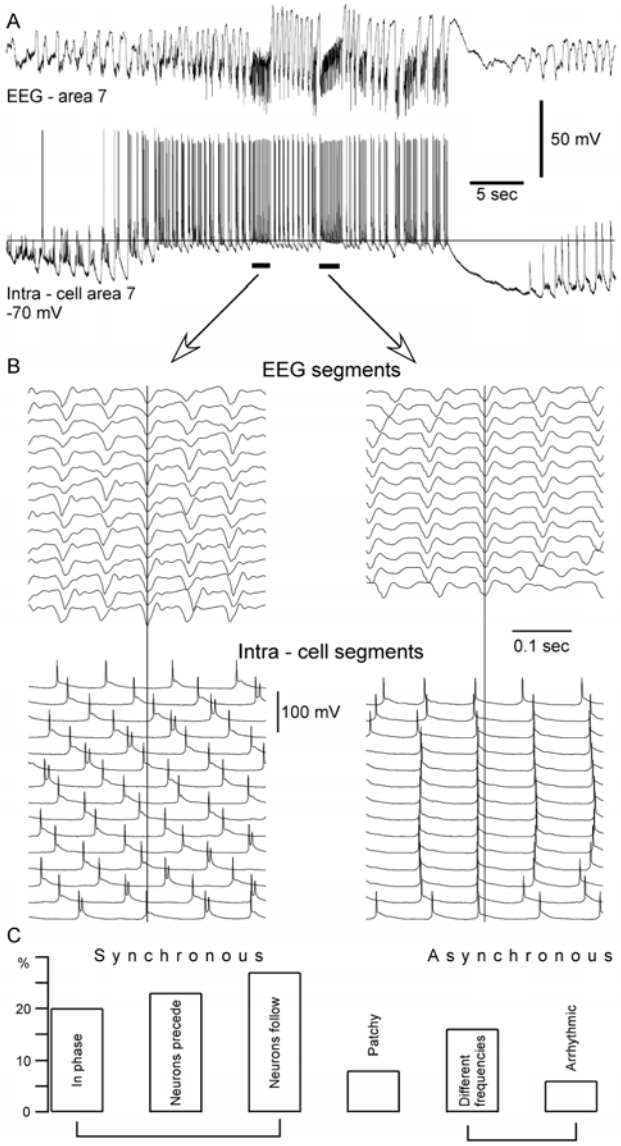

Figure 5. Variability in neuron – field synchronization during fast runs

A. Depth-EEG and simultaneous intracellular recordings during an electrographic seizure. The distance between field potential electrode and the intracellularly recorded neuron was 2 mm. B. A superposition of field potential (upper panels) and intracellular recordings (lower panels) during fast runs for the two consecutive periods of fast runs. Note the different frequencies of oscillations in the EEG and intracellularly recorded neuron during the first period and in phase synchronization during the second period. C. The distribution of patterns of synchronization for 312 periods of fast runs. The coherent patterns (0 time lag or with phase shift) constituted 70 % of the cases. "Arrhythmic" stands for periods of fast runs recorded at one electrode, while the activity in another electrode was not rhythmic (adapted from [174]).

Why is the local synchrony during seizures enhanced as indicated by large amplitude field potentials, and why is the long-range synchrony impaired, as shown by a variety of synchrony patterns (Figure 5)? We propose the following scenario that explains both enhanced local and decreased long-range synchrony. Seizures are associated with activation of a large variety of neuronal currents [161],[177]. During seizures, the extracellular levels of K^+ increase, and the

