Thalamocortical Oscillations: Local Control of EEG Slow Waves

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Abstract: This article starts with a brief review of the thalamocortical system architecture, which is composed of the projecting thalamic nuclei, the thalamic reticular nucleus, and the neocortex. Then we provide a description of the three states of vigilances followed by a detailed review of major brain rhythms present in the thalamocortical system, ranging from very slow to very fast oscillations. We provide descriptions of known mechanisms and hypotheses for unknown mechanisms for the generation of the different rhythms. The last part offers a detailed review on sleep slow oscillation describing its properties in the thalamocortical system, proposing a mechanism of generation of active states and a description of their propagation.

Keywords: Slow-wave sleep, Slow oscillation, sleep, thalamocortical, states of vigilance.

1. ARCHITECTURE OF THALAMOCORTICAL SYSTEM

The thalamocortical (TC) system is a site of generation of different types of oscillatory activities with distinct mechanisms. The TC network is organized in a loop Fig. (I).

1.1. Dorsal Thalamus

The dorsal thalamus receives specific inputs from ascending sensory pathways (medial lemniscus, optic tract, brachium of the interior colliculus, brachium conjunctivum, etc.) and from the brainstem modulatory systems (cholinergic, norepinephrinergic, serotoninergic, etc.) reviewed in [1]. In TC neurons the vast majority of fibers from ascending sensory pathways arrives on proximal dendrites and forms large synapses with multiple release sites, while corticothalamic fibers arrive mainly to distal dendrites [2], but could also form giant synapses on proximal dendrites [3]. Thalamocortical neurons are not interconnected via chemical synapses, but they might be electrically coupled as suggested by a study in cat’s thalamus [4]. A variety of thalamic nuclei of most of species contain GABAergic interneurons, constituting 20 to 30% of neurons. In rodents, interneurons are present in the lateral geniculate nucleus only [5, 6]. The TC neurons send their glutamatergic axons to the cerebral cortex and the reticular (RE) thalamic nucleus. The axons of specific TC neurons terminate in layers III, IV and VI, while TC projections from non-specific nuclei terminate in layers I and III Fig. (I) [1, 7]. The majority of specific TC projections terminate on dendritic spines and shafts of stellate and pyramidal neurons, and occasionally on the cell somata of aspiny interneurons (reviewed in [8]). In the visual system of cats, synapses of TC neurons form approximately 5-6 % of the total number of synapses on layer IV neurons [9, 10].

1.2. Thalamic Reticular Neurons

The sources of afferents to the RE thalamic nucleus are the collaterals of TC and corticothalamic fibers Fig. (I), all of which pass through the RE nucleus [11]. Both of these projections are glutamatergic and thus excitatory. The vast majority of corticothalamic fibers originate from layer VI small pyramidal neurons and project exclusively to relay (specific) nuclei and to the RE nucleus Fig. (I); other corticothalamic fibers originate from layer V pyramidal neurons and these projections target both specific and non specific thalamic nuclei, but not RE neurons (reviewed in [8]). Layer VI terminals form 60%, and TC terminals form 30%, of synapses on RE thalamic nucleus. However, EPSCs originating from TC neurons are faster rising and larger in amplitude as compared to those originating from corticothalamic fibers [12]. Minimal stimulations of corticothalamic fibers evoked EPSCs that are 2.4 times greater in RE than in relay neurons; and the quantal size of EPSCs is 2.6 times greater in RE neurons. Also, GluR4 subunits labeled at corticothalamic synapses on RE neurons outnumbered those on relay cells by 3.7 times [13]. Thus, the excitatory influence of corticothalamic fibers on RE neurons is much larger than their influence on TC neurons. Therefore, both TC and corticothalamic axons produce efficient activation of RE neurons. All neurons within the RE thalamic nucleus are GABAergic [14, 15], and their axons, after giving off one or two collaterals in the nucleus, enter the underlying dorsal thalamus and terminate [16-18]. A distinct feature of RE intranuclear connections is the presence of gap junctions, which couple electrotonically RE neurons [19, 20].

1.3. Neocortex

The neocortical tissue is composed of neuronal and glial cells; neocortical neurons being the principal elements of neocortex. They receive information from periphery, integrate the received signals, and send the received information to executive structures. Two major groups of neurons compose neocortex: pyramidal cells and interneurons.

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1.3.1. Pyramidal Neurons

In fixed tissue, pyramidal neurons have a pyramidal shape; in the unfixed tissue they usually look ovoid. Pyramidal cells are projecting neurons with long axon and constitute about 80% of all cortical neurons [21]. Their distinct morphological feature is the presence of a long apical dendrite that arise from the upper pole of the neuronal body toward cortical surface giving rise to several oblique branches, which in turn give second, third, (etc.) order branches. In most of pyramidal neurons, their apical dendrite reaches cortical layer I. A base of neuronal body gives rise to several basal dendrites oriented either horizontally or downward. Basal dendrites also produce branches. In some types of pyramidal cells, basal dendrites form about 90% of the total dendritic length [21]. And in large pyramidal cells, the diameter of the basal dendritic field covers up to 500 μm. The axon of pyramidal cells is oriented downward; it originates from the base of neuronal body or from the very proximal part of basal dendrites. Giving off several short-range local branches within the surrounding tissue, the axon leaves neocortex to innervate other cortical and subcortical structures [21].

