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Current Opinion in Neurobiology

Dynamical changes in neurological diseases and anesthesia

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Dynamics of neuronal networks can be altered in at least two ways: by changes in connectivity, that is, the physical architecture of the network, or changes in the amplitudes and kinetics of the intrinsic and synaptic currents within and between the elements making up a network. We argue that the latter changes are often overlooked as sources of alterations in network behavior when there are also structural (connectivity) abnormalities present; indeed, they may even give rise to the structural changes observed in these states. Here we look at two clinically relevant states (Parkinson's disease and schizophrenia) and argue that non-structural changes are important in the development of abnormal dynamics within the networks known to be relevant to each disorder. We also discuss anesthesia, since it is entirely acute, thus illustrating the potent effects of changes in synaptic and intrinsic membrane currents in the absence of structural alteration. In each of these, we focus on the role of changes in GABAergic function within microcircuits, stressing literature within the last few years.

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Current Opinion in Neurobiology 2012, **22**:693–703

This review comes from a themed issue on **Microcircuits**

Edited by **Edward M Callaway** and **Eve Marder**

For a complete overview see the Issue and the Editorial

Available online 23rd March 2012

0959-4388/$ – see front matter, Published by Elsevier Ltd.

http://dx.doi.org/10.1016/j.conb.2012.02.009

Introduction

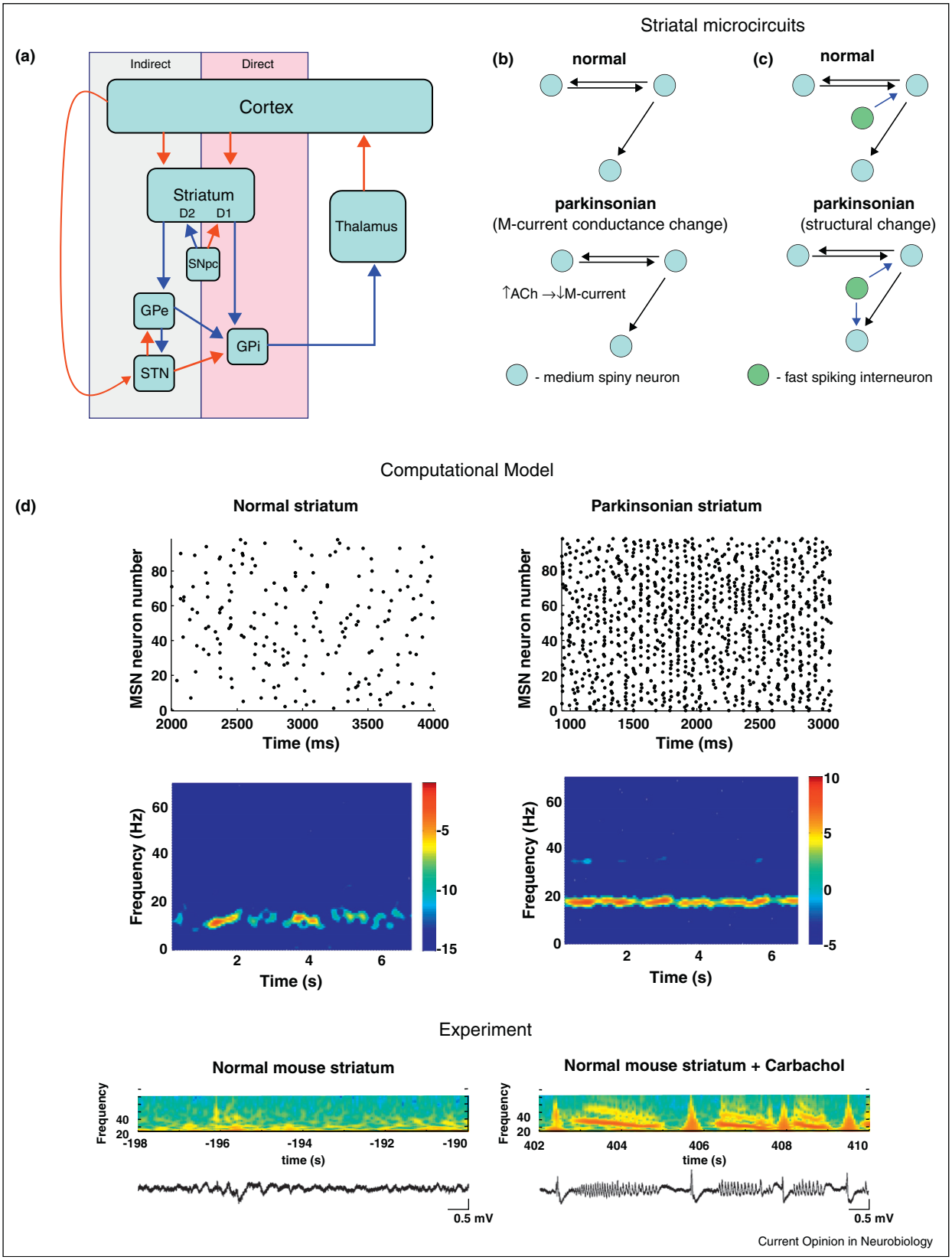
Parkinson's disease and schizophrenia are both diseases with significant alterations in neuronal network structure as well as alterations in brain rhythms. In each of these diseases, there are biochemical and structural changes that are associated with changes in network dynamics, including changes in rhythms. Much of the literature has emphasized the role of structural changes in the etiology of these diseases. By contrast, we focus here on changes in intrinsic and synaptic currents of microcircuits to show how these affect network dynamics. Furthermore, we discuss how some of these alterations in dynamics may lead to compensatory anatomical changes in the networks. Within this framework, the fundamental difference between Parkinson's disease and schizophrenia is that the former represents a derangement of established, normal brain dynamics whereas the latter represents a derangement of the processes needed to establish normal brain dynamics in the first place. In order to highlight that changes in sizes and dynamics of currents are tightly correlated with changes in network dynamics, we also discuss the changes in network rhythms that occur in anesthesia, and the potential relation to loss of consciousness. In each of these, changes in GABA functionality, or GABA interaction with other changed currents, are central to the changes in the microcircuit network dynamics.