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extracellular levels of Ca^{2+} decrease. While diffusion potentially reduces ion gradients in the extracellular space, a limited diffusion rate, further reduced by cell swelling during seizure, allows formation of local areas of "abnormal" ion concentrations. These changes are commonly found in different structures, including neocortex and hippocampus, and in both *in vivo* and *in vitro* recordings [44,47,178,179]. The changes in extracellular concentration of K^+ and Ca^{2+} occur simultaneously [47,180,181]. Low levels of extracellular levels of Ca^{2+} significantly dampen synaptic transmission [8,182]. Thus, chemical synaptic transmission cannot play a leading role in synaptic interactions during seizures. In addition, our recent data show that in high (12 mM) extracellular K^+ conditions, the action potential generation is impaired and action potentials fail to propagate via axons (Figure 6), probably due to a depolarizing block and decreased input resistance [49]. Therefore, action potentials do not reach target structures. All these factors lead to an impairment of long-range synchronization during seizures because the neurotransmitter mediating these interactions is not released. On the other hand, low Ca^{2+} conditions could favor local synchronization via gap junctions. Indeed, when extracellular levels of Ca^{2+} drops to 1 mM and lower, as it is observed during seizures, the hemichannels that form gap junctions remain open [43], while they are half closed at physiological Ca^{2+} conditions (1.2 mM). This strengthens electrical coupling between glial cells [183] and cortical interneurons [34,35] that mediate local synchrony. Furthermore, elevated extracellular levels of K^+ enhances cell excitability and promotes bursting activity [17,50,184] that is transmitted better through gap junctions than single action potentials. Potentially, electrical coupling between axons of pyramidal cells [37] could also contribute to local synchronization, although the major type of activities recorded in axons are action potentials, which could not be efficiently transferred via gap junctions, because they constitute a low pass filter. Accordingly, the use of halothane, a gap junction blocker, effectively blocks seizure generation [155].

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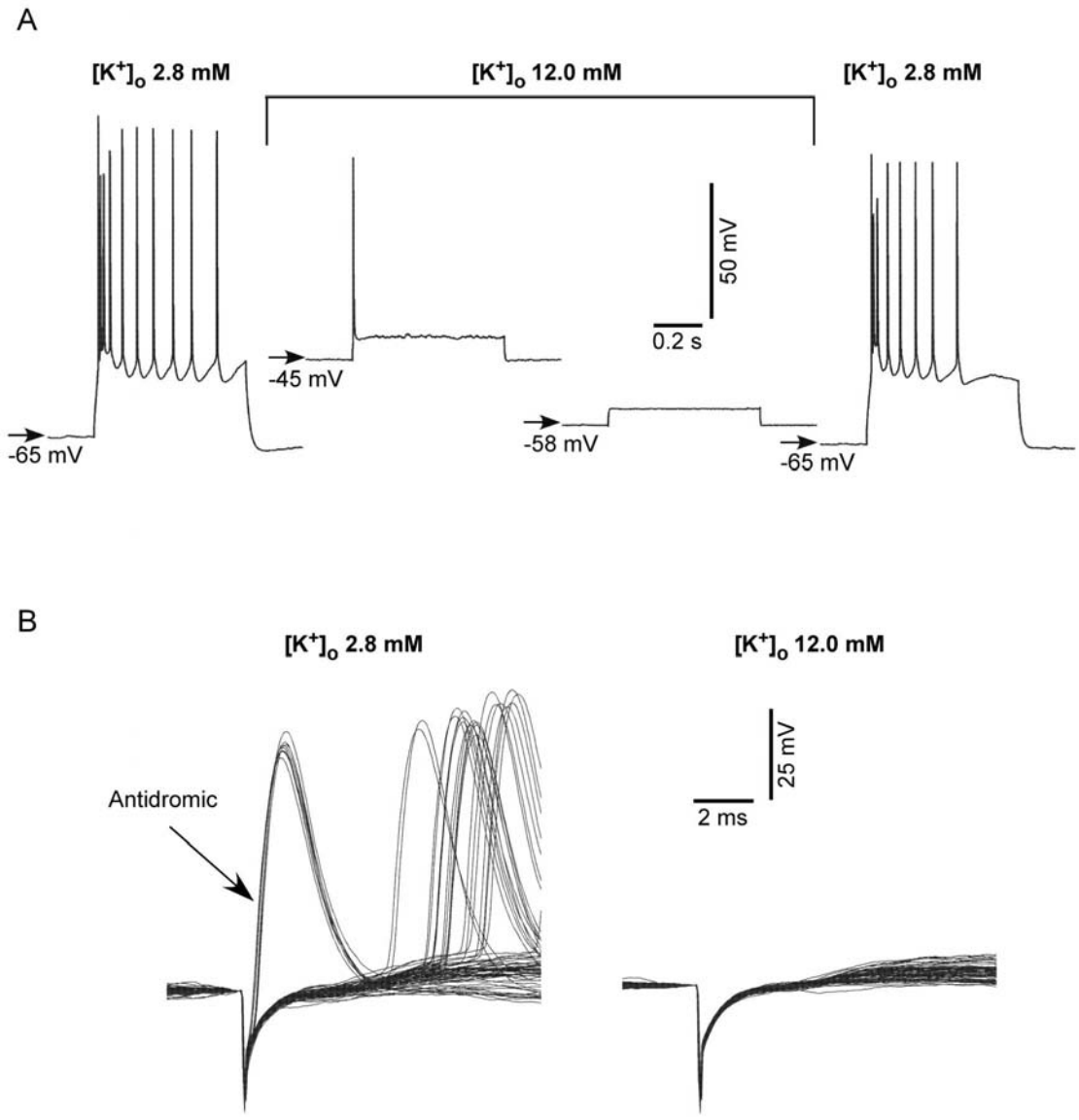