1.3.2. Interneurons

Interneurons are a very heterogeneous population of neocortical cells with diverse morphological, physiological, and molecular features. Detailed descriptions of interneuronal morphological and physiological types could be found in recent reviews [22, 23]. All known neocortical interneurons are local-circuit cells with axon arborizing within neocortex either in vertical direction forming neocortical column or horizontally. Different types of interneurons form synapses
at different locations on their target: proximal dendrites, distal dendrites, soma, axon initial segment, etc. Spiny stellate cells have a star-shaped dendritic arbor, possess spines, and they are the only type of interneuron to exert an excitatory action on its targets. The other interneurons are inhibitory. The major inputs on these neurons are axons of TC cells from specific thalamic nuclei and they project preferentially to cortical layers II-III (Fig. (1)).

1.3.3. Neocortical Layers and Columns

Despite a large complexity, neocortex has a stereotyped organization. A normal cortex has a specific cytoarchitecture, being horizontally organized into six laminae [24] and vertically into groups of synaptically linked cells, called neocortical minicolumns, that represent the basic processing units of the mature neocortex, and which are further grouped together by short-range horizontal connections into cortical columns [25-27].

Similar laminar cortical organization is found across multiple species. In cats the total thickness of neocortex in somatosensory and parietal areas in fixed and dry sections was estimated to be around 1.7-1.8 mm [28]. However, neuronal recordings in vivo demonstrated the presence of neuronal activities until the depth of 2.3 mm [29] suggesting that unfixed normal cortical tissue in cats could have a thickness of about 2.3 mm. Multiple original studies and reviews provided a description of cortical layers. We direct readers to a brief version of such description done by Creutzfeldt [30].

1.3.4. Synaptic Connections in Neocortex

The synaptic connectivity in the neocortex is very dense. Each pyramidal cell receives 5000 to 60000 synapses [21, 23, 31, 32]. Local-circuit synapses have been estimated to account for as many as 70 % of the synapses present in some areas of the cortex [33-35] and pyramidal cells constitute about 80 % of the total number of neocortical neurons [21]. Most of inhibitory synapses are located in the perisomatic region and most of excitatory synapses are located on dendrites and spines [21]. According to the cable theory of neuron [36], synapses that are located closer to the place of generation of action potentials (axon hillock in most of the cases, but in some occasions in dendritic triggering zones) have a stronger influence on action potential generation than synapses located remotely. However, due to high input resistance of dendrites, synaptic currents arriving to distal dendrites generate large amplitude responses, that can be amplified by a large variety of currents [37]. Therefore, synaptic potentials arriving to distal dendrites produce somatic EPSPs comparable to those produced by proximal inputs [38]. Shunting effects of network activities on cortical neurons [39, 40] and in particular on their dendrites might significantly influence the expression of the above mentioned phenomena. In addition to thalamic inputs (see above), corpus callosum neurons, connecting the 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 [41-44]. The other inputs to a given cortical area come from multiple ipsilateral cortical fields. A given intracortical excitatory presynaptic axon forms from one to eight synaptic contacts with postsynaptic neurons [45, 46] that elicit excitatory postsynaptic potentials from 0.1 to 10 mV, with a total mean of about 1 mV [46-48]. Similarly to RE neurons, a network of inhibitory interneurons in the neocortex is coupled via electrotonic synapses [49, 50].

The vertical cortical organization is complex and basically each layer is connected to each layer. However, some connections are more numerous and more powerful than others. When sensory inputs from thalamus arrive to layer IV, layer IV neurons excite layer III, which in turn excite layer II, layer IV, and layer V neurons. Layer V neurons excite other layer V neurons, layer III neurons, and layer VI neurons. Layer VI neurons excite layer IV neurons [7, 51]. This morphological background is reflected in consecutive pattern of activation of cortical tissue [52].

There are important species-related differences in intracortical organization among species of mammals. These differences include basic features that are determinant of the emergent activity such as the density of neurons, patterns of connectivity, density of synaptic connections, cell types, proportion of inhibitory / excitatory cells, etc [53]. There are also differences in horizontal connectivity. Intracortical network forms horizontal patchy connections in cats, ferrets and primates, but not in rodents (Fig. (1), reviewed in [54]). This suggests that the patterns of synchronous oscillations and their propagation in different species can be different.

