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Chapter 1

MECHANISMS AND BIOLOGICAL ROLE OF THALAMOCORTICAL OSCILLATIONS

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Abstract

Oscillatory activity is an emerging property of thalamocortical system. The patterns and the dominant frequencies of these oscillations 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), fast (20-60 Hz) and ultra-fast (100-600 Hz) activities. The fast and ultra-fast activities may be present in various states of vigilance and frequently coexist with slower rhythms. Pathological oscillations within thalamocortical system take place in a form of electrographic seizures. Thus, the same neuronal network in different conditions generates diverse forms of oscillation. Each oscillation is generated by a particular set of intrinsic neuronal currents, synaptic interactions and extracellular factors. Little is known about the functional role of oscillations. Slow activities whereas normal, during sleep or due to anesthesia or paroxysmal are usually associated with the lost of conscious perception. A number of recent studies suggest that sleep slow brain rhythms mediate the processes of synaptic plasticity and thus could contribute to the memory formation. Faster oscillatory activities are associated with cognitive processes and are involved in the transmission of information in thalamocortical pathways. This chapter will provide: (a) a brief description of thalamocortical network architecture, (b) a brief description of intrinsic and synaptic neuronal currents contributing to the generation of oscillations in thalamocortical system, (c) a classification, description and mechanisms of oscillations generated within thalamocortical system, (d) a functional role of various oscillations generated in thalamocortical system.

1 Architecture of Thalamocortical Network

The thalamocortical (TC) network is a site of generation of different types of oscillatory activities with distinct mechanisms. The general architecture of TC network is organized in a

loop as follows. The main gateway of TC system is dorsal thalamus, which receives specific inputs from ascending sensory pathways (medial lemniscus, optic tract, brachium of the interior colliculus and brachum conjuctivum etc.) and from the brainstem modulatory systems (cholinergic, norepinephrinergic, serotoninergic etc.) reviewed in (Steriade et al. 1997). The general organization of TC system is shown in the Fig. 1. The TC neurons send their glutamatergic axons to the cerebral cortex and the reticular (RE) thalamic nucleus. The axons of TC neurons terminate in the middle layers of neocortex (primarily layer IV), but some branches of axons ascending from associative and nonspecific nuclei of dorsal thalamus may terminate in layers I and VI (Steriade et al. 1997). In the visual system of cats the synapses of TC neurons form approximately 5-6 % of the total number of synapses on layer IV neurons (Ahmed et al. 1994; Peters and Payne 1993). The sources of afferents to the RE thalamic nucleus are the collaterals of TC and corticothalamic fibers (Fig. 1) and brainstem modulatory systems (Jones 1985). Both, the TC and corticothalamic fibers are glutamatergic and thus excitatory. Amplitudes of excitatory postsynaptic conductances evoked in RE neurons by minimal stimulation of corticothalamic fibers are 2.4 times larger than in relay neurons, and quantal size of RE excitatory postsynaptic conductances is 2.6 times greater. GluR4-receptor subunits labeled at corticothalamic synapses on RE neurons outnumbered those on relay cells by 3.7 times (Golshani et al. 2001). Thus, the excitatory influence of corticothalmic fibers on RE neurons is much larger than their influence on TC neurons. All the neurons within the RE thalamic nucleus are GABAergic (Houser et al. 1980; Oertel et al. 1983). The axons arising from RE neurons, after giving off one or two collaterals in the nucleus enter the underlying dorsal thalamus and terminate (Liu et al. 1995; Scheibel and Scheibel 1966; Yen et al. 1985). The main axons of RE thalamic cells ramified in the thalamus, and in the ventrobasal nucleus of thalamus they form three branching patterns cluster, intermediate, and diffuse (Cox et al. 1996). A distinct feature of RE intranuclear connections is the presence of gap junctions, which couple electrotonically RE neurons (Fuentealba et al. 2004d; Landisman et al. 2002).

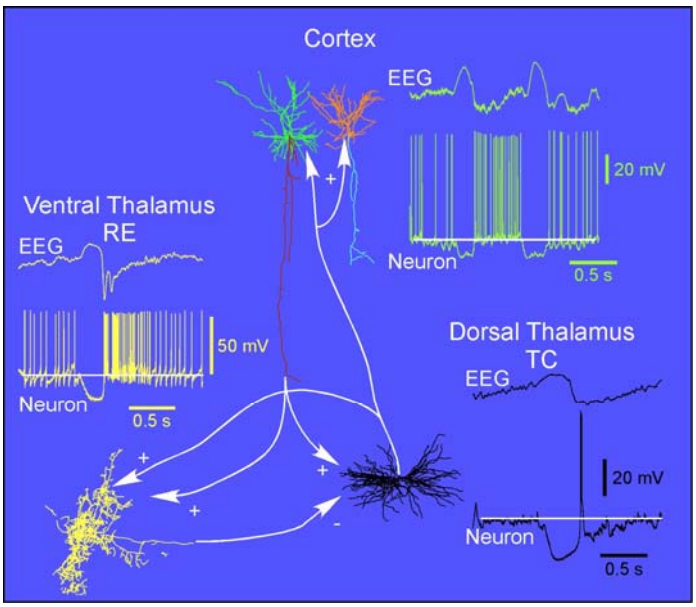

Figure 1. Thalamocortical architecture and main patterns of neuronal activities during slow oscillation.

The neurons are stained intracellularly with neurobiotin in anesthetized cats. The direction of their axons is indicated by arrows. Cortical layer III pyramidal neuron and its intrcellular activity during natural slow-wave sleep are shown in green. During depth-positivity the neuron reveals a long-lasting hyperpolarizingpotential. Cortical layer III interneuron is shown in orange. RE thalamic neuron from rostrolateral sector and its activity in ketamine-xylazine anesthetized cat are shown in yellow. Similarly to cortical neurons the neurons from RE nucleus are hyperpolarized during field depth-positivity. At the onset of depth-negative field potential they reveal high-frequency spike-bursts. TC neuron from VPL nucleus and its activity in ketamine-xylazine anesthetized cat are shown in black. During field-depth positivity TC neurons are hyperpolarized. At the transition to the field depth-negative potentials, TC neurons may generate rebound spike-burst and the TC neurons are hyperpolarized and often reveal spindle sequences during field depth-negative potential being a subject of strong inhibitory influences from RE neurons (I.Timofeev, M. Rosanova, unpublished).

Despite a large complexity, neocortex has stereotyped organization. One of examples of spatial stereotypy are the layering of neurons in the neocortex and the specific distributions of different cell types across neocortical layers and areas (White 1989). The other example is the vertical column organization (Mountcastle 1997). Recent publication point also to the stereotyped organization of cortical microcircuits (Kozloski et al. 2001; Silberberg et al. 2002). The major local functional intracortical synaptic pathways start from layer IV, ascend to layers II-III and than descend to layers V-VI (Contreras and Llinas 2001; Thomson and Bannister 2003).

The synaptic connectivity in the neocortex is very dense. Each pyramidal cell receives 5000 to 60000 synapses (Cragg 1967; DeFelipe and Farinas 1992; Mountcastle 1998; Somogyi et al. 1998). Local-circuit synapses have been estimated to account for as many as 70 % of the synapses present in some areas of the cortex (Gruner et al. 1974; Szentagothai 1965) and pyramidal cells constitute 70-80 % of the total number of neocortical neurons (DeFelipe and Farinas 1992). Most of inhibitory synapses are located in the perisomatic region and most of excitatory synapses are located on dendrites and dendrites spines (DeFelipe and Farinas 1992). According to the cable theory of neuron (Rall 1977), synapses that are located closer to the place of generation of action potential (axon hillock in most of the cases, but in some occasions dendritic triggering zones) have a stronger influence on action potential generation than synapses located remotely. However, the influence of remotely connected synapses on the generation of action potentials might be significantly facilitated by a variety of dendritic intrinsic currents (Amitai et al. 1993; Benardo et al. 1982; Crill 1996; Huguenard 1996; Larkum and Zhu 2002; Llinás 1988; Magee and Johnston 1995; Pape 1996; Schwindt and Crill 1995; Spencer and Kandel 1961; Turner et al. 1991; Wong et al. 1979) and simultaneous or close time-related activation of several synapses (Azouz and Gray 2000; Markram et al. 1997a; Palva et al. 2000; Stuart and Hausser 2001; Wang et al. 2000). Shunting effects of network activities on cortical neurons (Borg-Graham et al. 1998; Hirsch et al. 1998) and in particular on their dendrites might significantly influence the expression of the abovementioned phenomena. In addition to thalamic inputs (see above), corpus callosum neurons, connecting two hemispheres of the cerebrum, provide inputs to neocortical areas. These neurons are located mainly in cortical layers II/III but also in infragranular layers, among them layer V, in different neocortical areas (Barbaresi et al. 1989; Barbaresi et al. 1994; Cisse et al. 2003; Porter and White 1986). The other inputs to a given cortical area come from ipsilateral cortical fields. A given intracortical excitatory presynaptic axon forms from one to eight synaptic contacts with postsynaptic neurons (Krimer and

Goldman-Rakic 2001; Markram et al. 1997b) that elicit excitatory postsynaptic potentials from 0.1 to 10 mV, with a total mean of about 1 mV (Buhl et al. 1997; Feldmeyer et al. 1999; Krimer and Goldman-Rakic 2001; Markram et al. 1997b; Thomson et al. 1995). Similarly to RE neurons, inhibitory interneuronal networks in the neocortex are coupled via electrotonic synapses (Galarreta and Hestrin 1999; Gibson et al. 1999).

2 A Description of Intrinsic Firing Patterns and Underlying Currents in Thalamocortical System

The intrinsic properties of a neuron depend on unique set of ionic channels, specific to a given neuron and on their distribution in different compartments of the neuron. The diversity of channels in neurons is large and results in a variety of patterns of action potential generation induced by a constant input.

2.1 Thalamocortical Neurons

TC neurons posses a large set of intrinsic currents that enable them to contribute to the various oscillatory activities and/or mediated some of them. The electrophysiological identification of a TC neuron is shown in Fig. 2. Usually, a small depolarization of TC neurons with intracellular DC current pulses produces passive response (not shown). Progressive increase in the intensity of the depolarizing current leads to the generation of action potentials followed by increase in their discharge frequency (Fig. 2, left). The enhancement of depolarization in TC neurons over the stimulus duration is probably generated by persistent Na^+ current, I_{NaP} (Jahnsen and Llinás 1984b; Parri and Crunelli 1998). This firing mode of TC neurons is called tonic. Each fast spike produced by TC neuron is followed by an afterhyperpolarizing potential (AHP). Neuronal firing is associated with Ca^{2+} influx (Abel et al. 2004; Markram et al. 1995). Rise of intracellular Ca^{2+} concentration during tonic spiking activates Ca^{2+} activated K^+ currents ($I_{K(Ca)}$) that produces afterhyperpolarizing potential (AHP) (Sah and Louise Faber 2002; Storm 1987). At the offset of the depolarizing current pulse most TC neurons generate a medium or slow afterhyperpolarizing potential (Fig. 2, left). Application of low-amplitude hyperpolarizing current pulse results in passive responses (not shown). An increase in the pulse amplitude hyperpolarizes the TC neuron to a level of activation of hyperpolarization-activated cation current, I_h, that produces depolarizing sag (McCormick and Pape 1990; Pape 1996). At the offset of the hyperpolarizing current pulse, the TC neuron generates a depolarizing response, commonly called LTS for low-threshold spike, that is generated due to the inactivation of low-threshold Ca^{2+} current, I_T, (Hernandez-Cruz and Pape 1989; Huguenard 1996; Jahnsen and Llinás 1984a, b; Tarasenko et al. 1997). Recent study suggests that the LTS also contains a component mediated by I_{NaP} (Parri and Crunelli 1998). This type of response is called bursting mode of firing. An increase in the amplitude of the hyperpolarizing current pulse produces an increase in both the depolarizing sag and the rebound excitation that leads to a burst of Na^+ spikes (up to eight spikes in the experiment shown in Fig. 2). Both spontaneous and evoked LTSs of TC neurons reveal gradual properties (Timofeev et al. 2001b). Thus, both excitatory and inhibitory inputs are able to induce firing of TC neurons. Excitatory inputs lead a generation of firing in a tonic

firing mode, while LTSs are generated at the end of inhibitory responses and TC neurons fire in the bursting mode. Some studies report the presence of electrical coupling between TC neurons (Hughes et al. 2002a).