Figure 6. High K^+ concentration impairs generation of action potentials in neocortical neurons

A. Responses of a cortical neuron to depolarizing current pulses in control (2.8 mM) and 'paroxysmal' (12 mM) K^+ conditions. When 12 mM K^+ was used the neuron became depolarized and generated maximum one spike in response to intracellularly applied current pulse. When the membrane potential was returned close to control values (−58 mV) by injection of a negative holding current, action potentials were not generated. B. Electrical stimulation of neighboring cortical tissue induced antidromic and orthodromic responses in recorded neurons. Both anti- and orthodromic spikes were abolished when 12 mM K^+ was used,. (Seigneur, Timofeev, unpublished observations).

Hence, the decrease in extracellular levels of Ca^{2+} and the increase in extracellular levels of K^+ to those concentrations that occur during seizures, significantly impair long-range neuronal synchronization, due to a decrease in neuronal firing ability and a diminution of transmitter release. However, the same changes may increase local synchrony, mediated via gap junctions and possibly ephaptic interactions.

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CONCLUSIONS

We propose that neocortical synchronization can be achieved via intracortical and thalamocortical mechanisms. Four leading mechanisms of synchronization play a distinct and important role: (i) chemical synaptic transmission, (ii) electrical coupling, (iii) ephaptic interactions and (iv) activity-dependent changes in ionic concentrations. Major types of cortical rhythmic activities (slow oscillation, delta, spindles, beta-gamma, ripples, paroxysmal spike-waves and fast runs) are generated using these mechanisms. It is difficult, however, to identify the exact contribution of each mechanism to a specific type of oscillation. It is clear that long-range synchronization is achieved using chemical synaptic interactions. Due to the low-pass filtering properties of gap junctions, electrical coupling should play a smaller role in synchronization of fast rhythmic activities as compared to slower activities. Nevertheless gamma rhythm depends on activity of interneurons, which are known to be interconnected via gap junctions; therefore, gap junctions should play a critical role in the generation of these oscillations. Weak electrical fields in the EEG range synchronize effectively cortical activities at low, but not at high frequencies. Finally, activity-dependent ionic changes may influence local synchronization by modulating neuronal excitability; however, since ionic changes also affect synaptic transmitter release, this could result in impairment of long-rage synchrony.

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