2. STATES OF VIGILANCE AND THALAMOCORTICAL SYSTEM

All normal brain activities occur during three major states of vigilance. These are waking state, slow-wave sleep (SWS, sometimes called non-REM sleep), and REM (rapid-eye-movement) sleep (sometimes called paradoxical sleep). The earliest electrophysiological study of brain activities demonstrated that the waking state is characterized by low amplitude fast waves, sleep is dominated by large amplitude slow waves, but a part of sleep (called fair sleep in that study) was characterized by low amplitude fast waves [55]. It was shown later that electroencephalogram (EEG) activated patterns recorded during waking state and REM sleep can be elicited by electrical stimulation of the reticular formation of the brain stem or ascending reticular activating system [56]. Modern formal electrophysiological description of states of vigilance requires the evaluation of three criteria: EEG, electromyogram (EMG) and electrooculogram (EOG).

The waking state is characterized by the presence of activated EEG patterns (high frequency low amplitude waves; Fig. (2a), the presence of muscle tone (usually irregular), and occasional eye movements. During SWS the EEG is dominated by large amplitude slow waves that may contain fast components (see below), steady muscle tone, and absence of eye movements. REM sleep is characterized by an activated EEG pattern (similar to wake), absence of muscle tone (except muscles of respiratory system and occasional twitches), and rapid ocular saccades (REMs, reviewed in [57]). The membrane potential of cortical neurons during waking state and REM sleep is relatively depolarized (around -62 mV); during SWS cortical neurons oscillate between depolarizing (mean around -62 mV) and hyperpolarizing (mean around -70 mV) states [58, 59].

The brain ascending activating system is constituted of several neuromediator (neuromodulator) systems with a ma-
2.1. Thalamocortical Oscillations During Slow-Wave Sleep

We have recently provided a detailed description of TC oscillations and their functional role [63]. A simplified version of this review on TC oscillations is freely available online [64]. Therefore, we provide only a brief description of oscillations generated within TC system Fig. (2). The frequency of oscillations spans from 0.02 Hz to 600 Hz. Therefore, thalamocortical oscillations are grouped in several frequency bands, for some of which the mechanisms of generation are known.

2.1.1. Infra-Slow Oscillation

This type of oscillatory activity has a period within the range of tens of seconds to a minute [65]. Very little is known about the underlying mechanisms of these oscillations but at least some of the factors responsible for their generation could depend on non-neuronal dynamics [66], such as changes in CO₂ concentration [67]. Infra-slow activities likely have a cortical origin given that they can be recorded from neocortical slabs [68].

2.1.2. Slow Oscillation

During slow-wave sleep (SWS) and some types of anesthesia the dominant activity is generated with a frequency (0.3 - 1 Hz), termed slow oscillation [58, 59, 69, 70]. In both, anesthetized [71, 72] and naturally sleeping animals [58, 59, 73], during slow oscillation the entire cortical network alternates between silent (Hyperpolarizing, or Down) and active (Depolarizing, or Up) states that correspond to depth-positive and depth-negative waves of local field potentials Fig. (2b). Most studies point to a cortical origin of slow oscillation. In section 3 we will describe the current state of knowledge regarding mechanisms of origin, synchronization, and propagation of slow oscillation.

2.1.3. Delta Oscillation

The delta oscillation occurs during slow-wave sleep with frequencies of 1 Hz to 4 Hz. The fact that delta and slow oscillation represent two distinct phenomena was demonstrated by Achermann and Borbély [74] who showed differences 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. At least in anesthetized animals, slow oscillation groups delta waves [75]. There are some evidences suggesting that slow oscillation and delta waves do not represent separate phenomena (reviewed in [76]). Cortically recorded delta oscillation has likely two components: one of which originates in the neocortex and the other in the thalamus. Both surgical removal of thalamus [77, 78], and neocortical slabs in chronic conditions (Timofeev, unpublished observation) result in a significant enhancement of neocortical delta activity. Little is known about the cellular mechanisms mediating cortical delta oscillation. One of the hypotheses suggests that cortical delta activity could be driven by the discharge of intrinsically-bursting neurons [79]. This is unlikely, because in order to induce a burst, intrinsically-bursting neurons have to be driven by either intrinsically or synaptically generated depolarization [80]. Therefore, it is unclear what would drive these neurons, in conditions of decreased activity of neuro-modulatory systems, which removes the depolarizing drive in the majority of cortical neurons (see section 2). On the other hand, thalamic delta (1-4 Hz) is a well-known example of rhythmic activity generated intrinsically by thalamic relay neurons as a result of an interplay between their low-threshold Ca²⁺ current (I₉) and hyperpolarization-activated cation current (I₉) [80a] Properties of a hyperpolarization-activated cation current and its role in rhythmic oscillation in thalamic relay neurons. J Physiol 431:291-318. As such, the delta oscillation may be observed during deep sleep when thalamic relay neurons are hyperpolarized sufficiently to deactivate I₉ [81-84]. It was also shown that at a certain level of leak current (I₉), the ‘window’ component of I₉ in thalamocortical neurons, may create oscillations similar in frequency to the intrinsic thalamic delta oscillation [85]. However, multi-site unit recordings demonstrated that TC neurons generate delta oscillations in an asynchronous manner [86]. Asynchronous firing of TC neurons cannot produce effects appearing as large amplitude synchronized slow waves. Therefore, it is unlikely that intrinsic delta oscillation of TC neurons is implicated in the generation of cortical delta rhythm.