Parkinson's disease

Parkinson's disease is a neurodegenerative disorder involving loss of dopaminergic neurons of the substantia nigra pars compacta (SNpc) that project primarily to the striatum. The efficacy of new treatments for Parkinson's disease, such as deep brain stimulation (DBS) to the subthalamic nucleus (STN) or the internal segment of the globus pallidus (GPi), highlights the fact that Parkinson's disease not only affects the SNpc and the striatum, but is a network disorder, involving alteration of the dynamics within and between the nuclei of the basal ganglia, the thalamus and the cortex.

A well-known dynamical abnormality in parkinsonian networks is the emergence of a prominent beta frequency rhythm in the basal ganglia and more coherent beta oscillations in the cortex [1–3,4] (Figure 1a). There exists correlation between the exaggerated beta oscillations and the bradykinesia and rigidity characteristic of the parkinsonian state [5]. Interestingly, both in the basal ganglia and cortex, modulation of beta oscillations occur with movement [6,1,7–9]. This indicates that the prominent beta rhythms in the basal ganglia and cortex found in Parkinson's disease may be an abnormal expression of a normal dynamical state of the network. A contrary point of view is that structural changes must occur before the increase in beta. Supporting evidence for this viewpoint is that a rat model of Parkinson's disease require several days post lesion before increases in beta oscillations are observed, and prominent beta oscillations do not occur immediately in response to dopamine antagonists [10].

Figure 1


Striatal microcircuits
(a)
Indirect
Direct
Cortex
Striatum
D2
D1
SNpc
GPe
GPi
STN
Thalamus
(b)
normal
parkinsonian
(M-current conductance change)
↑ACh →↓M-current
(c)
normal
parkinsonian
(structural change)
- medium spiny neuron
- fast spiking interneuron
Computational Model
(d)
Normal striatum
Parkinsonian striatum
MSN neuron number
Time (ms)
Frequency (Hz)
Time (s)
Experiment
Normal mouse striatum
Normal mouse striatum + Carbachol
Frequency
time (s)
0.5 mV
Current Opinion in Neurobiology

The search for the origin of pathologic rhythmic activity in Parkinson's disease has recently focused on striatum (Figure 1b and c): a recent study suggests that structural changes in striatal networks may be responsible for the rhythmic changes seen in Parkinson's disease patients by showing that chronic dopamine depletion increased connectivity between fast-spiking interneurons (FS cells) and 'indirect-pathway' medium spiny neurons (MSNs) in mouse striatum [11•] (Figure 1c). Computational modeling of the striatal MSN-FS network showed increased connectivity between FS cells and MSNs resulted in increased synchrony between MSNs, suggesting that this structural change in striatum may underlie the pathologic oscillatory changes seen in Parkinson's disease. (We note that the simulations in the Gittis *et al.* [11•] paper did not display synchrony in the beta frequency range.)