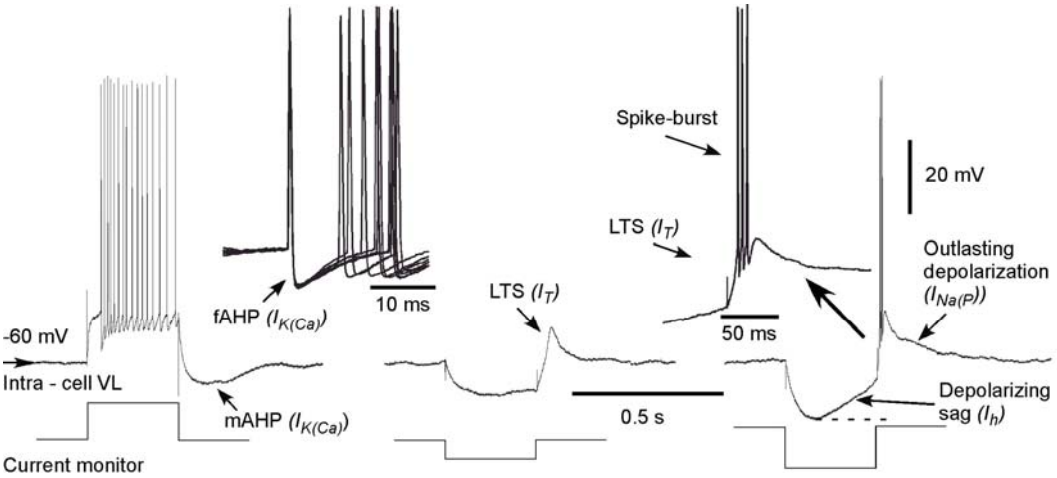

Figure 2. Intrinsic electrophysiological properties of thalamocortical neurons.

Barbiturate anesthesia. The membrane potential for this neuron was -60 mV. Depolarizing current pulse elicited tonic firing (Left). Each action potential was followed by fast AHP (fAHP). At the end of the current pulse a long-lasting AHP (mAHP) was generated. At the end of small amplitude hyperpolarizing current pulse the neuron generated a low-threshold spike (LTS) in isolation (Middle). During large amplitude hyperpolarizing current pulse (Right) depolarizing sag was obvious. At the end of the current pulse the neuron generated an LTS accompanied with spike-burst. (I.Timofeev, unpublished).

2.2 Reticular Thalamic Neurons

Electrophysiological properties of RE neurons have some similarities with those of TC neurons, which consist in the bursting and tonic discharge modes present in both of them. The bursting mode is exhibited during EEG-synchronized sleep, while tonic discharge is detected during waking and rapid eye movement sleep (Mukhametov et al. 1970; Steriade and Wyzinski 1972; Steriade et al. 1986). These two firing modes depend on the membrane potential of the cell (Bal and McCormick 1993; Contreras et al. 1992; Gentet and Ulrich 2003). At depolarizing membrane potential (positive to -65 mV), intracellular injection of positive current pulse induces train of action potentials. In contrast, intracellular injection of the same current pulse at hyperpolarized membrane potential (negative to -65 mV) reslts in the generation of high frequency (300-500 Hz) bursts of action potentials (Bal and McCormick 1993; Contreras et al. 1993). Similar firing patterns could be found during spontaneous activity. Much like TC neurons, when the RE neuron is depolarized, it fires spikes in tonic mode, and when it is hyperpolarized, it fires spikes in bursting mode (Fig. 1, left). A subgroup (about 30%) of neurons reveals the presence of prolonged hyperpolarizing potentials preceding spindles in RE neurons, which facilitated occurrence of bursts (Fuentealba et al. 2004a). The high-frequency bursts in RE neurons are generated through the activation of low-threshold Ca^{2+} current (I_T) (Avanzini et al. 1989; Huguenard and Prince

1992). *In vitro*, an intracellular injection of negative current pulse is typically followed by the generation of rebound LTS and burst of action potentials (Avanzini et al. 1989). Following this LTS, an AHP hyperpolarizes RE neuron and a second LTS is generated as a rebound on this hyperpolarization (Bal and McCormick 1993). Such activity could be maintained for several cycles with frequencies reaching 12 Hz. The low threshold spikes in RE neurons are gradual in nature (Brunton and Charpak 1998; Destexhe et al. 1996b). Current-clamp intracellular recordings of RE neurons in cats under barbiturate anesthesia revealed the presence of membrane bistability in ~20% of neurons. Bistability consisted of two alternate membrane potentials, separated by ~17-20 mV. While non-bistable (common) RE neurons fire rhythmic spike-bursts during spindles, bistable RE neurons fire tonically, with burst modulation, throughout spindle sequences. Bistability is strongly voltage dependent and only expressed under resting conditions (Fuentealba et al. 2005).

2.3 Neocortical Neurons

Neocortical neurons reveal at least four distinct electrophysiological types (see Fig. 3): (a) regular-spiking (RS), (b) intrinsically-bursting (IB), (c) fast-rhythmic-bursting (FRB) and (d) fast-spiking (FS, Fig. 3) (Connors and Gutnick 1990; Gray and McCormick 1996; McCormick et al. 1985; Steriade et al. 1998a). Neurons belonging to different neuronal classes do not have preferential anatomical distribution and can be found in different layers of neocortex (Timofeev et al. 2000b).

The RS neurons, when depolarized with intracellularly applied steady current pulses, could not maintain steady output frequency and fire with spike-frequency adaptation. The mean duration of action potentials of RS neurons in awake cats is about 0.6 ms (Steriade et al. 2001). RS cells are further classified as slow- and fast-adapting according to the adaptation of spike frequency during long-lasting depolarizing current pulses. RS, slow-adapting neurons (Fig. 3 left) exhibit a monophasic AHP or a biphasic AHP with fast and medium components (fAHP, mAHP). Slow-adapting behavior was observed in about 80% of the RS cells. RS, fast-adapting cells (not shown) only fire a train of spikes at the beginning of the intracellularly applied current pulse. Thereafter, the membrane potential remains as a depolarizing plateau crowned by occasional spikes. These neurons show a monophasic AHP only.

IB neurons respond to depolarizing inputs with high frequency spike-bursts. Each action potential of IB neurons is followed by a marked depolarizing afterpotential. The first interspike interval in the burst is usually longer than the other intervals. Roughly, at least two types of IB neurons could be identified. The neurons belonging to the first type generate a single burst, which follows by single spikes similar to RS neurons. The neurons belonging to the second IB class would generate repeated bursts as shown in the figure 3. *In vivo*, the intraburst frequency is between 4 and 10 Hz (Nuñez et al. 1993). The mean duration of action potentials of IB neurons in awake cats is 0.55 ms (Steriade et al. 2001).

The FRB neurons display fast (300-600 Hz), rhythmic (20-50 Hz) spike-bursts at a given levels of depolarization. Below that level they exhibit RS firing patterns and above it they discharge like FS neurons (Steriade et al. 1998a). While some FRB neurons are pyramids located in layers II/III (Gray and McCormick 1996), the other FRB neurons belong to different groups. Some of them were identified as deeply lying corticothalamic cells, as shown by their antidromic activation from the thalamus, and the other FRB neurons were

intracellularly stained and found to be local-circuit, sparsely spiny or aspiny, presumably inhibitory neurons (Steriade et al. 1998a). The mean duration of action potentials of FRB neurons in awake cats is 0.3 ms (Steriade et al. 2001).

The FS neurons fire high frequency spike trains without spike frequency adaptation (Fig. 3). This is the only type of neurons that has linear input output relationship (injected current vs. firing frequency). Morphologically, all fast spiking neurons are aspiny interneurons, and thus, they are inhibitory GABAergic neurons (Connors and Gutnick 1990). However, not all inhibitory interneurons are FS. Generally, the classification of intrinsic firing patterns of inhibitory interneurons is complex and could contain 3 classes (non-accommodating, accommodating and stuttering) and 8 subclasses (Gupta et al. 2000). Intrinsic properties of neurons influence not only their response patterns to steady inputs, but also to sinusoidal ones (Brumberg 2002). Only the FS (inhibitory) neurons are able to transmit signals to postsynaptic cells with linear dependency, whereas the other neuronal classes would modify the input activities. The IB and presumably the FRB neurons via their propensity to burst responses could amplify the input signals (Timofeev et al. 2000c) or at least could make more reliable the synaptic transmission (Lisman 1997). Due to their intrinsic properties these cellular types (IB and FRB) might also induce the network oscillations at their intrinsic frequencies (7-10 and 20-50 Hz, respectively). By contrast, RS neurons should diminish the input signal, due to their property of spike frequency adaptation.

The intrinsic patterns of neuronal discharges are not fixed and could be modified by a variety of factors. An intracellular injection of depolarizing current transforms intrinsically-bursting firing pattern to RS one (Timofeev et al. 2000c; Wang and McCormick 1993). Similar effect was observed after the bath application of acetylcholine to neocortical slices maintained *in vitro* (Wang and McCormick 1993), the brain activation induced by stimulation of mesopontine cholinergic nuclei (Steriade et al. 1993d) or by transition from the natural slow-wave sleep to REM sleep (Steriade et al. 2001). Even in the absence of activity in cholinergic structures, the network activity, likely due to its depolarizing effects, decreases the incidence of IB neurons. The occurrence of cortical intrinsically-bursting neurons is much higher (up to 40-60%) in cortical slices (Yang et al. 1996) or cortical slabs *in vivo* (Timofeev et al. 2000c) than in the anesthetized animals (10 %) (Nuñez et al. 1993) and it decreases to 4% in neocortex of waking cats (Steriade et al. 2001). The increase in extracellular K^+ concentration, $[K^+]_o$, may convert firing patterns of RS-type neurons to the intrinsically-bursting one (Jensen and Yaari 1997; Jensen et al. 1994). In recent study we have shown that either the presence of spontaneous activity or lowering of extracellular Ca^{2+} concentration, $[Ca^{2+}]_o$, may convert firing patterns of some RS neurons to the bursting response (Boucetta et al. 2003).

The FRB neurons are found mainly *in vivo* (Gray and McCormick 1996; Steriade et al. 2001; Steriade et al. 1998a). In slices maintained *in vitro*, FRB-type firing pattern could be induced either by prolonged intracellular stimulation (Kang and Kayano 1994) or by the use of modified artificial cerebrospinal fluid, which contained physiological levels of $[Ca^{2+}]_o$ (Brumberg et al. 2000). The strong AHP postpones the generation of consecutive spikes, thus preventing the generation of bursts. Since the AHP is generated due to activation of $I_{K(Ca)}$, its amplitude decreases with the decrease in the $[Ca^{2+}]_o$ either due to spontaneous fluctuations of $[Ca^{2+}]_o$ (Crochet et al. 2004; Massimini and Amzica 2001) or due to the artificial changes induced by dialysis 0 Ca^{2+} solution. Thus, the activity dependent changes in firing patterns could be partially ascribed to the changes in $[Ca^{2+}]_o$. Despite the presence of high-threshold

Ca^{2+} spikes in neocortical neurons *in vivo* (Paré and Lang 1998), the bursts in neocortical neurons are not Ca^{2+} dependent (Brumberg et al. 2000; Mantegazza et al. 1998). Only some neocortical neurons generate low-threshold Ca^{2+} spikes mediated by I_T. These neurons may generate Ca^{2+}-dependent bursts as rebound to prolonged hyperpolarizing potentials (de la Peña and Geijo-Barrientos 1996).

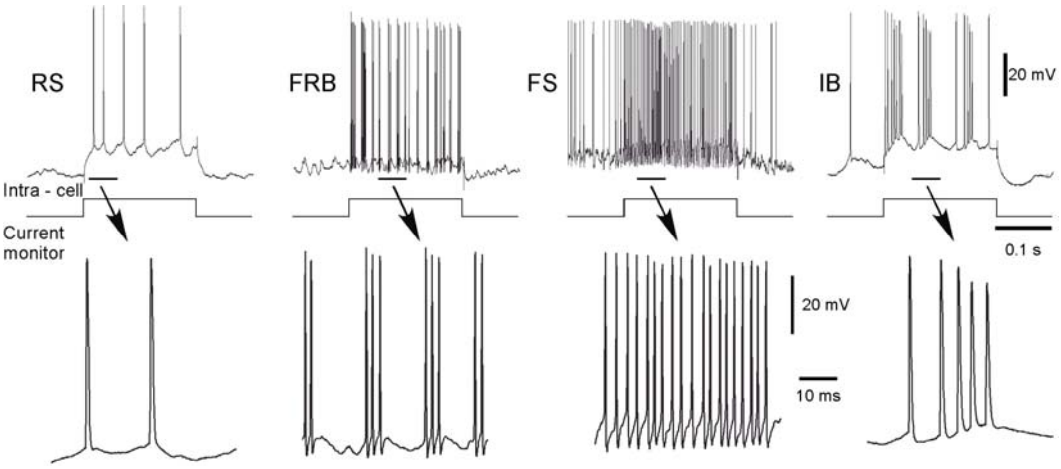

Figure 3. Electrophysiological identification of different cell-classes.