2.1.4. Spindle Oscillation

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, spindle oscillations are typically observed during light sleep or during active phases of SWS oscillations Fig. (2c). In cats, the maximal occurrence of sleep spindle was found in motor, somatosensory, and to a lesser extent in associative cortical areas [87]. In vivo, in vitro, and modeling studies suggest that the minimal substrate contributing to the generation of spindle oscillations is the thalamus [88-93]. A presence of spindle oscillations after decortication [86, 94-96] provides strong evidence to the thalamic origin of this activity. Spindle-like activity was found in thalamic LGN (lateral geniculate nucleus) slice preparations of ferrets with preserved interconnections with perigeniculate nucleus [91, 97, 98]. The well accepted mechanism of spindle oscillation is following: the RE inhibitory neurons fire a spike-
burst that elicit IPSP in TC neurons, at the end of the IPSP, TC neurons generate a rebound spike-burst that excite 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 [99, 100]. (b) During the early 3-4 IPSPs composing the spindle, TC neurons do not display rebound spike-bursts [96, 101], suggesting that the positive feedback from TC to RE neurons does not contribute to the early phase of a spindle sequence. Generally, the early part of spindles is not seen or less marked at the neocortical level [96]. A more complex model suggests the presence of at least three phases with different underlying mechanisms that contribute to the spindle generation [96]. Cortical firing can trigger the onset of spindles by exciting hyperpolarized RE neurons that generate low-threshold calcium spikes (LTS) accompanied with high frequency spike-bursts. During an early phase of spindles, the RE nucleus is driving the spindles by its own mechanisms [100]. The membrane potential of RE neurons during network silence is hyperpolarized by about 8-10 mV below the reversal potential for IPSP mediated by chloride. An initial spike-burst in RE neurons generate depolarizing IPSPs in their synaptically connected RE target, which then drive LTS in those target neurons [100]. The second part of spindles primarily develops as a result of interactions between RE and TC neurons as described above, but the cortical firing contributes to the spindle synchronization via firing of corticothalamic neurons imposing simultaneous excitation of RE and TC neurons. Given the robust cortical influence on RE neurons [13], the inhibitory projections of RE neurons onto TC neurons reinforce the spindle. The waning phase occurs as a result of Ca²⁺ induced cAMP up-regulation of Ih in TC cells [102-105] and network desynchronization [96]. The active role of neocortex in spindle generation is emphasized by the fact that in cats anesthetized with ketamine-xylazine, the overall length of spindles constitutes less than 400 ms, while after decortications, in the same anesthesia conditions, spindles last more than 1 second.

Therefore, neocortex does not only reflects spindle activities originating in thalamus Fig. (2c), but actively contribute to the initiation and termination of spindles.

**2.1.5. Beta-Gamma Activities**

The waking state of the brain is characterized by low correlation of spike discharges across neighboring neurons [106] and the predominance of the frequencies in the beta (15-30 Hz) and gamma (30-60 Hz) ranges [107, 108]. Studies have indicated that cortical gamma activity is associated with attentiveness [109, 110], focused arousal [111], sensory perception [112], and movement [113, 114]. It has been proposed that synchronization in the gamma frequency range is related to cognitive processing and to the temporal binding of sensory stimuli [115-117]. The fast rhythms are also synchronized between neighboring sites during deep anesthesia, natural SWS, and REM sleep [118-120], when conscious state is either suspended (anesthesia, SWS) or illogical (REM sleep). Therefore, beta-gamma activities should not be associated exclusively with aroused states. During SWS, fast rhythms follow the onset of depth-negative EEG wave. Large-scale network simulations revealed that coherent gamma range oscillations may appear through occasional increases in spiking synchrony within local groups of cortical neurons [121, 122].

At least two non-exclusive basic mechanisms have been proposed to explain the origin of beta-gamma oscillations.