In contrast, another study suggests that the pathologic beta oscillations in Parkinson's disease may be the result of neuromodulation of a normal striatal network. Computational modeling of striatal networks shows that interactions between striatal MSNs, which account for 90–95% of the neurons in the rodent striatum [12] and are the only output neuron of the striatum, have the ability to generate robust beta oscillations under conditions that increase MSN excitability, including high cholinergic tone, loss of dopamine or increased background excitation from cortex or thalamus [13••] (Figure 1b and d). This model striatal MSN network produces beta oscillations independent of striatal FS interneurons. Experimentally, infusion of carbachol, a cholinergic agonist, into normal mouse striatum produced prominent beta frequency rhythms [13••] (Figure 1d). High striatal cholinergic tone is relevant to Parkinson's disease since dopamine tonically inhibits release of striatal ACh [14] and loss of dopamine increases ACh levels in the 6-OHDA rat, an animal model of Parkinson's disease [15].

We argue here that, although structural changes to networks may take place in Parkinson's disease, consideration should be given to viewing certain aspects of the pathologic dynamics as abnormal dynamical states of underlying normal networks. The increase in FS-MSN connectivity with dopamine depletion occurred within 3 days [11•], whereas high cholinergic tone promotes exaggerated beta oscillations within minutes [13••]. This suggests that the underlying network connectivity already exists in striatum to support the pathologic beta oscillations in Parkinson's disease and that structural changes are not necessary to promote exaggeration of network dynamics. Furthermore, since increased ACh decreases FS cell GABAergic inhibition of MSNs through presynaptic muscarinic receptors, FS cells are likely not necessary for the production of the exaggerated beta oscillations due to high cholinergic tone [16]. Gittis *et al.* [11•] find increased mIPSC frequencies in the D2 MSNs of the parkinsonian mouse; although they attribute this to increased FS to MSN connections, it could also be attributed to increased spiking of MSN neurons, a prediction of the MSN model network [13••]. The increased connectivity between FS and MSN cells seen in the 'indirect pathway' after chronic dopamine depletion could be a homeostatic response to the increased MSN spiking. A similar reactive response has been noted in mouse GPe neurons, which develop an HCN channelopathy after being rendered parkinsonian [17•]. Loss of HCN current can lead to increased synchronization between GPe neurons [17•]. However, viral introduction of the HCN subunits to GPe neurons did not eliminate the motor pathology in the parkinsonian mice, indicating that the HCN channelopathy is a reaction to, rather than an underlying cause of, network pathology.

Another study suggesting that normal circuitry is implicated in parkinsonian symptoms is [18••], in which optogenetic activation of D2-expressing MSN neurons caused parkinsonian symptoms in normal mice. Importantly, this study also showed that increased D1 MSN activation relieved the motor deficits caused by D2 MSN stimulation, indicating multiple points of interception in the normal network for abnormal network behavior. The MSN network model of [13••] predicts that the increased beta oscillations in Parkinson's disease occur in the MSNs with D2 receptors, since loss of dopamine increases activity in the D2 pathway [19].

Dopamine has been implicated in alterations of the dynamics of synaptic currents in other nuclei of the basal ganglia including GPe, GPi, STN and SNpr, many involving changes to the GABAergic system within these