Upper panels depict responses of regular-spiking (RS), fast-rhythmic-bursting (FRB), fast-spiking (FS) and intrinsically-bursting (IB) neurons from area 4 to depolarizing current pulses (0.2 s, 0.8 nA). At bottom of each depolarizing response expanded fragments of each cell classes as indicated by horizontal lines and arrows.

3 Oscillations Generated within Thalamocortical System and their Mechanisms

Various oscillatory rhythms generated in TC system may be divided in two main classes: intrinsic that are generated by a single neuron as a result of interplay between specific intrinsic currents and extrinsic or network that requires interaction in a population of neurons. Typically later means excitatory and/or inhibitory interactions between neurons of the same or different classes. Intrinsic neuronal currents contribute to the generation of network oscillations. Oscillations may be also generated in a population of nonpacemaker neurons coupled though gap junctions. Below, we will describe the major properties and mechanisms of normal (not paroxysmal) oscillations recorded with field potential electrodes form neocortex, independently of their site of origin, during different states of vigilance. The order would be descending based on dominant frequency.

3.1 Infra-slow Oscillation

This is type of oscillatory activities with a period from tens of seconds to a minute range (Aladjalova 1957). Very little is known about the mechanisms of these oscillations. At least

some of the factors responsible for the generation of these oscillations could depend on nonneuronal dynamics, such as changes in CO_2 concentration (Nita et al. 2004). Likely, the infra-slow activities have cortical origin, because they could be recorded from neocortical slabs (Aladjalova 1962).

3.2 Slow Oscillation

While some types of thalamic and cortical oscillations (such as, e.g., thalamic delta (2-3 Hz) and spindle (7-14 Hz) oscillations) are presumably result of interaction of a few intrinsic currents or a few neurons of different types and could be reproduced with a scaled down computer models (see below), there are oscillatory rhythms which are observed only in large enough populations of neurons. An important example of such dynamics is slow-wave sleep (SWS) oscillation, a low-frequency (0.3 - 1 Hz) rhythm, dominating cortical activity during natural sleep and under some types of anesthesia (Steriade et al. 1993a; Steriade et al. 1993c; Steriade et al. 2001; Timofeev et al. 2001a).

Some remarks on terminology

Slow oscillation was originally identified at the cortical level by M. Steriade and his colleagues (Steriade et al. 1993a), who discovered that the de- and hyperpolarizing phases of neuronal activities respectively give rise to EEG depth-negative and EEG depth-positive waves. Later, similar patterns were recorded in neostriatal neurons by Wilson and Kawaguchi 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 (Wilson and Kawaguchi 1996). Cortically generated slow oscillation was also found to entrain the thalamus (Contreras and Steriade 1995; Steriade et al. 1993e; Timofeev and Steriade 1996). Similar to neocortical and neostriatal neurons, both the thalamic reticular and TC neurons are hyperpolarized during depth-positive EEG waves (Fig. 1) due to disfacilitation, i.e. an absence of spontaneous synaptic activities (Contreras et al. 1996a; Steriade et al. 2001; Wilson et al. 1983; Wilson 1986). During depth-negative EEG waves, cortical, neostriatal and inhibitory thalamic reticular neurons are depolarized and fire spikes, while TC neurons are primarily hyperpolarized, reveal rhythmic IPSPs and occasionally fire rebound spike-bursts (Fig. 1) (Contreras and Steriade 1995; Timofeev and Steriade 1996). Thus, in the dorsal thalamus, the intracellular activities occurring during depth-negative EEG waves cannot be characterized as either depolarizing or up state. Here, we use 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 TC network during the slow oscillation.

The survival of slow oscillations after extensive thalamic lesions (Steriade et al. 1993b) and the absence of slow oscillations in the thalamus of decorticated cats (Timofeev et al. 1996) point to an intracortical origin for this rhythm. Single study shows 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 TC neurons *in vitro* with frequencies similar to those observed *in vivo* (Hughes et al. 2002b).

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, TC and RE neurons (Contreras et al. 1996a; Timofeev et al. 1996; Timofeev et al. 2001a). Even a moderate spontaneous hyperpolarization of TC 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 (Bazhenov et al. 1998a; Timofeev et al. 1996). An absolute blockage of information transmission through the thalamus occurs only when prethalamic (lemniscal) stimuli are used (Bazhenov et al. 1998a; Fuentealba et al. 2004c; Timofeev et al. 1996). Responses to peripheral sensory stimuli still may reach cerebral cortex during sleep or anesthesia (Azouz and Gray 1999; Cauller and Kulics 1988; Emerson et al. 1988; Istvan and Zarzecki 1994; Kisley and Gerstein 1999; Massimini et al. 2003; Rosanova and Timofeev 2005; Sachdev et al. 2004; Zhu and Connors 1999), but the precision of cortical network to respond to peripheral volley during disfacilitation periods is lost (Massimini et al. 2003; Rosanova and Timofeev 2005). The spike timing is critical in cortical information processing (Foffani et al. 2004) and a minimal time interval of stable TC activity is required to achieve conscious perceptions (Libet et al. 1967). 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. The transmission of peripheral information to the cerebral cortex during periods of disfacilitation still may occur when peripheral stimuli elicit barrages of EPSPs in TC neurons that trigger LTSs crowned by spike-bursts at hyperpolarized voltages and tonic firing at depolarized voltages (Rosanova and Timofeev 2005). During disfacilitation the membrane potential of cortical neurons is mediated by K^+ currents, primarly leak current (Timofeev et al. 2001a). The long-lasting hyperpolarizations of cortical neurons are absent when brain cholinergic structures are set into action (Metherate and Ashe 1993; Steriade et al. 1993b) or during rapid eye movement (REM) sleep and waking (Fig. 4) (Steriade et al. 2001; Timofeev et al. 2001a).

Human studies have shown that each wave of slow oscillation originates at a definite site, more frequently in prefrontal-orbitofrontal regions and propagate in an anteroposterior direction (Massimini et al. 2004). Different hypotheses suggest different basis mechanisms of the active state generation: (a) spontaneous mediator release in a large population of neurons leading to occasional summation and firing (Timofeev et al. 2000c; Bazhenov et al. 2002), (b) spontaneous intrinsic activity in layer 5 intrinsically bursting neurons (Sanchez-Vives and McCormick 2000) and (c) the selective synchronization of spatially structured neuronal ensembles involving a small number of cells (Cossart et al. 2003).

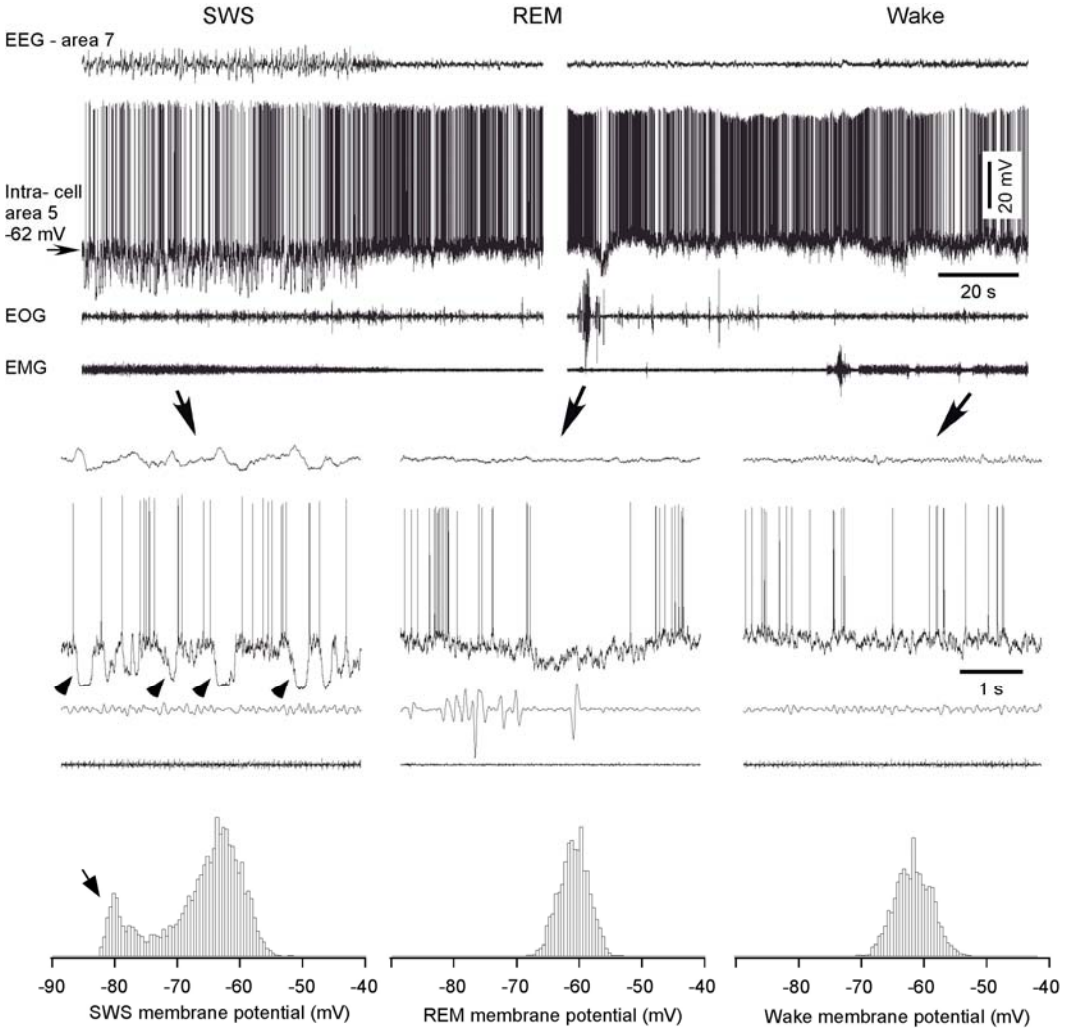

Figure 4. Cortical intracellular correlates of natural slow-wave sleep (SWS), REM sleep and waking states.

The four traces depict (from top to bottom): EEG from area 7, intracellular activity of area 5 RS neuron (membrane potential is indicated, -62 mV), EOG and EMG. High-amplitude and low-frequency field potentials, intracellular cyclic hyperpolarizing potentials and stable muscle tone are distinctive features of SWS. Low-amplitude and high-frequency field potential oscillations, tonic neuronal firing with little fluctuations in the membrane potential, rapid eye movements, and muscle atonia are cardinal features of REM sleep. Low-amplitude and high-frequency field potential oscillations, tonic firing with little fluctuations in the membrane potential, and muscle tone with periodic contractions are characteristics of the waking state. Parts indicated by arrows are expanded below (arrows). Note cyclic hyperpolarizations in SWS (indicated by arrowheads) and diminished firing rate during ocular saccade in REM sleep. The histograms of membrane potential in SWS, REM sleep and wake are illustrated below. Note the bimodal distribution of the membrane potential and the presence of hyperpolarizing mode of membrane potential during SWS (indicated by arrow). Modified from (Timofeev et al. 2001a).