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**Fig. (2). Oscillations in thalamocortical system.** a. Frequency band of oscillations recorded in the thalamocortical system. b. Segment of intracellular recording (black) recorded during slow-wave sleep in cat’s associative cortex. The signal was then filtered for slow oscillation (0.1-1 Hz, red trace). c. Segment of intracellular recording (black) recorded during slow-wave sleep in cat’s somatosensory cortex. A segment filtered for spindle (7-15 Hz, green). Panel a from http://www.scholarpedia.org/, panels b and c, unpublished observations by Timofeev and Chauvette.
One emphasizes on extracortical while the other point to an intracortical origin of these activities. A high-frequency peripheral (retinal, lemniscal or cerebellar) oscillations [123, 124] could impose peripheral fast activities onto thalamocortical system. Intracortical mechanisms itself include several possibilities. The first one is based on the intrinsic property of fast-rhythmic-bursting (FRB) neurons to fire fast spike-bursts at frequencies of 20-60 Hz. These neurons were first described as fast pyramidal tract neurons from somatosensory cortex [125], later found in layer II-III of visual cortex (small pyramids called “chattering cells” [126]). 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 [127, 128]. Experimental and modeling studies provide two possible mechanisms of fast-rhythmic-burst generation. The first depends on the interplay of Na⁺ and K⁺ currents [129, 130] and the second requires a reduction of intracellular Ca²⁺ concentration [131, 132]. This second mechanism of gamma activity generation was described both in vitro and in computational models. According to this mechanism the activity of inhibitory interneurons is essential to obtain oscillations at gamma range [133-136]. Lastly, FRB neurons hypothesis 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 [137]. The resulting network gamma oscillation demonstrated in computational model shares all the properties of gamma oscillations and shows a critical dependence on multiple spiking in FRB cells.

2.1.6. 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 [138-142]. In the neocortex, fast oscillations (>200 Hz, up to 600 Hz) have been found in sensory-evoked potentials in rat barrel cortex [143, 144] and during high-voltage spike-and-wave patterns in rat [145]. During natural states of vigilance in cats, ripples were generally more prominent during the depolarizing component of the slow oscillation in SWS than during wake or REM sleep [146]. Around epileptic foci in humans and cats, the amplitude of ripples is dramatically enhanced [147-151]. Studies in epileptic patients have revealed the presence of high-frequency oscillations also in the hippocampus and entorhinal cortex [152-154].

The high-frequency field potential oscillations during ripples are phase-locked with neuronal firing [144, 146, 149, 155]. 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 [146]. Of all types of electrophysiologically identified neocortical neurons, FRB and fast-spiking cells displayed the highest firing rates during ripples and the inhibitory processes controlled the phase precision of ripple-dependent neuronal firing [142, 146]. As ripples can be generated within small isolated slabs of cortex, neocortical networks seems to be sufficient to produce them [146]. In addition to active inhibition, the electrical coupling mediated by gap junctions contributes to the ripple synchronization [149, 155, 156]. The electrical coupling may occur between axons of principal cells [157] or via a network of inhibitory interneurons [49, 50, 158-160]. The field potentials increase neuronal excitability, and by a positive feedback loop they could be also involved in the generation of neocortical ripples [151]. Since ripples are recorded also in glial cells, the electrical coupling between glial cells could also play a role in the synchronization of LFP ripples [149].

2.1.7. Paroxysmal Oscillations

Electrographically, seizures are often composed of spike-wave/polyspike-wave (SW/PSW) electroencephalographic (EEG) discharges at 1.0-2.5 Hz and runs of fast spikes at 7-16 Hz. However, on some occasions neocortical seizures are characterized by SW complexes at approximately 3 Hz. Spontaneously occurring SW complexes at 1-2.5 Hz and fast runs at 7–16 Hz develop without discontinuity from slow (mainly 0.5–0.9 Hz) cortically generated oscillations. At the focus, the onset of neocortical seizures is accompanied with generation of ripples (>120 Hz). During seizure, the ripples can be recorded at multiple cortical locations. Detailed description of paroxysmal activities generated by thalamocortical system and their cellular mechanisms were subjects of our recent reviews and can be found in [161-163].

3. SLOW OSCILLATION, LOCAL ORIGIN, SYNCHRONIZATION, PROPAGATION

3.1. Description of Slow Oscillation

The initial description of slow oscillation suggested that this rhythm has a cortical origin [69, 75, 164]. Intracellular recordings from both regular-spiking (excitatory) and fast-spiking (inhibitory) cortical neurons demonstrated that these neurons reveal alternation of depolarizing and hyperpolarizing states Figs. (2b, 3d, and 4d). During depolarizing states, cortical neurons show barrages of synaptic activities and occasionally fire action potentials. Only the initial phase of hyperpolarizing state was affected by recordings with CI-containing pipette, demonstrating that essentially, the hyperpolarizing phase was not mediated by GABAA-dependent inhibition. A later study on cats anesthetized with ketamine-xylazine demonstrated that hyperpolarizing states were associated with surface-negative (depth-positive) field potential waves and depolarizing states were associated with surface-positive (depth-negative) waves Fig. (4) [71]. During depopolarizing wave, both RE and TC neurons are hyperpolarized like cortical neurons; during depth-negative field potential wave RE neurons are depolarized and either fire tonically or reveal spindle-like high frequency spike-bursts [71, 165, 166]. By contrast, TC neurons display rhythmic IPSPs with spindle frequency and occasional rebound spike-bursts [71, 86, 96]. Later studies demonstrated that neuronal hyperpolarization taking place during the depth-positive field potential waves is a period of disfacilitation, i.e. the absence of synaptic activity. Because all major neuronal populations within TC system are hyperpolarized during depth-positive field potential wave, unitary synaptic activities originating (evoked) within ascending prethalamic fibers induces simple EPSPs in TC neurons, that are not accompanied with action potentials [167, 168]. Due to the absence of synaptic activities in TC system, the input resistance of cortical, TC and RE neurons is higher during these hyperpolarizing or silent
states as compare to depolarizing (hyperpolarizing in TC cells) or active states [166].