(Figure 1 Legend) A prominent beta oscillation emerges in the basal ganglia and cortex of Parkinson's disease patients. **(a)** Schematic diagram of some of the major connections between the nuclei of the cortico-basal ganglia-thalamic loop (note: not all connections are shown). Excitatory connections are denoted by a red arrow and inhibitory connections are denoted by a blue arrow. (b, c) Highly schematic diagrams of striatal microcircuits of possible importance in the generation of rhythmic activity in Parkinson's disease. **(b)** Model networks of medium spiny neurons (MSNs) connected to each other *via* GABAa synapses can produce beta oscillations. Beta oscillations are amplified in the presence of high ACh, which lowers the MSN M-current conductance and increases the excitability of the individual MSNs [13••]. Lowering the maximal MSN M-current conductance is sufficient to amplify beta oscillations in the model MSN network. **(c)** Model networks of MSNs and fast-spiking interneurons show increased synchrony as additional FS-MSN connections are added [11•]. **(d)** Computational modeling of networks of striatal MSNs suggests that lower M-current conductance due to high ACh (the 'parkinsonian' state) can induce MSNs to spike more synchronously, as seen in the raster plots (top row) producing a beta frequency rhythm seen in the model spectrogram (second row). Experimental testing of the computational model revealed that the striatum of normal mice produces a beta frequency rhythm seen in the spectrogram (third row) and the LFP trace (last row) in the presence of the cholinergic agonist, carbachol. Subfigure d adapted from McCarthy *et al.* [13••].

nuclei [20•]. Some alterations to synaptic currents, such as decreasing the GABAergic conductance between GPe neurons and increasing GABAergic inhibition from striatum to GPe, have been shown to increase oscillatory activity in mathematical models of the STN-GPe network [21]. Both computational modeling and experimentation give evidence that the STN-GPe network is capable of generating rhythmic activity, which may have implications for rhythm generation in Parkinson's disease [22,23,24]. Furthermore, a cortical component of the pathologic beta rhythm is suggested by the evidence that beta frequency oscillations can be elicited in slices of primary motor cortex (M1) following application of the glutamate receptor agonist, kainate and the muscarinic agonist, carbachol in a manner dependent on intact GABAergic connections [25]. Additionally, beta rhythms can be generated from networks of layer V pyramidal cells of somatosensory cortex in a manner dependent on intact gap junctional connections but independent of input from higher cortical layers and independent of AMPA input [26]. Again, this argues that networks in M1 and S1 are both capable of generating robust beta frequency rhythms independent of structural changes within these networks. Beta oscillations in these networks are relevant to Parkinson's disease since beta oscillations are more coherent in the cortical EEG in untreated Parkinson's disease [4] and cortical layer V pyramidal neurons are the cells of origin of the corticospinal pathway.

Although the origin of the beta rhythms in Parkinson's disease is still under debate, the findings of multiple sites within the cortico-basal ganglia-thalamic loop that support oscillatory activity in response to changes in the dynamics of synaptic and membrane currents suggest that the exaggeration of beta oscillations in Parkinson's disease may be primarily due to alterations in the currents, rather than structural network changes.

Schizophrenia

Unlike Parkinson's disease, schizophrenia is not considered a neurodegenerative disorder. Instead, failure of neuronal networks to develop into a normal, mature brain is currently being proposed [27••]. These authors argue that the normal global connectivity changes associated with adolescence are left incomplete in affected individuals — a scenario that fits very well with the peak onset age [28]. Structurally, changes in both gray matter volume (usually highly lateral [29]) and white matter tracts are evident, with suggestions of interrelatedness in these two measures [30]. Such changes are also seen in non-schizophrenic siblings and prodromally [31,32] so it is difficult to determine whether they are a direct cause or merely one of many risk factors. However, functionally, such large-scale changes in anatomy are paralleled by global network function changes. In the resting state, there is loss of weak connections between brain areas; this correlates with deficits in cognitive function (attention and memory in particular [33]). In addition recent novel network analyses have revealed large differences in 'community structure' — which brain regions commonly interact with others — in schizophrenic patients [34].