3.2.1 Mechanisms Underlying the Generation of Slow Oscillation in Neocortex

Spontaneous miniature synaptic activities (minis) (Fatt and Katz 1952) are caused by spike-independent release of transmitter vesicles and are regulated at the level of single synapses (Paré et al. 1997; Salin and Prince 1996). Such spike-independent synaptic release occurs during the silent state of the cortical network, for example in slices, in neocortical slabs (Timofeev et al. 2000b; Timofeev et al. 2000c), or during the hyperpolarizing components of slow sleep oscillation. Occasionally, summation of spike-independent minis depolarizes cortical neurons to the level of activation of the persistent Na^+ current (Crill 1996; Stafstrom et al. 1982). This minis dependent depolarization may activate IB neurons whose spikes then trigger synaptic potentials that result in depolarization and spiking of a population of postsynaptic neurons; activity spreads thus triggering onset of an active state. Shunting inhibition (Borg-Graham et al. 1998; Hirsch et al. 1998) and activity dependent increase of failures of synaptic transmission (Crochet et al. 2005) 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 (Thomson 1997), it is unlikely that minis-dependent spontaneous activity would lead to active periods in slices. 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. These patterns were similar to the active states of SWS, but the frequency was low presumably because a relatively small amount of cells was interconnected. Assuming minis-dependent mechanism of active states generation, increasing the size of the isolated cortical tissue to a gyrus should increase the number of sites where activity could arise (Bazhenov et al. 2002; Timofeev et al. 2000c). This would lead to an increased probability of occurrence of the active periods, thus attending frequencies similar to those of the cortical slow oscillation. This hypothesis was tested with the analytical model where the mean and standard deviation of interburst intervals were estimated as a function of number of neurons in a network (Timofeev et al. 2000c) (Fig. 5). For the small slab the estimated mean between active states was about 24±21 sec; this mean decreased with the size of the network and reached 4.9±2.3 sec for a network the size of a gyrus. 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 hypothesis was directly tested using Hodgkin-Huxley based thalamocortical network model (Bazhenov et al. 2002). Based on the analytical model it was estimated that the mini-dependent mechanism can drive periodic network oscillations at frequencies 0.2-0.5 Hz when the network size exceeds ~ 10^8 neurons (Timofeev et al. 2000c). To scale down the network size, in computer simulations the amplitude of miniature events was increased by about 50%. In these conditions the slow periodic oscillations similar to those observed *in vivo* were found (see Fig. 6 in (Bazhenov et al. 2002)). Each active phase was initiated in one of the cortical pyramidal cells and then spread over TC network. While thalamic RE and TC cells were not necessary to maintain slow sleep oscillations in the model, their presence changed spatio-temporal patterns of slow sleep activity.

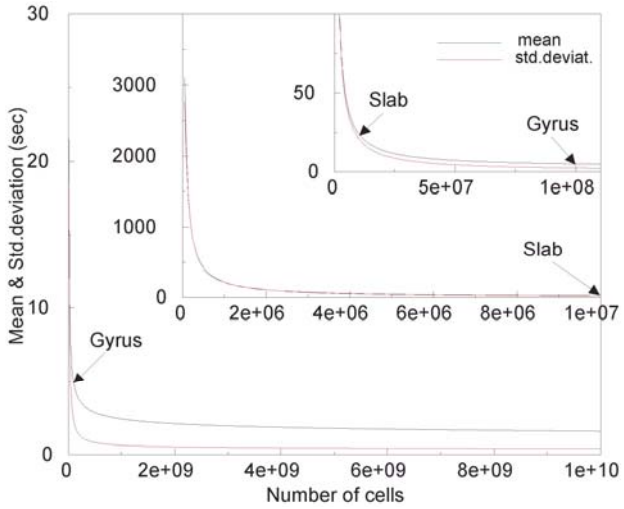

Figure 5. Estimated mean T and standard deviation σ of interburst intervals for networks of different size.

Analytical curves estimated based on *in vivo* data. Estimated mean of interburst intervals for a slab (about 10^7 neurons) is 24 sec (standard deviation is 21 sec) and for a gyrus (about 10^8 neurons) the mean is 4.9 sec (standard deviation 2.3 sec.) [Modified from (Timofeev et al. 2000c)].

The synaptic depression of active synaptic connections (Galarreta and Hestrin 1998; Tsodyks and Markram 1997), the slow inactivation of the persistent Na^+ current (Fleidervish and Gutnick 1996; Fleidervish et al. 1996), the activation of Ca^{2+}-dependent K^+ current (Schwindt et al. 1992), and the activation of Na^+-dependent K^+ current (Schwindt et al. 1989), would displace the membrane potential of neurons from the firing level and the entire network would go to the hyperpolarized or silent state. These observations were confirmed in modelling studies (Bazhenov et al. 2002; Hill and Tononi 2004).

Another possible mechanism for recovery of active states during SWS 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 (Curró Dossi et al. 1992; Leresche et al. 1991; McCormick and Pape 1990; Soltesz et al. 1991). Recently, it was shown using a cortical slice preparations that, in a relatively high concentration (3.5 mM) of extracellular K^+, cortical slices can oscillate in the frequency range of slow sleep oscillations (Sanchez-Vives and McCormick 2000). This activity was usually initiated in layer 5 and propagated over the whole slice. It is not clear, however, how the specific conditions in those slice preparations affected the excitability of cortical neurons and the temporal patterns of their activity. A slight increase in $[K^+]_o$ may depolarize some neurons to the firing threshold (see Fig. 2-3 in (Sanchez-Vives and McCormick 2000)). 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 (Markram et al. 1997b; Thomson and Deuchars 1997). 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 the transitions from down (silent) to up (active) state were initiated by spontaneous spike discharges in a small random group of neurons (Compte et al. 2003). Once started, the up states were maintained by strong recurrent excitation, and the transitions to the down state were due to a slow Na^+-dependent K^+ current. *In vitro* studies indicate that a group of neurons, which could initiate active periods could be either layer 5 IB neurons (Sanchez-Vives and McCormick 2000) or spatially structured neuronal ensembles (Cossart et al. 2003).

The transition from slow-wave sleep to activated states depends on the increase in the activity of neuromodulatory systems (Steriade and McCarley 1990). The level of acetylcholine is increased in both REM sleep and waking, whereas the level of noradrenaline and serotonin is increased only during waking (Steriade et al. 1997). The increase in the level of activity of neuromodulatory systems leads to significant increase in the input resistance of neurons (Steriade et al. 2000). *In vitro* data revealed that increase in the input resistance of cortical neurons following application of some activating neuromodulators is due to the blockage of K^+ currents (McCormick 1992). In anesthetized cats, blocking K^+ channels with intracellular Cs^+ produced negligible effect on the membrane potential of neurons during EEG-activated states elicited by basal forebrain stimulation (Metherate and Ashe 1993). Our experiments in waking cats support this data. Long-lasting intracellular recordings with Cs^+-filled pipettes in awake animal did not affect the membrane potential (Timofeev, Grenier, Steriade, unpublished observations) indicating that K^+ currents are less active during waking than during slow-wave sleep. This observation indicates that K^+ currents of cortical neurons are largely depressed in waking cats and, consequently, they do not tend to hyperpolarize cortical neurons. A second factor responsible for the maintenance of a stable depolarization of cortical neurons during waking and REM sleep is the decrease in synaptic depression within the thalamocortical system. Although there are no reliable *in vivo* data supporting this idea, experiments conducted *in vitro* revealed that synaptic depression was significantly reduced following application of neuromodulators (Gil et al. 1997). It suggests that sufficient level of synaptic activities may keep the membrane potential at a certain level of depolarization. Since all neuronal types fire during the depolarizing states in SWS, REM sleep and waking, IPSPs should participate in the maintenance of membrane potential by counterbalancing the excitatory drive. Indeed, the presence of IPSPs in depolarizing phases of slow oscillation in anesthetized animals was previously shown (Steriade et al. 1993a). During natural waking, the spontaneous IPSPs of cortical neurons are of small amplitude and short lasting, thus, they do not produce significant hyperpolarization (Timofeev et al. 2001a), but rather shunt the membrane preventing neurons from overexcitation (Borg-Graham et al. 1998; Hirsch et al. 1998). The third important factor controlling the level of cortical depolarization is activities arising from the thalamus. At least during REM sleep, the TC neurons are significantly depolarized (Hirsch et al. 1983), and during both REM sleep and wake extracellular recordings from TC neurons reveal their tonic firing (Steriade et al. 1997) that imposes tonic excitatory influences onto neocortical neurons.

Our intracellular data strongly suggest that the persistent Na^+ current participates in the maintenance of the depolarizing state of the membrane potential (Timofeev, Grenier, Steriade, unpublished observations). This suggestion is based on two facts. *(a)* Voltage-current characteristics demonstrate the linear relations over a wide voltage range. However, the slope of this linearity is changed and becomes steeper at voltages below -65 mV. *(b)* At voltages above -65 mV, the spontaneous fluctuations of the membrane potential are flattened.

Direct hyperpolarization of neurons below -65 mV produces significantly increased fluctuations of the membrane potential, revealing sharply rising synaptic potentials and indicating that some currents maintaining the membrane potential at a certain level of depolarization are now absent. The persistent Na^+ current in cortical neurons is activated at approximately - 65 mV. Furthermore, at these voltages no other intrinsic currents are activated (Crill 1996). Thus, it seems that the persistent Na^+ current may contribute to the maintainance of depolarizing membrane potential that is primarily set up by synaptically generated potentials. This current becomes extremely important in various depolarizing states of cortical neurons. Overall, our data indicate that hyperpolarizing states present during SWS, result from disfacilitation and leak currents predominately influencing the membrane potential of neurons. The depolarizing states, which are present during the slow oscillation in SWS as well as throughout REM sleep and waking, are composed of postsynaptic potentials that are amplified by the persistent Na^+ current.

3.3 Delta Oscillation

The field potential recordings from neocortex in human and animals during sleep reveal the presence of delta oscillation with frequencies 1-4 Hz. The fact that delta and slow oscillation represent two distinct phenomena was demonstrated by Achermann and Borbély (Achermann and Borbely 1997) who showed a difference in the dynamics between the slow and the delta oscillations, as the latter declines in activity from the first to the second non-REM sleep episode, whereas the former does not. The delta oscillation has likely two different components, one of which originates in neocortex and another one in the thalamus. Surgical removing of the thalamus or recordings from neocortical slabs in chronic conditions demonstrated significant enhancement of delta activity in neocortex (Ball et al. 1977; Houweling et al. 2004; Villablanca and Salinas-Zeballos 1972). Little is known about the cellular mechanisms mediating cortical delta oscillation. One of the hypothesis suggests that cortical delta activity is driven by intrinsic discharge of IB neurons (Amzica and Steriade 1998). The legitimacy of this hypothesis is not clear, because firing pattern of IB neurons could be revealed only by intracellular application of depolarizing current pulses (Fig. 2), however intracellular recordings from cortical neurons during sleep demonstrated the presence of long-lasting hyperpolarizing, but not depolarizing potentials (Steriade et al. 2001; Timofeev et al. 2000a, 2001a). Therefore, IB neurons can contribute to the spread of activity, but the initial group of neurons driving delta activity remains unidentified.

3.3.1 Thalamic Delta Oscillation

Thalamic delta (1-4 Hz) oscillation is well known example of rhythmic activity generated intrinsically in thalamic relay neurons. These oscillations arise as an interplay of low-threshold Ca^{2+} current (I_T) and hyperpolarization activated cation current (I_h) and may be observed during deep sleep when TC neurons are hyperpolarized sufficiently to deinactivate I_T (Curró Dossi et al. 1992; Leresche et al. 1991; McCormick and Pape 1990; Soltesz et al. 1991). Sufficiently long and deep hyperpolarization of TC neuron removes I_T inactivation and makes possible rebound burst generation triggered by a depolarized input (Jahnsen and Llinás 1984a; Timofeev et al. 2001b). Additional factor required for sustained bursting in the isolated TC cell is the presence of I_h (McCormick and Pape 1990; Pape 1996). The interplay

of I_T and I_h during delta oscillation was first described *in vitro* (McCormick and Pape 1990) and later was studied with computational models (Lytton et al. 1996). The mechanisms of single cell delta activity is following: a long-lasting hyperpolarization of TC neuron leads to slow I_h activation that depolarizes the membrane potential and triggers rebound burst, mediated by I_T, which was deinactivated by the hyperpolarization. Both I_h (because of voltage dependency (Pape 1996)) and I_T (because it is transient current (Huguenard 1996)) inactivate during the burst, so membrane potential becomes hyperpolarized after burst termination. This afterhyperpolarization starts the next cycle of oscillations (Fig. 6). Synchrony between different TC neurons during delta activity has not been found in decorticated cats (Timofeev and Steriade 1996). Thus, it is unlikely that thalamic delta activity could play a leading role in the initiation and maintenance of cortical delta rhythm. However, the presence of a corticothalamic feedback in intact-cortex animals could synchronize thalamic burst-firing at delta frequency and generate field potentials (Curró Dossi et al. 1992; Steriade et al. 1991). In such conditions the cortical network plays a critical role in the generation of delta. At certain level of leak current (I_{leak}), the 'window' component of I_T may create oscillations similar in frequency to the intrinsic thalamic delta oscillation (Williams et al. 1997).