The cortical origin of slow oscillation was shown by the facts that (a) slow oscillation was preserved two days after a complete kainic acid lesion of thalamus [69], (b) a single hemisphere decortication abolishes slow oscillation in this hemisphere, but does not affect slow oscillation in contralateral (intact) hemisphere [86], and (c) slow oscillation can be obtained in isolated neocortical preparation such as slices maintained in vitro [169] and large neocortical slab in vivo [180].

3.2. Slow Oscillation Occurs During Slow-Wave Sleep

Intracellular recordings from cortical neurons during states of vigilance demonstrated that an alternation of active and silent states occurs only during SWS and not in any other state of vigilance [58, 59, 120, 170]. Similar alternations of active and silent states in neocortical neurons were recorded in associative, motor, somatosensory, and visual cortices of cats. Waking state and REM sleep show a single mode distribution of membrane potential and silent states are absent during these states of vigilance [58, 171]. Similar results were obtained in striatal medium spiny neurons [172] or cortical neurons [73] of rats. In intracellular recordings the mean firing rates of cortical neurons during all states of vigilance were similar, although instantaneous firing and occurrence of intrinsically-bursting cells during SWS were higher than in other states of vigilance [58]. However multiunit recordings show about 40% increase in mean firing rates during activated brain states as compare to SWS [173]. Similar to anesthetized preparations, silent states during natural SWS were periods of disfacilitation [59]. It was concluded that the presence of hyperpolarizing silent states makes SWS so distinct from other states of vigilance [174]. In contrast to above, large amplitude fluctuations of membrane potential (unlikely states) were found during quiet wakefulness in mice barrel cortex [175-177]. In these studies, states of vigilance were not identified formally. However, in the available example [[177], see their Fig. (2b), the large amplitude
membrane potential fluctuations occur only when slow waves are present in local field potential recordings, suggesting that at this time the mice was either in the state of SWS or drowsiness. A more speculative alternative explanation is that slow waves in mice somatosensory cortex can occur during waking state.

3.3. Propagation of Slow Oscillation

The above studies showed a quite homogeneous pattern of activities in all investigated cortical areas. However, it was unclear whether slow waves of SWS start simultaneously in all cortical areas and in this case, what is the trigger of these slow waves, or slow waves start in some specific location and from that location they propagate to other cortical regions. High density EEG studies in humans demonstrated that each individual cortical wave can start at any location and then propagate to other cortical regions [178]. However, in adult human, slow waves preferentially start in frontal cortical areas and propagate from there to more posterior regions. It was unclear from these scalp EEG recordings what component of slow waves (active or silent states or both) starts and propagates. Multisite intracellular recordings associative cortex of cats anesthetized with ketamine-xylazine showed that active states start in some point of neocortex and propagate to other regions [174, 179]. Similar to humans, in cats active states can start in any point of neocortex, but within suprasylvian gyrus most of active states originate around the border of cortical area 5 and 7. Topographically, these are different areas Fig. (3a), but they share some similarities. Both human frontal cortex and parietal cortex of cats are poly-sensory, receive extensive connections from multiple cortical and subcortical structures and are responsible for highest brain functions in respective species. Surprisingly, the onset of silent states occurred almost simultaneously in cortical regions separated by up to 12 mm Fig. (3), which suggests the presence of a global mechanism of synchronization. Although silent states are mediated by potassium conductance [59], a recent computational model suggest a role for active inhibition at the onset of silent state (Chen et al., submitted).

3.4. Origin of Active States

3.4.1. Possible Mechanisms of Origin of Active States

Active states start when all cortical neurons are in silent state. How does activity originate during silent state, when no action potentials are generated by neocortical neurons? Three hypotheses on the origin of activity have been proposed. The first hypothesis suggests that spontaneous transmitter release in large neuronal populations occasionally depolarizes some cells to the firing threshold, thus initiating an active state in the network [180]. The spontaneous release hypothesis predicts that activity may start in any neuron, although cells receiving largest excitatory convergence will have higher probability of being activated before the others. The second hypothesis suggests that transition from silence to activity is mediated by intrinsic oscillations of layer V pyramidal neurons, which remain more depolarized because of their intrinsic or synaptic properties, and generate some spikes between the active states when other cortical neurons are silent [169]. Once initiated by layer V neurons, activity then propagates to other cortical layers. The layer V neurons hypothesis predicts, that activity always originates in these neurons, while appears later in other cells. The third hypothesis attributes transitions from silent to active states to the selective synchronization of spatially structured neuronal ensembles involving a small number of cells [181]. The selective synchronization hypothesis predicts that even during the silent states, some neurons of the network still generate irregular spontaneous firing. More recent studies provided controversial results. Intracortical recordings from epileptic patients demonstrated that active states originate in superficial layers [182, 183]. However, optical and patch-clamp recordings from layer II-III neurons from visual and somatosensory cortex of healthy rats demonstrated very low firing rates of these neurons, making them unlikely candidates for active state initiation [184, 185]. Extracellular unit recordings from layer V neurons revealed that each neuron has its unique spiking pattern [186] that contradicts the idea of stochastic origin of active states [180, 181], but supports the hypothesis that particular set of neurons lead active state origin [169, 187, 188].