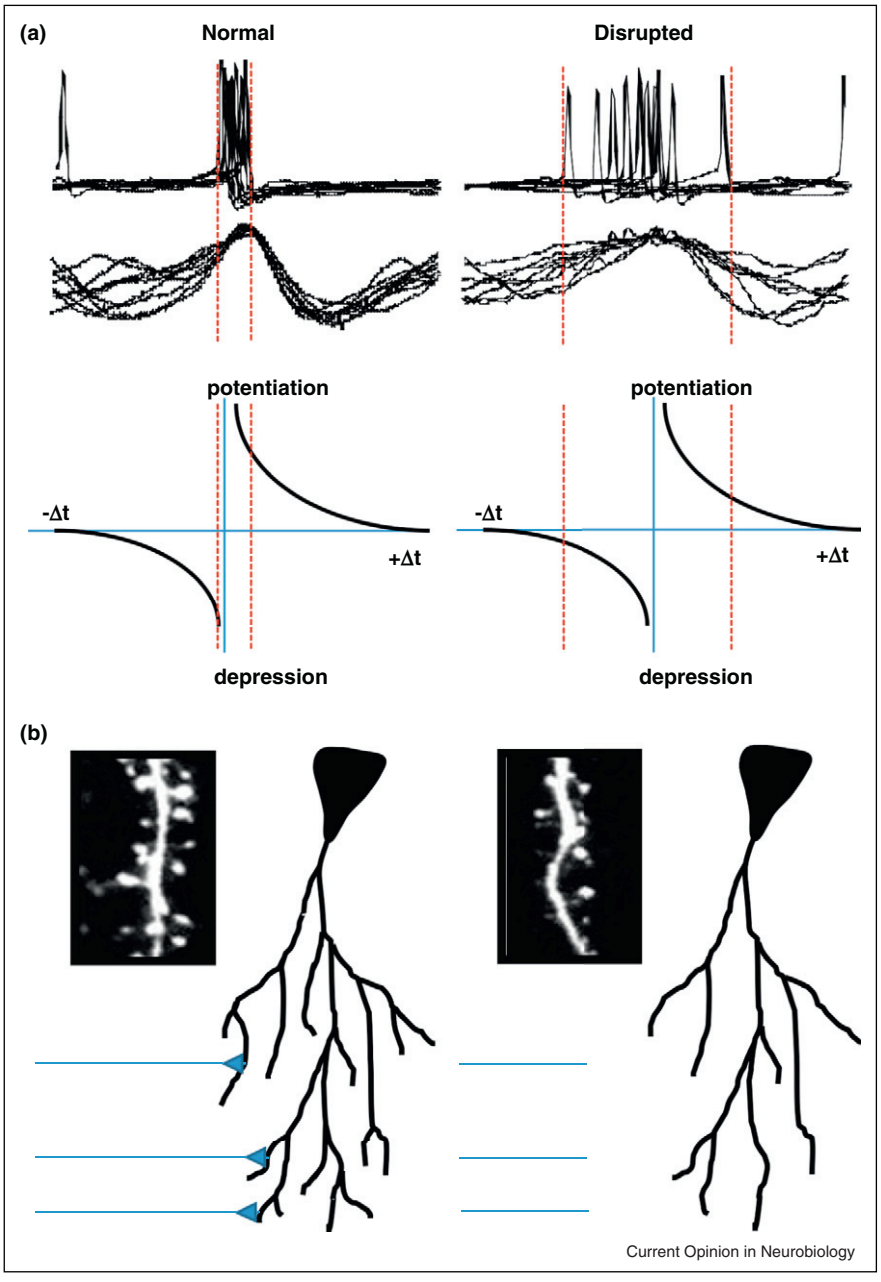
Given the accepted neurodevelopmental nature of schizophrenia, it is perhaps not surprising that such global structure and function deficits are seen. However, it is not clear whether relationships between structure and function are casual or causal and, if the latter, which causes which. Here we propose that the majority — if not all — of the structural changes above may arise secondary to the failure to produce appropriate cortical dynamics during brain development. Models of neurodevelopmental abnormalities linked to schizophrenia provide clues here. Dysbindin-1 is a candidate susceptibility gene in schizophrenia and linked to gray and white matter structural changes [35]. However, the predominant effect of mutation of this gene is reduction in synaptic inhibition in local circuits [36•]. Such inhibition plays a critical role in many aspects of brain function: It is critical for visual orientation tuning, a psychophysical measure disrupted in patients [37]. It is vital for the generation of many EEG rhythms of cognitive relevance (auditory beta rhythms [38], hippocampal theta rhythms [39] and gamma rhythms [40,41]). Each of these readily recordable features of cognitive function, but particularly gamma rhythms, is affected in schizophrenia and experimental models in a highly region-specific manner [42]. The interregional interaction between brain rhythms has been proposed to be critical for the formation of cortical networks during cognitive tasks [43]. Thus, a region-by-region difference in rhythm generation would be expected to contribute to a functional disconnect in cortex as seen in patients [44].