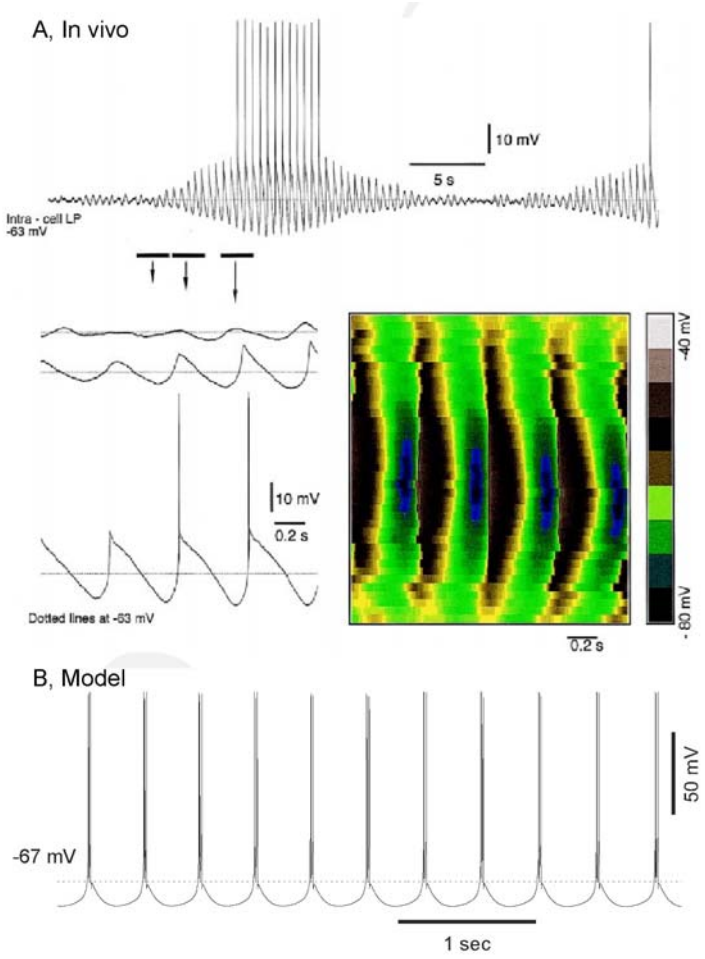

Figure 6. Thalamic delta activity.

A, Waxing and waning delta activity in LP thalamocortical neuron in decorticated cat. Ketamine-xylazine anaesthesia. Periods of delta-like oscillation start from subtle fluctuations of the membrane potential. The amplitude of such activity starts and declines without changes in frequency (2.2 Hz). Periods indicated by horizontal bars are expended *below*. *Right* topographical plot of delta-like activity emphasises the stable frequency of delta-like activity regardless of the amplitude of LTSs. From bottom to top, successive sweeps; from left to right, time; colors code the voltage. B, Intrinsic delta oscillations in the model of a single TC neuron. Upon hyperpolarization the modeled TC neuron shows periodic ~2.5 Hz bursting mediated by interplay of I_T and I_h. Blocking either of these two current abolishes oscillations. (A – from (Timofeev et al. 2001b), B- Bazhenov and Timofeev – unpublished observation).

3.4 Sleep Spindle Oscillations

Sleep spindle oscillations consist of waxing-and-waning field potentials of 7-14 Hz, which last 1-3 sec and recur every 5-15 sec. *In vivo*, the spindle oscillations are typically observed during early stages of sleep or during active phases of slow-wave sleep oscillations. In cats, the maximal occurrence of sleep spindle was found in motor, somatosensory and to a lesser extent in associative cortical areas (Morison and Dempsey 1942). A presence of spindle oscillations after decortication (Contreras et al. 1996b; Morison and Bassett 1945; Timofeev and Steriade 1996) provides strong evidence to the thalamic origin of this activity. Spindle-like activity was found in thalamic LGN slice preparations of ferrets with preserved interconnections with perigeniculate nucleus (Bal and McCormick 1993; Kim et al. 1995; von Krosigk et al. 1993). However, the spindle activity was not reported in the visual cortex of cats and ferrets, where the LGN nucleus projects, and thus, the mechanisms of spindle-like activity found in the LGN slices from ferrets maintained *in vitro* may not be directly applied to the interpretation of spindle activity generated in the intact brain.

In vivo, *in vitro* and modeling studies suggest that the minimal substrate contributing to the generation of spindle oscillations is the thalamus, and the spindles are generated as a result of interaction between thalamic RE and TC cells (Steriade and Deschénes 1984; Steriade and Llinas 1988; Steriade et al. 1990; Steriade et al. 1985; von Krosigk et al. 1993.). According to this hypothesis, the RE inhibitory neurons fire a spike burst that elicit IPSP in TC neurons, at the end of IPSP the TC neurons generate rebound spike-burst that excites RE neurons, which then generate spike-burst starting the next cycle of spindle oscillation. There are at least two sets of data, which demonstrate that this hypothesis does not represent all spindle generating mechanisms. (a) Spindles are generated in isolated RE nucleus (Steriade et al. 1987) and spindles are absent in the dorsal thalamus that is desconnected from RE nucleus (Steriade et al. 1985). (b) During the early 3-4 IPSPs composing the spindle, the TC neurons do not display rebound spike-bursts (Bazhenov et al. 2000), suggesting that the return TC-RE connections are not contributing to the early phase of a spindle sequence. Generally, the early part of spindles is not seen or less marked at the neocortical level. More complex model suggests the presence of at least three phases with different underlying mechanisms that contribute to the spindle generation (Timofeev et al. 2001b) (Fig. 7, A). The waxing phase of spindle oscillations is associated with recruitment of neurons from dorsal thalamic and RE nuclei (Steriade et al. 1993c). During the early phase of spindles, the RE nucleus is driving the spindles by its own mechanisms (see below). The second part of spindles primarily develops as result of interactions between RE and TC neurons as described above, but cortical firing contributes to the spindle synchronization, where the firing of cortico-thalamic neurons

imposes the simultaneous excitation of RE and TC neurons. Given robust cortical influence on RE neurons (Golshani et al. 2001), the inhibitory influences of RE neurons onto TC neurons reinforce the spindle. The waning phase occurs as a result of Ca^{2+} induced cAMP up-regulation of hyperpolarization activated cation current, I_h, in TC cells (Bal and McCormick 1996; Budde et al. 1997; Luthi et al. 1998) and network desychronization (Timofeev et al. 2001b).

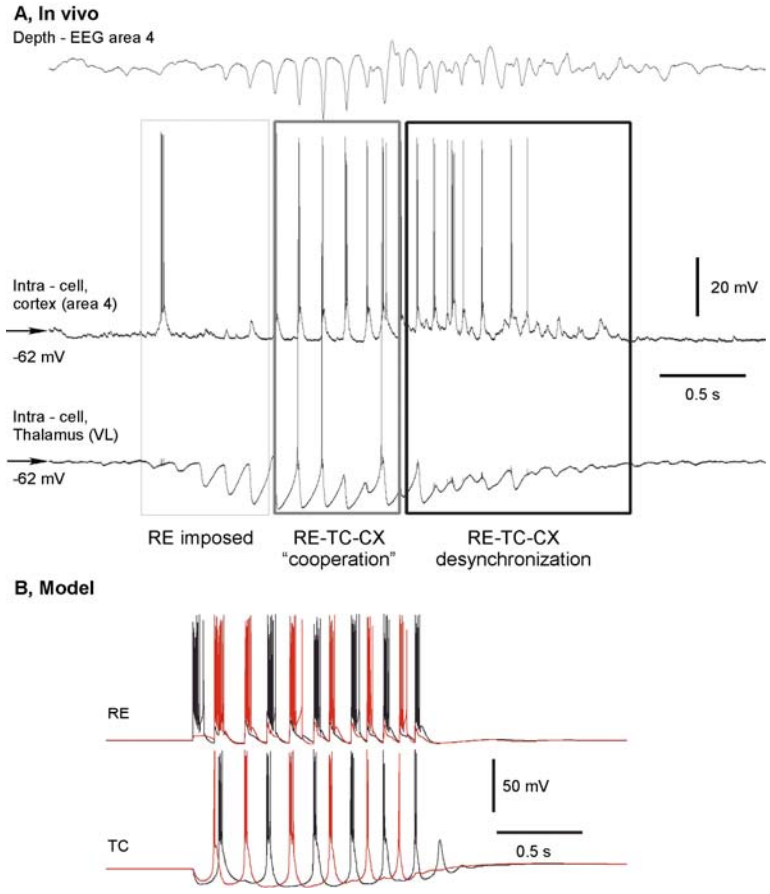

Figure 7. Cellular basis of spindle activity.

A, *In vivo* recordings. Three phases of a spindle sequence. Dual intracellular recording of cortical (area 4) and TC (VL) neurons. 1) Initial phase consists of series of IPSPs in TC neurons that are not followed by rebound spike-burst, suggesting that they are imposed from RE network. Spontaneous firing of some cortical neurons may trigger activities of RE network. 2) During the middle phase of the spindle, the rebound spike-bursts of TC neurons excite both RE and cortical neurons. The activity of cortical, RE and TC neurons is phase-locked. 3) At the end of spindles the cortical neurons no longer fire in phase-locked manner. This un-synchronous firing induces depolarization of both RE and TC neurons that create conditions for the spindle termination. B, Computational model. Spindle oscillations in the circuit of 2 RE and 2 TC cells. RE cells fire every cycle of oscillations, while TC cells skip every second cycle. Progressive increase of intracellular Ca^{2+} concentration during spindle increases a fraction of I_h channels in the open state. It leads to depolarization that eventually terminates spindle. (A – modified from (Timofeev et al. 2001b), B - Bazhenov and Timofeev, unpublished observations)

In modeling experiments, the reciprocal RE-TC pair represents a minimal model that is capable to generate spindle-like oscillations (Destexhe et al. 1993). In this model the TC-mediated EPSPs trigger rebound burst in RE cell. In return, the RE-mediated IPSPs enhance TC cell hyperpolarization after bursts thus increasing I_T deinactivation and making possible next rebound burst in TC neuron. Therefore, both RE and TC cells oscillate at the same 7-10 Hz frequency (Destexhe et al. 1993). This is not consistent with experimental data where TC neurons do not fire every cycle of oscillations but intermit bursting with subshreshold oscillations (see, e.g., (Kim et al. 1995)). A simplest circuit model sufficient to generate this type of spindle oscillations includes 2 reciprocally coupled RE neurons and 2 TC cells providing excitation to and receiving inhibition from RE neurons (Destexhe et al. 1996a). In such a model, the RE cells fire at spindle frequency, while each TC neuron generates burst of spikes every second cycle of oscillations (Fig. 7, B). GABAa input from RE neuron is required to provide hyperpolarization that deinactivates I_T channels. For low to moderate levels of GABAa inhibition more than one cycle of oscillations is required to sufficiently deinactivate I_T, therefore, TC neuron fires a single burst every few cycles. Enhancing GABAa inhibition increases the frequency of TC firing and eliminates the burst skipping.

The termination of spindles may be mediated by three different mechanisms. (a) First, during the waxing phase of spindles the TC neurons are hyperpolarized to a level that significantly activates I_h; this current tends to repolarize TC neurons preventing their rebound spike-bursts. Ca^{2+} accumulation leading to cAMP upregulation of I_h enhances this effect (Bal and McCormick 1996; Budde et al. 1997; Luthi et al. 1998). (b) Second, repetitive stimulation of the dorsal thalamus with low intensity pulse-trains at spindle frequencies induces decremental responses in RE neurons (Timofeev and Steriade 1998). This might mediate a depression of inhibition induced by rhythmic volleys from RE neurons to TC neurons (Steriade and Timofeev 1997; von Krosigk et al. 1999). (c) A third mechanism for the termination of spindle depends on desynchronization of activity (Andersen and Andersson 1968; Timofeev et al. 2001b), based on dissimilarity of intrinsic responses in different cortical and TC neurons. There are several sources of desynchronization that facilitate spindle termination. The first is related to the generation of LTS in TC neurons with different delays from the onset of IPSP. The asynchronous burst firing of TC neurons will keep the membrane potential of RE cells at relatively depolarized steady level, thus preventing the de-inactivation of T-channels and diminishing the probability of burst firing. Barrages of EPSPs from prethalamic relay stations (e.g. cerebellum) may produce a small, but long-lasting, depolarization and decreased input resistance of TC neurons that could desynchronize the thalamocortical network and disrupt the spindles (Timofeev and Steriade, 1997; Bazhenov et al., 2000). Because the trains of prethalamic EPSPs would occur only randomly, the most important source of spindle desynchronization, leading to decrease in their duration, is probably long-lasting spike-trains from neocortical neurons. Several specific mechanisms may be involved: (i) Cortical IB neurons fire with bursts that may significantly outlast the duration of thalamically generated EPSPs (Baranyi et al. 1993). (ii) Slightly depolarized FRB neurons (some are corticothalamic projecting cells) could fire high frequencies, non-accommodating trains of spikes throughout the spindle (Steriade et al. 1998a). Those bursting neurons would recruit other cortical neurons into an excited state that is out-of-phase with the thalamic neurons. (iii) In addition, we have recently shown that short depolarizing inputs to cortical neurons may elicit firing responses outlasting the stimulus by tens of milliseconds (Timofeev et al. 2000c), producing excitation in the network with up to 180° phase shift.