3.4.2. Active States Start Preferentially in Layer V Neurons

In a recent study, we directly investigated where and how the active states start at the border of area 5 and 7 of cats associative cortex, the place with the highest probability of active state onset in this species [189]. Multisite field potential recordings during SWS using a silicone probe containing 16 electrodes separated by 0.1 mm revealed that the onset of active states was probabilistic, i.e. it could start at any depth but most of the cycles started in deep electrodes and from there propagated upwards Fig. (4 a-c). Findings with extracellular unit recordings during SWS were congruent with field potential observations. The neurons located at the depth of 0.8-1.2 mm from surface (layer V [28]) were the first to fire action potentials during onset of active states. In addition, upper layer neurons rarely fired action potentials during spontaneous active states, but deep layer neurons reveal the highest incidence of firing [189]. Multunit recordings in naturally sleeping cats revealed no firing during silent states. Multisite intracellular recordings from local neuronal constellations in anesthetized cats demonstrated that spontaneous onset of active states took place in deep layers Fig. (4 d-h). Detailed analyzes of intracellular activities during silent states show that deeply located neurons had more numerous synaptic events during silent states, and some of these neurons also showed a strong buildup of these synaptic events prior to the onset of a new active state [189]. Because neuronal firing is absent during silent states, spike-independent spontaneous transmitter release (minis) might still take place [180, 190, 191].

If all other conditions are identical, the number of minis depends on the number of synapses of a given neuron. The number of synapses varies with the dendritic tree size. The number of synapses on small pyramidal neurons is in the order of 10000, while in large layer V pyramidal cells it can reach 50000 [21]. According to the cable theory [36], distally arriving events should attenuate while reaching the soma. However, because of the small diameter of distal dendrites and therefore their high resistance, the same size synaptic current will generate a much larger response in distal
Fig. (4). Vertical propagation of slow oscillation. a. Local field potential recordings of one cycle of slow oscillation obtained with a 16-channel silicon probe, inserted perpendicularly to the cortical surface at the border of areas 5 and 7 of cat’s suprasylvian gyrus. Red lines show sigmoidal fits of the transitions from silent to active states. The time at ten percent of voltage amplitude in the transition was used to detect active state onset. b. same cycle as in a is shown at expanded scale. c. Depth profile of active state onsets. For each channel, a Gaussian fit of the distribution of activity onset delays relative to channel 16 is shown, color-coded for n cycles as indicated by the scale bar. d. LFP and intracellular activities of four simultaneously recorded neurons separated by less than 0.2 mm in lateral distance. e. Dependence of activity onset on the recording depth in cell pairs. Each pair of simultaneously recorded neurons is represented by two symbols connected with a line. Y-coordinates show the depth at which the cell was recorded. Positive delays (blue) indicate pairs with deeper cell leading; negative delays (green) indicate pairs with upper cell leading. Grey indicate recordings with similar depth (vertical difference <100 μm). (f, g) Distributions of the delays in cell pairs, color coded as in e. h. Dependence of the delay of activity onset in state clusters on recording depth. Each blue diamond symbol represents data for one cell. Running averages (red symbols) were calculated for sets of 17 neurons. For gross averages (cycles, ±SD) cells were segregated in three nearly equally populated groups, above 575 μm (n=27), between 575 and 1050 μm (n=27), and deeper than 1050 μm (n=27). (Modified from [189]).

dendrites as compared to one arriving directly at the soma and even the attenuated synaptic potential will be sizable at the level of the soma (reviewed in [192]). In addition, the presence of numerous intrinsic currents amplifies distally generated potentials on their way toward the soma [193]. Thus, the cells with larger number of synapses have better chance to be the first in the generation of spontaneous active states.