In terms of functional cortical connectivity in schizophrenia, gamma rhythms have received intense interest. Abnormalities in gamma rhythms have been repeatedly observed in schizophrenic patients [45••]. Gamma rhythms are associated with several correlates of cognitive function including perception, attention, memory, and experimental and computational modeling have shown the importance of fast-spiking interneurons in the generation of cortical gamma rhythms [46]. Optogenetic activation of fast-spiking interneurons has been shown to increase cortical gamma oscillations both *in vitro* and *in vivo* [47,48]. Interestingly, optogenetically increasing, but not decreasing, the interplay between local circuit excitatory and inhibitory synaptic activity in the medial prefrontal cortex of mice reversibly both engendered cognitive and social dysfunction and increased oscillations in the gamma frequency range [49••]. This deficit appears to be the result of an acute dysfunction of information processing within cortical circuitry. In contrast, in other brain regions

schizophrenia is associated with decreases in gamma power. This has been seen in primary auditory and visual cortices as well as parietal regions [50], and is particularly marked in entorhinal cortex in animal models [51].

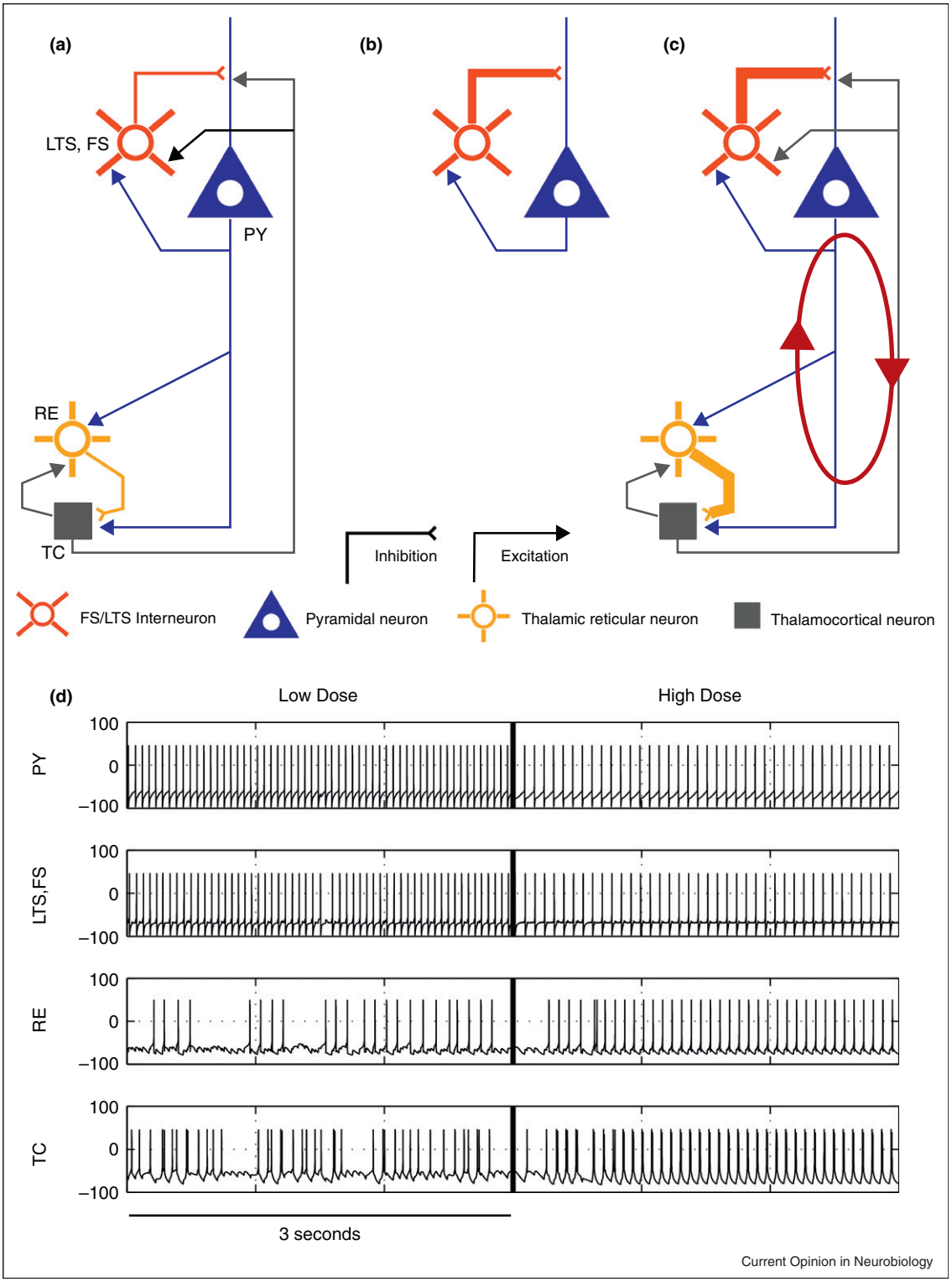
The key role played by gamma rhythms in timing neuronal activity patterns implicates it in controlling synaptic plasticity — a process which in turn can change both structural and functional connections within and between brain regions (Figure 2). The precise timing