Strong depolarizing cortical inputs onto thalamic (primarily RE) neurons will prevent LTSs generation and thus will lead to the spindle termination.

3.4.1 Role of RE Nuclei in Spindle Initiation

The patterns of spindles and their synchronization are not identical in the intact brain and in thalamic slices. The depolarizing plateau of the spindle envelope recorded from thalamic RE neurons *in vivo* (Deschénes et al. 1984) was not initially observed in RE neurons from ferret slices that, instead, displayed a sustained hyperpolarization during spindles (von Krosigk et al. 1993). This difference may be due to a lack of brainstem activating systems and corticothalamic depolarizing inputs in thalamic slices. More recently, the recordings in thalamic slices (Kim and McCormick 1998) revealed depolarizing plateaus in about a half of recorded RE neurons during spindles at membrane potentials closer to those recorded *in vivo*. Spindles have been reported in the deafferented RE nucleus *in vivo* (Steriade et al. 1985) and *in computo* (Bazhenov et al. 1999; Houweling et al. 2000), but are absent *in vitro* (von Krosigk et al. 1993). One major difference between *in vivo* and *in vitro* conditions is that the long dendrites and axonal collaterals of RE neurons are likely cut when the slices are prepared and the modulatory systems arising in the brainstem are absent in thalamic slices. The depolarization of RE neurons by inputs arising in monoamine-containing systems, such as the serotonin released by dorsal raphe afferents and noradrenaline released by locus coeruleus afferents, promotes the sensitivity of RE neurons to the IPSPs generated by intra-RE GABAergic connections, with the consequence of generating spontaneous oscillations within the frequency range of spindles (Destexhe et al. 1994a). In 2-D network simulations (Destexhe et al. 1994b), the RE neurons organized with "dense proximal connectivity" were examined in a hyperpolarized state (-65 to -75 mV), similar to the *in vitro* condition when no monoaminergic synapses were activated, and in a more depolarized state (-60 to -70 mV) that would correspond to a weak monoaminergic activity. In the latter condition, the RE neurons generated spindle-like oscillations, whereas in the former condition the oscillatory behavior was absent.

Another proposed mechanisms of spindle generation in the isolated RE nuclei depends on the reversed IPSPs between RE neurons. For the reciprocal $GABA_A$ synapses between RE cells, the Cl^- reversal potential is about -71 mV, which is depolarized compared to the reversal potential in TC cells (Ulrich and Huguenard 1997). Thus, at a resting membrane potential of about -78 mV (Fuentealba et al. 2004b; Fuentealba et al. 2005; Ulrich and Huguenard 1996) a $GABA_A$ IPSPs in an RE cell will be reversed and could trigger a burst of Na^+ spikes (Contreras et al. 1993). *In vivo* recordings and computational models of RE cells were used to investigate cellular dynamics at different levels of membrane potential. It was found that the reversed IPSPs between the RE neurons can directly trigger LTSs bursts at membrane potentials close to those seen during natural sleep (Bazhenov et al. 1999). Furthermore, a subgroup of about 30% of RE neurons revealed prolonged hyperpolarizing potentials just preceding spindles that would facilitate the reversed IPSP to trigger an initial LTS (Fuentealba et al. 2004a). Only a fraction of RE neurons needs to be hyperpolarized to generate self-sustained spindle-like activity in the model of isolated RE nucleus (Houweling et al. 2000). In a one-dimensional RE network hyperpolarized below the Cl^- reversal potential, the $GABA_A$-mediated depolarization initiated isolated patterns of spike-burst activity that traveled through the RE network with a velocity that depended on the intrinsic and synaptic properties (see Fig. 5-6 in (Bazhenov et al. 1999)). Similar patterns were described in some

other network models (Ermentrout 1998; Golomb and Amitai 1997; Golomb and Ermentrout 1999). In a two-dimensional model of RE network, the activity persisted in the form of rotating spiral waves if the network size was large enough (Bazhenov et al. 1999). It produced almost periodic bursting in RE cells at the frequency about 3 Hz. The frequency of spontaneous oscillations increased up to about 10 Hz, when the resting potential of RE neurons was depolarized more closely to the Cl^- reversal potential. In the spiral wave mode, the RE cells placed at different network foci fired with a constant phase shift, which depended on their relative location. Thus, this network state may be synchronized, but in an essentially different way from simple in-phase or anti-phase oscillations previously described in the isolated RE networks (Destexhe et al. 1994b; Wang and Rinzel 1993). It is likely that multi-spiral states will be observed in the much larger networks of isolated RE cells, so the large-scale synchrony of RE oscillations will be limited to within the domains of individual spirals.

A possibility of self-sustained activity within RE nuclei suggests a mechanism for spindle initiation. Each sequence of spindle oscillations is followed by waves of activity that persists in the RE network during interspindle lulls and initiated new spindle sequences. These patterns of RE activity could not trigger bursts of Na^+ spikes in the TC cells, which were depolarized after the spindle sequence, until the slow repolarization of TC cells deinactivated the low-threshold Ca^{2+} current and the local RE-evoked IPSPs could initiate a new sequence of spindle oscillations. Therefore, the rate of repolarization determines the duration of interspindle lull. This mechanism is illustrated in Fig. 8 with a network model of 100 TC and 100 RE neurons (Bazhenov et al. 2000).

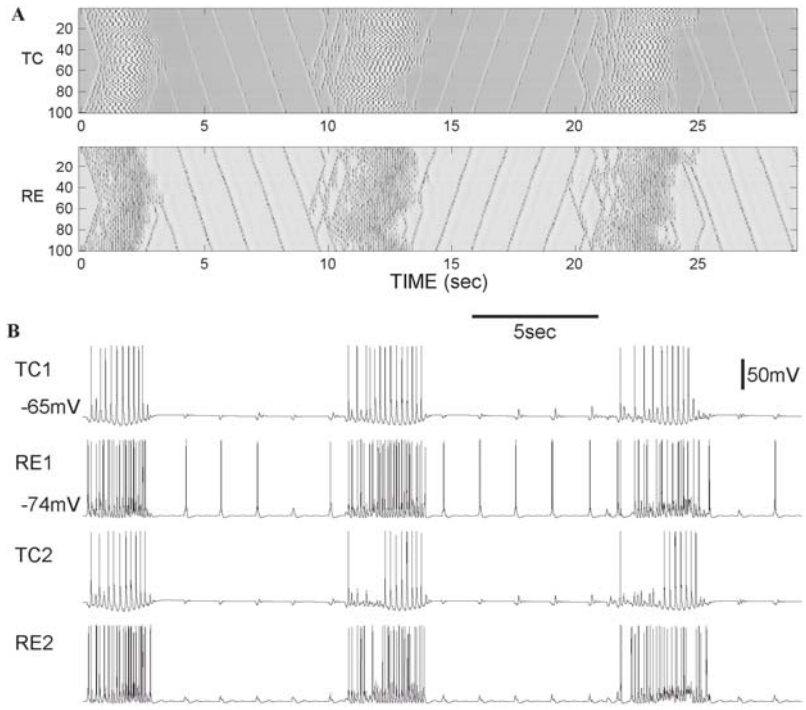

Figure 8. Initiation of spindle sequences in RE-TC network with periodic boundary conditions.

A, The sequence of spindle oscillations was initiated at t=0 by the local stimulation of TC cell #1 (left upper corner of the panel) and then propagates in both directions with constant velocity. After 2-4 sec the spindle sequence is terminated because of the Ca^{2+} up-regulation of I_h current and is followed by localized patterns traveling through the RE nuclei. This activity triggeres a new spindle sequence at about t=10sec. B, Membrane potentials for two RE-TC pairs. (Modified from (Bazhenov et al. 2000)).

3.5 Beta-Gamma Oscillation

The waking state of the brain is characterized by low correlation of spike discharges across neighbouring neurons (Noda and Adey 1970) and the predominance of the frequencies in the beta (15-30 Hz) and gamma (30-60 Hz) ranges (Bressler 1990; Freeman 1991). Studies have indicated that cortical gamma activity is associated with attentiveness (Bouyer et al. 1981; Rougeul-Buser et al. 1975), focused arousal (Sheer 1989), sensory perception (Gray et al. 1989) and movement (Murthy and Fetz 1992; Pfurtscheller and Neuper 1992). It has been proposed that synchronization in the gamma frequency range is related to cognitive processing and to the temporal binding of sensory stimuli (Joliot et al. 1994; Llinas and Ribary 1993; Singer and Gray 1995). The fast rhythms are also synchronized between neighboring sites during deep anesthesia, natural SWS and REM sleep (Steriade et al. 1996a; Steriade et al. 1996b), when consciousness is either suspended or bizarre. During slow-wave sleep the fast rhythms follow the onset of depth-negative EEG wave (Fig. 9). Large-scale network simulations revealed that coherent gamma range oscillations may appear through occasional increases in spiking synchrony within local groups of cortical neurons (Rulkov et al. 2004).

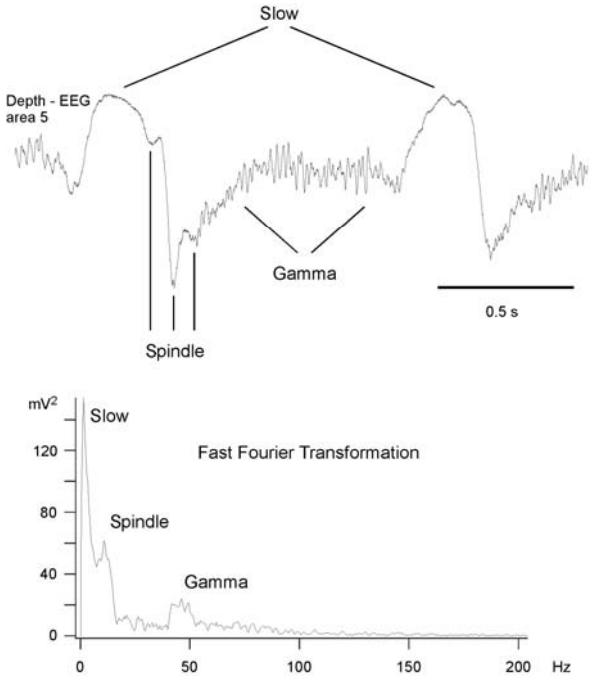

Figure 9. Gamma oscillation is an important component sleep wave slow oscillation.

Upper panel, a fragment of EEG trace recorded from the depth of area 5. Slow oscillation, spindles and gamma activities are indicated. Below, Fast Fourier Transformation of a fragment shown above. (I. Timofeev, unpublished observations).

3.5.1 Mechanisms of Beta-Gamma Oscillations

At least two non-exclusive basic mechanisms have been proposed to explain the origin of beta-gamma oscillations. One of them emphasizes extracortical and another one point to intracortical origin of these activities. A transient feed forward synchronization to high-frequency peripheral (retinal, lemniscal or cerebelar) oscillations (Castelo-Branco et al. 1998; Timofeev and Steriade 1997) could impose peripheral fast activities onto TC system. Intracortical mechanisms itself include several possibilities. The first one is based on the intrinsic property of FRB neurons to fire fast spike-bursts at frequencies 20-60 Hz. These neurons were first described as fast pyramidal tract neurons from somatosensory cortex (Calvin and Sypert 1976), later found in layer II-III visual cortex (small pyramids called "chattering cells" (Gray and McCormick 1996)). Later studies demonstrated that FRB neurons could be found in most of cortical layers (they are seemingly absent in layer I) and they could be both aspiny non-pyramidal and pyramidal cells (Steriade et al. 1998a; Timofeev et al. 2000b). Experimental and modeling studies provide two possible mechanisms of fast rhythmic burst generation. First depends on the interplay of Na^+ and K^+ currents (Brumberg et al. 2000; Wang 1999) and second requires a reduction of intracellular Ca^{2+} concentration (Boucetta et al. 2003; Traub et al. 2003). The second mechanism of gamma activity generation was described both *in vitro* and computational models. According to this mechanism the activity of inhibitory interneurons controls synchronization and is essential to obtain oscillations at gamma range (Lytton and Sejnowski 1991; Traub et al. 1996; Traub et al. 1999b; Traub et al. 1998). Lastly, the FRB neurons may function by providing a large-scale input to an axon plexus consisting of gap-junctionally connected axons from both FRB neurons and their anatomically similar counterparts, regular spiking neurons (Cunningham et al. 2004). The resulting network gamma oscillation demonstrated in computational model shares all of the properties of gamma oscillations and shows a critical dependence on multiple spiking in FRB cells.