3.4.3. Extracellular Currents During Slow Waves

To investigate further the depth distribution of possible sources of activity during sleep slow oscillation, we per-
formed current-source density analysis from local field potential recordings [194-196]. This method basically shows the flow of transmembrane currents. For example, when a distal part of an apical dendrite receives excitatory drive, the positively charged ions go into that part of the dendrite (inward current) creating a transient negativity in surrounding extracellular space (sink). The negativity is created because the flow of positive charges into the neuron leaves uncompensated negative charges. This negative charge is recorded by an electrode as negative voltage. This sink generates extra- and intracellular current flow trying to compensate for charge misbalance and therefore, extracellular recordings from the vicinity of cell soma will indicate the presence of positive charges (extracellular source). A similar picture may be observed, if the cell soma receives strong inhibitory (hyperpolarizing) drive. In these conditions, an extracellular source will be created around the cell soma that will engender an extracellular sink in the vicinity of the apical dendrite. The extent of extracellular currents depends on the cell size and polarity. Large layer V pyramidal neurons create strong extracellular sinks and sources because the tips of their apical dendrites are located in upper layers and the soma is in layer V. Therefore, the extracellular current flows between these layers Fig. (5a). Layer III pyramidal neurons, for instance, create a much smaller impact on local field potentials, because the maximal extent of extracellular current flow generated by these neurons is located within layers I and III. Interneurons with radially oriented dendrites play an even smaller role, because extracellular sinks and sources created by their activity usually go in opposite directions Fig. (5a).

The current-source density plot reveals that during silent states, strong sinks were observed in the upper layers and sources in deeper layers Fig. (5c). Upon the transition to active states, the picture reverses to the opposite: sinks in the deeper layers and sources in the upper layers. During active states, the sources and sinks are generally weaker and much more variable both in space and in time than during silent states, indicating that during activity in neocortical networks, the flow of currents through the cortical depth is less regular and subject to stronger variability. The reversal of the depth profile of sinks and sources is typical for the transition from silence to activity; a sharp transition from a strong superficial sink and deeper source to weaker deep sinks and superficial sources stands out very clear in Fig. (5c-d). Examination at higher temporal resolution reveals that during the transition to activity, a switch from sources to sinks occurs earlier around channel 12 Fig. (5d) and then “spreads” upwards, towards channel 8. This observation is consistent with the depth profile of activity onset, described above.

As we mentioned above, all cortical neurons are hyperpolarized and silent during silent cortical states. What creates such strong superficial sinks and deep sources during this state? That is the difference in voltage of different neuronal compartments during this silent state. Indeed, because the dendrites are thin, their axial resistance has large values [197]. Due to the large electrotonic distance, the membrane potential at two compartments may differ by several millivolts [198, 199] and thus cause significant current flow along the apical dendrites.

4. CONCLUSION

Stimulation of ascending sensory pathways induces initial activation in cortical layer 4 and from that layer the activity spreads to more superficial and deep layers [194, 195] see Fig. (1). Local field potential, extracellular unit and intracellular recordings during spontaneous slow oscillation point to an earlier activation in deep layers, and both multi-unit and intracellular recordings point to an earlier firing of cells located in layer V. This activation starts from the silent state, when no cells are firing. Because slow oscillation has a cortical origin, the absence of neuronal firing during silent states restricts the possible mechanisms of active state gen-

![Fig. (5)](image_url)

**Fig. (5).** Leading impact of large layer V pyramidal neurons in the generation of cortical field potentials. a. Reconstruction of a small pyramidal cell from layer III (red), an interneuron (pink), and a large pyramidal cell from layer V (orange). Respective dipoles of these cells are indicated. b. One cycle of slow oscillation recorded with a silicon probe containing 16 contacts separated by 0.1 mm. Note that the reversal of local field potentials occurs around the middle upper part of layer V pyramidal cell. c. Current-source density plot of averaged cycle of slow oscillation. The zero time corresponds to half amplitude of transition from silent to active state. d. Same as c, but with higher temporal resolution around transition from silent to active states. (Panels a and b, unpublished observations by Chauvette and Timofeev, panels c and d from [189]).
eration to spike-independent processes. The spike-independent process causes a buildup of depolarization that occasionally reaches spike threshold in some cells [180, 189]. The firing of these cells initiates the activity in the rest of the network. The spontaneous releases necessary for active state initiation may occur not only from nerve terminals, but also from glial cells surrounding synapses [200]. In contrast to earlier hypotheses, we suggest that activity does not necessarily originate in layer V cells. Due to the stochastic nature of spontaneous transmitter release, the first transition from silence to activity may occur in any neuron. However, because of the large number of synaptic inputs, layer V neurons are better situated to initiate the active state. The intracortical patterns of connectivity Fig. (1) transmit this excitatory drive to more superficial layers and to neighboring cortical territories. The strong dipole generated by layer V pyramids; generate the major local field potential that influences excitability of local neuronal networks. The specific cortico-thalamo-cortical loop may reinforce local intracortical excitation during active states. If non-specific thalamic nuclei are involved, the thalamus may contribute to the generation of active states in other cortical territories, but will diminish the density of sink and sources. Because the axons of non-specific nuclei arrive preferentially to superficial cortical layers, they will excite dendrites of neurons located in these layers, including layer V pyramidal cells that will generate superficial sinks and deep sources although other local activities during active states generate deep sinks and superficial sources. The overall outcome is reduced sinks-sources density during active states Fig. (5).

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Thalamocortical Oscillations


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