3.6 Ripples (Very Fast Oscillations, >100 Hz)

Fast oscillations (>100 Hz), termed ripples, were described in CA1 hippocampal area and perirhinal cortex, where they were associated with bursts of sharp potentials during anesthesia, behavioral immobility, and natural sleep (Chrobak and Buzsáki 1996; Collins et al. 1999; Csicsvari et al. 1999a, b; Ylinen et al. 1995). In the neocortex, fast oscillations (>200 Hz, up to 600 Hz) have been found in sensory-evoked potentials in rat barrel cortex (Jones and Barth 1999; Jones et al. 2000), during high-voltage spike-and-wave patterns in rat (Kandel and Buzsaki 1997). During natural states of vigilance in cats, the ripples were generally more prominent during the depolarizing component of the slow oscillation in slow-wave sleep than during the states of waking and rapid-eye movement (REM) sleep (Grenier et al. 2001). Around epileptic foci in humans and cats the amplitude of ripples is dramatically enhanced (Allen et al. 1992; Fisher et al. 1992; Grenier et al. 2003a; Grenier et al. 2003b; Steriade et al. 1998c). Studies in epileptic patients have revealed the presence of high-

frequency oscillations also in the hippocampus and entorhinal cortex (Bragin et al. 2002; Bragin et al. 1999a; Bragin et al. 1999b).

3.6.1 Mechanisms of Ripples

The high-frequency field potential oscillations during ripples are phase-locked with neuronal firing (Draguhn et al. 1998; Grenier et al. 2001, 2003a; Jones et al. 2000). The dependence of ripples on neuronal depolarization was shown by their increased amplitude in field potentials in parallel with progressively more depolarized values of the membrane potential of neurons (Grenier et al. 2001). Of all types of electrophysiologically identified neocortical neurons, fast-rhythmic-bursting and fast-spiking cells displayed the highest firing rates during ripples and the inhibitory processes controlled the phase precision of ripple-dependent neuronal firing (Grenier et al. 2001; Ylinen et al. 1995). As ripples can be generated within small isolated slabs of cortex, a neocortical network seems to be sufficient to produce those (Grenier et al. 2001). In addition to active inhibition, the electrical coupling mediated by gap junctions contributes to the ripple synchronization (Draguhn et al. 1998; Grenier et al. 2003a; Traub et al. 1999a). The electrical coupling may occur between axons of principal cells (Schmitz et al. 2001) or via a network of inhibitory interneurons (Galarreta and Hestrin 1999, 2001a, b; Gibson et al. 1999; Gibson et al. 2005). The field potentials increase neuronal excitability, and by a positive feedback loop they could be also involved in the generation of neocortical ripples (Grenier et al. 2003b). Since ripples are recorded also in glial cells, the electrical coupling between gial cells could also play a role in the synchronization of ripples (Grenier et al. 2003a).

4 Possible Physiological Role of Oscillations

Rhythmic activities (from 0.5 to 200 (but may be up to 600 Hz) are emerging property of living brain. What we described above is mainly focused on the mechanisms of their generation. The functional role of these activities is less studied. We propose that the occurrence of either spontaneous or evoked brain oscillations could modulate the signal processing. We hypothesize that the brain oscillations generated within the TC system are not epiphenomenona, but serve to mediate different functions. The fast rhythmic brain activities maintain a certain tonic activation of the TC network, thus, facilitating signal processing, while slower activities influence the synaptic plasticity and may affect memory consolidation (Destexhe and Sejnowski 2001; Steriade and Timofeev 2003).

4.1 Infra-slow Oscillation

Indirect evidences suggest that infra-slow oscillations (0.02-0.2 Hz) synchronize faster activities, modulate cortical excitability and could contribute to aggravation of epileptic activity during sleep (Vanhatalo et al. 2004).

4.2 Slow Oscillation, Delta

When the brain falls asleep, the spatio-temporal patterns characterizing waking in corticothalamic system (Steriade et al. 2001; Timofeev et al. 2001a) are replaced by low-frequency synchronous rhythms that are relatively insensitive to incoming signals (Steriade et al. 1993c). Recent studies have reported that slow wave sleep may be essential for memory formation and memory consolidation (Gais et al. 2000; Huber et al. 2004; Stickgold et al. 2000). It has been proposed that synaptic plasticity associated with brain rhythms could contribute to the memory formation (Steriade and Timofeev 2003). What are the alternations of synaptic plasticity associated with slow sleep oscillation?

Short-term synaptic plasticity is a ubiquitous property of cortical circuitry. Both the synaptic impact (Abbott et al. 1997; Timofeev et al. 2000c; Tsodyks and Markram 1997) and the balance of synaptic excitation and inhibition (Galarreta and Hestrin 1998; Houweling et al. 2002; Varela et al. 1997) depend on spike frequency. Connections between excitatory cells display short-term depression (Abbott et al. 1997; Finnerty et al. 1999; Galarreta and Hestrin 1998; Hempel et al. 2000; Thomson and Deuchars 1997; Tsodyks and Markram 1997; Varela et al. 1999) or facilitation (Reyes and Sakmann 1999; Stratford et al. 1996) that is frequency dependent. Connections from excitatory cells onto inhibitory cells facilitate (Gibson et al. 1999; Markram et al. 1998; Reyes et al. 1998; Thomson et al. 1993a) or depress (Buhl et al. 1997; Galarreta and Hestrin 1998; Gibson et al. 1999; Reyes et al. 1998; Rozov et al. 2001; Tarczy-Hornoch et al. 1998). Connections from inhibitory cells onto excitatory cells depress (Castro-Alamancos M.A. 1996; Deisz and Prince 1989; Galarreta and Hestrin 1998; Gupta et al. 2000; Reyes et al. 1998; Tarczy-Hornoch et al. 1998; Varela et al. 1999). Connections between inhibitory cells depress (Galarreta and Hestrin 1999; Gibson et al. 1999; Gupta et al. 2000; Tamas et al. 2000) or facilitate (Gupta et al. 2000). Extrinsic afferents from the thalamus depress (Gibson et al. 1999; Gil et al. 1997, 1999; Sanchez-Vives et al. 1998; Stratford et al. 1996). A partial recovery from synaptic depression occurs within several hundreds of milliseconds (Galarreta and Hestrin 1998). Thus, the majority of synapses reveal short-term synaptic depression during long trains of stimuli, and the depression becomes reduced during the silent phases of slow oscillation.

In cortical pyramidal neurons, each synapse contains one active zone with 2-20 docked vesicles (Harris and Sultan 1995; Schikorski and Stevens 1997, 1999). Some *in vitro* studies indicate that at most a single vesicle can be released in response to an action potential (Auger and Marty 2000; Hanse and Gustafsson 2001; Redman 1990; Stevens and Wang 1995; Triller and Korn 1982), while others found evidence for multiple quantal release (Auger et al. 1998; Conti and Lisman 2003; Isaac et al. 1998; Oertner et al. 2002; Tong and Jahr 1994; Wadiche and Jahr 2001). In any case, only one or few vesicles could activate a postsynaptic neuron when a presynaptic cell fires a spike. In these conditions, changes in release probability would have a dramatic effect on postsynaptic responses. One of the critical factors regulating the vesicle release is $[Ca^{2+}]_o$. The baseline $[Ca^{2+}]_o$ *in vivo* is around 1.2 mM (Heinemann et al. 1977) and decreases with an increase in the level of neocortical activity (Crochet et al. 2005; Heinemann et al. 1977; Massimini and Amzica 2001). The release probability at a synapse depend critically on $[Ca^{2+}]_o$ (Markram et al. 1998; Silver et al. 2003; Thomson 1997; Thomson et al. 1993b). The spontaneous decrease in the $[Ca^{2+}]_o$ during depolarizing phases of slow oscillation is associated with an increase in the synaptic failures, and the opposite, the efficacy of synaptic transmission increases during silent phases of slow oscillation (Fig. 10)

(Crochet et al. 2005). Thus, we postulate here that slow sleep oscillation contributes to the reshaping of synaptic efficacy. Traveling of slow waves of activity during sleep in preferential directions (Massimini et al. 2004; Timofeev et al. 2000c) could create pathways with modified synaptic efficacy. These changes in the synaptic efficacy acquired during slow wave sleep could be either permanent or transient but still may remain for long periods of time.

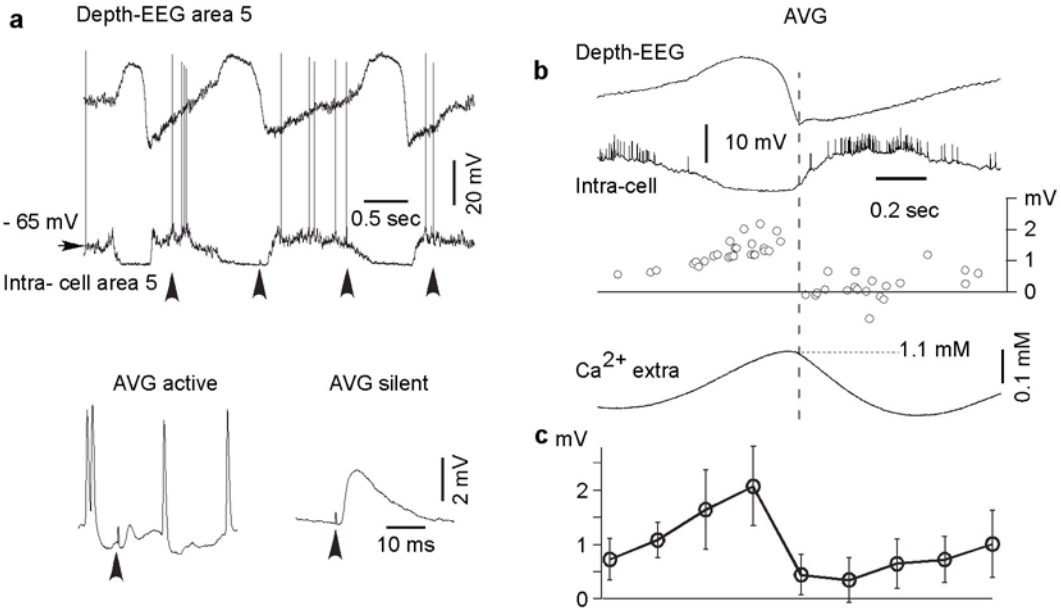

Figure 10. Activity dependent modulation of responses elicited by microstimulation.

a. A period of spontaneous activity in neocortex in ketamine-xylazine anesthetized cat (upper panel) and averaged responses (total averages) to microstimulation during active and silent network states (lower panel). Each average was obtained from more than 10 segments that preceded (right) or followed (left) the onset of EEG depth negativity. Arrowheads indicate the time of stimulation. b. Wave-triggered average of EEG, intracellular activities and $[Ca^{2+}]_o$ as well as amplitude of intracellular events (responses and failures) triggered by microstimuli applied during different phases of slow oscillation. The first maximum of EEG-depth negativity was taken as 0 time. c. Averaged amplitude of microstimulus-evoked events from 9 neurons during different phases of slow oscillation. The amplitude was averaged for successive time windows of 200 ms. The time base in b and c is the same. (Modified from (Crochet et al. 2005)).

4.3 Spindles

Recent studies show that sleep related spindle oscillations are essential for memory formation (Gais et al. 2002) and demonstrate the presence of efficient spindle-dependent short- and middle term synaptic plasticity (reviewed in (Steriade and Timofeev 2003)). It was suggested that the rhythmic spike-trains or spike-bursts fired by cortical and thalamic neurones during low-frequency sleep oscillations may be involved in the consolidation of memory traces acquired during wakefulness (Steriade and Timofeev 2003; Steriade et al. 1993c) by massive Ca^{2+} entry in cortical pyramidal neurons. Spindling may activate the molecular “gate”

mediated by protein kinase A, thus opening the door for gene expression (Sejnowski and Destexhe 2000) a process that may allow long-term changes to subsequent inputs following sleep spindles.

The easiest model to study plasticity associated with spindle oscillations is the augmenting response, which represents a neuronal response for a train of electrical stimuli applied with spindle frequency (8-14 Hz). Augmenting responses are defined as potentials with progressively growing amplitudes starting with the second or third stimulus in a pulse-train (Morison and Dempsey 1943). There are thalamic and cortical components of augmenting responses. Experiments in decorticated cats demonstrated the presence of augmenting responses in thalamus (Bazhenov et al. 1998b; Morison and Dempsey 1943; Steriade and Timofeev 1997; Timofeev and Steriade 1998). There are at least two types of intrathalamic augmenting responses. The first one high-threshold, which occurs as progressive depolarization associated with the decrease in IPSPs produced by preceding IPSPs (Steriade and Timofeev 1997; Timofeev and Steriade 1998). This type of augmenting responses likely depends on the high-threshold Ca^{2+} currents (Hernandez-Cruz and Pape 1989) in TC neurons. To obtain the high-threshold augmenting responses the discharge pattern of RE neurons has to be decremental (Timofeev and Steriade 1998). The second type of augmenting response is based on progressively growing low-threshold responses. It results from the enhancement of Cl^--dependent IPSPs, giving rise to postinhibitory rebound bursts, followed by a self-sustained sequence of spindle waves (Steriade and Timofeev 1997; Timofeev and Steriade 1998). This type of responses is associated with an increased number of spikes in RE neurons that follow each consecutive stimulus (Timofeev and Steriade 1998). The low-threshold augmenting responses are significantly reduced during cholinergic activation (Timofeev and Steriade 1998). Dual intracellular recordings in anesthetized cats show that thalamically evoked augmenting responses of neocortical neurons are associated with secondary depolarization (mean onset latency of 11 msec) that develops in parallel with a diminution of the early EPSPs (Steriade et al. 1998b). The rebound spike bursts initiated in simultaneously recorded TC cells preceded by ±3 msec the onset of augmenting responses in the cortex and were identified as a primary cause of cortical augmenting responses (Bazhenov et al. 1998a; Steriade et al. 1998b). Thalamic stimulation is more efficient than cortical stimulation at producing the augmenting responses. Despite of that cortical network has its own machinery enabling generation of augmenting responses. Experiments in slices maintained *in vitro* suggested that the primary cause of augmenting responses depends on intrinsic property of IB neurons (Castro-Alamancos and Connors 1996a; Castro-Alamancos and Connors 1996b, c). Later, *in vivo* and modelling studies demonstrated that synaptic plasticity may be a primary source of augmenting responses in isolated neocortical networks (Houweling et al. 2002; Timofeev et al. 2002).

Neuronal plasticity induced by augmenting responses recorded *in vivo* in cortical slabs was compared to plasticity that develops from natural spindles in intact-brain preparations (Timofeev et al. 2002). In isolated slabs (~10 mm long, 6 mm wide and 4-5 mm deep), the greatest increase in the amplitude of depolarization and the most dramatic increase in the number of action potentials with successive stimuli at 10 Hz was found in fast-spiking (FS), presumably local inhibitory, neurons. In the intact brain, the cortical stimuli applied during the depolarizing envelope of spindle sequences accompanied by firing elicited an enhancement of the control response, which lasted from tens of seconds to several minutes (Fig. 11, left column). Testing cortical excitability with repeated pulse-trains giving rise to

augmenting responses (Fig. 11, right column), revealed that: first, the IPSP of the control response was progressively reduced in amplitude and replaced by an early depolarization and, second, single stimuli applied after the rhythmic pulse-trains elicited exclusively depolarizing responses, an enhancement that remained unchanged for several minutes. This enhancement was not voltage-dependent, as it observed with little changes at rest and after slight DC hyperpolarization. One possible mechanism for increased responsiveness depends on high-frequency firing in response to rhythmic, repeated pulse-trains. This firing would result in activation of high-threshold Ca^{2+} currents and elevated $[Ca^{2+}]_i$ that, in association with synaptic volleys reaching the neuron, may activate protein kinase A (Abel et al. 1997) and/or Ras/mitogen-activated protein kinase (Dolmetsch et al. 2001). These enzymes are known to be involved in the processes of memory consolidation.

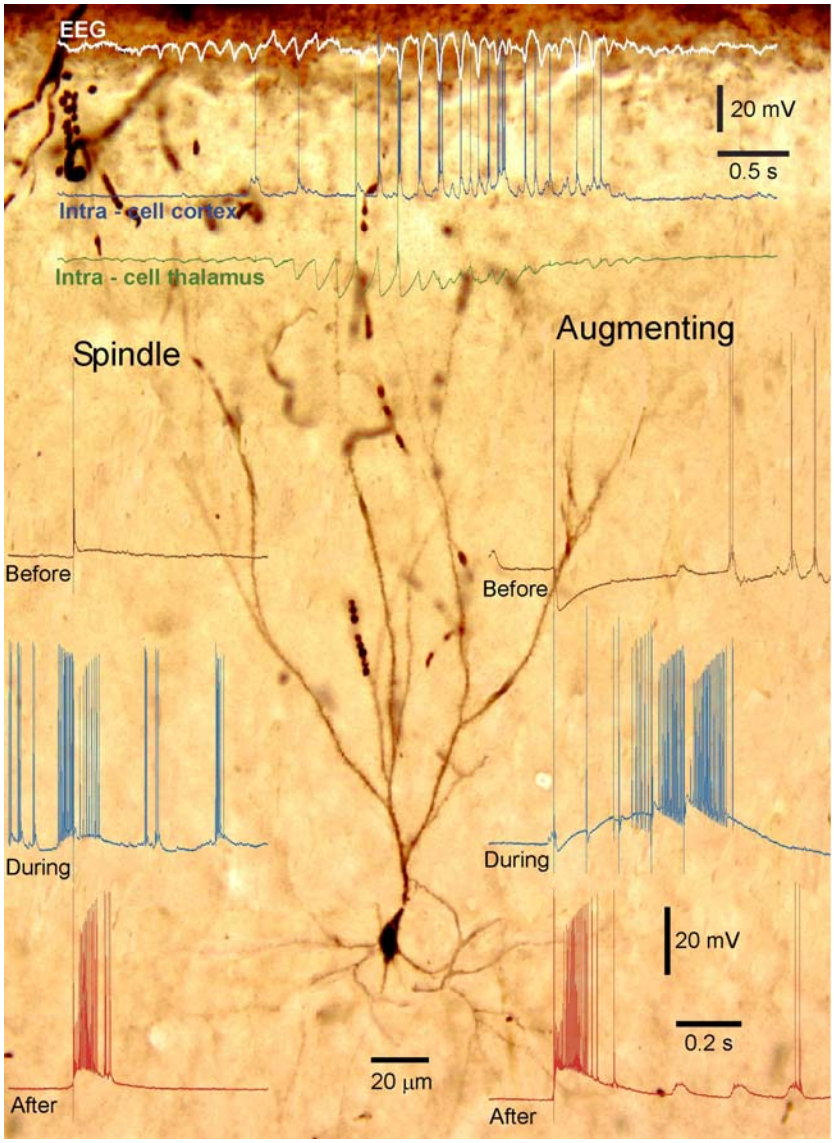

Figure 11. Long-lasting changes in cortical responsiveness after spindles and augmenting responses.

Cats under sodium pentobarbital (top three traces) and ketamine-xylazine anesthesia. Top three traces depict a spontaneously occurring spindle sequence, with simultaneous recordings of field potentials from the depth of cortical area 4 and dual intracellular recordings from area 4 cortical neuron and thalamocortical cell from ventrolateral (VL) nucleus. Note sustained activity in cortical neuron despite the fact that the spindle sequence was terminated in VL. Below, neuronal plasticity in fast-rhythmic-bursting neuron (FRB) from area 21 following spontaneously occurring spindles (left column), and in regular-spiking (RS) neuron from area 7 following augmenting responses (right column). Middle part depicts the morphologically (Neurobiotine staining) identified RS neuron whose electrophysiological activity is depicted in the right column. *Left column:* three traces show responses of FRB neuron to control cortical stimuli (*Before*), during spindle sequence (*During*) and after spindle (*After)*. *Right column:* three traces depict control response to the cortical stimulus applied close to the recorded RS cell (*Before*), responses to a pulse-train at 10 Hz applied 12 min after rhythmic pulse-trains (*During*), and response to a single stimulus (same parameters as *Before*) applied 16 min after the onset of pulse-train stimulation (*After*). Enhanced responsiveness lasted for 15 min. (Modified from (Steriade and Timofeev 2003)).

4.4 Gamma Activities

As we mentioned earlier, the gamma activity is associated with attentiveness (Bouyer et al. 1981; Rougeul-Buser et al. 1975), focused arousal (Sheer 1989), sensory perception (Gray et al. 1989) and movement (Murthy and Fetz 1992; Pfurtscheller and Neuper 1992). It has been proposed that synchronization in the gamma frequency range is related to cognitive processing and important for temporal binding of sensory stimuli (Joliot et al. 1994; Llinas and Ribary 1993; Singer and Gray 1995). Why gamma activities are implicated in cognitive functions? The frequency of gamma oscillations is relatively low (around 40 Hz) and therefore the coding of information with these frequencies is not efficient. Our current study suggests, however, that cortical network is tuned to transmit information over long-range oligosynaptic cortical chains at frequencies around 40 Hz (Rosanova et al. 2003). We showed that transmission of activities through intracortical chains involves a combination of synaptic depression and temporal summation. *In vivo*, at low frequencies stimuli (<25 Hz), the induced firing in neurons located only close to the stimulating electrode and elicited postsynaptic EPSPs in isolation at increasing distances. Thus, distant signal propagation was limited at these frequencies. At moderate frequencies (25-45 Hz), the temporal summation compensated for synaptic depression and the more distant neurons started to fire spikes after a few initial cycles of stimulation. This firing elicited the EPSPs in neurons located further down the synaptic chain, therefore, providing a mechanism for long-lasting stimuli propagation. At high frequencies of stimulation the synaptic depression overcame temporal summation and response in remote sites was absent after a few initial stimuli. The responses to sensory stimuli that occurred during spontaneous gamma activities were of shorter latency as compared to the responses occurring outside periods of gamma activities. An additional factor assisting the successful summation is that during active network states the first few presynaptic stimuli at gamma frequency reveal synaptic facilitation (Crochet et al. 2005; Timofeev et al. 2000b) and not depression which is the case *in vitro* (see above). Similar to *in vitro* findings, during silent network states the same connections showed synaptic depression (Crochet et al. 2005). The easiest explanation for this phenomena is based on spontaneous fluctuations of $[Ca^{2+}]_o$ (Crochet et al. 2005; Massimini and Amzica 2001), which affect the release probability. Consistent with the residual calcium hypothesis (Katz and Miledi 1968; Zucker and Regehr 2002), the high release probability (*in vitro* or during silent network

states) would be associated with synaptic depression and low release probability would be associated with synaptic facilitation. Thus, short-term synaptic dynamics mediate both the generation of gamma activities and intracortical long-range transmission of information, essential for conscious functions.

4.5 Ripples

Cortical ripples are generated during a large amplitude spontaneous or evoked field potential deflections (Chrobak and Buzsáki 1996; Collins et al. 1999; Csicsvari et al. 1999a, b; Grenier et al. 2001; Jones and Barth 1999; Jones et al. 2000; Ylinen et al. 1995). 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 certain threshold of excitability, leading to the onset of seizure (Grenier et al. 2003a; Grenier et al. 2003b). Indeed, the onset of seizures (cortical or hippocampal) in the focus of seizure generation is often associated with ripples (Allen et al. 1992; Fisher et al. 1992; Grenier et al. 2003a; Grenier et al. 2003b; Steriade et al. 1998c).

5 Conclusion

The oscillatory rhythmic activities (from 0.5 to 200 (600 Hz) are emerging property of living brain. In this chapter we described the known mechanisms and the current knowledge of functional role of various groups of oscillations generated by TC system. We postulate that brain oscillations generated within the TC system are not epiphenomenon, but serve to mediate different functions. We suggest that fast rhythmic brain activities maintain a certain tonic activation of the thalamocortical network, thus, facilitating signal processing, while slower activities influence the synaptic plasticity that affects memory consolidation.

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