Figure 2



Altered interneuron recruitment disrupts gamma rhythm-associated spike timing and thus functional and anatomical plasticity. **(a)** Example of precise spike timing in principal cells afforded by normal gamma rhythms (left) and gamma rhythms disrupted by genetic manipulation of interneuron glutamatergic excitation (right). Data show local field potential triggered averages of concurrent field and intracellular records (data adapted from Fuchs *et al*. [86]). Below, cartoons of the standard spike timing-dependent plasticity (STDP) curves show the marked discontinuity around 0 ms difference between presynaptic and postsynaptic spiking. Disrupted spike timing would therefore be expected to detrimentally affect such an STDP process. **(b)** Synaptic plasticity is vital for formation and maintenance of connections between principal cells. Use-dependent formation of excitatory synapses is intrinsically linked to dendritic spine dynamics and extent of dendritic arborization. In the absence of appropriate pre-synaptic and postsynaptic timing, spines may shrink (as seen in schizophrenia and animal models). Insets show pictures of spines from Cahill *et al*. [53]. Principal cells illustrated, and the connections from distal regions are shown as cartoons.

Figure 3



Local effects of propofol anesthesia manifest in thalamocortical networks. **(a)** In a normal state, thalamocortical networks are governed by an interaction between low threshold interneurons (LTS), fast-spiking interneurons (FS), pyramidal cells, thalamic reticular cells (RE) and thalamocortical cells (TC). **(b)** With a low dose of propofol anesthesia, cortical networks experience an increase in GABAergic inhibition that interacts with intrinsic properties of LTS cells to produce beta oscillations [64]. **(c)** With a higher dose, inhibition increases further in cortical networks leading to a further decrease in cortical oscillation frequency. Simultaneously, elevated inhibition in thalamic networks interacts with h-currents to promote thalamic rebound spiking at alpha frequency. **(d)** These effects combine to produce an alpha rhythm that coalesces within the entire thalamocortical network [72]. Example of model spiking activity in the

of pre-synaptic and postsynaptic excitation in neurons is critical for the control of synaptic strength (spike timing-dependent plasticity, STDP). If synaptic strength is modified, then so are the spine densities and dendritic arbors of principal cells. These two factors are well characterized as local cytoarchitectonic changes in brains of patients with schizophrenia [52•,53]. These plastic changes, and in certain areas the very gamma rhythm that may control STDP in the first place, are all dependent on NMDA receptor function [51,54,55]. Changes in NMDA receptor activation may, in turn, feed back to control genetic and histochemical factors implicated in schizophrenia such as DISC1 [56] and parvalbumin immunoreactivity [57].

A selective deficit in NMDA receptor-mediated drive to parvalbumin-immunopositive interneurons forms a core feature of the glutamate hypothesis of schizophrenia [58••]. Not all interneurons maintain NMDA receptor mediated excitation into adulthood, perhaps explaining the region specificity of deficits despite more global changes in markers such as GAD67. However, in interneurons that do lose this drive, compensatory effects may follow in an attempt to boost what inhibitory signal is present presynaptically and postsynaptically — thus generating the array of postmortem findings reported for the inhibitory system in schizophrenia: Reducing calcium sequestration by parvalbumin boosts inhibition and gamma rhythms [59]. Changes in $GABA_A$ receptor subunit expression [41] may serve to boost postsynaptic signals. Cannabinoid receptor changes associated with schizophrenia may enhance GABA release [60]. Reduced GAT function may increase the time released GABA spends in the synaptic cleft, thus increasing inhibitory charge transfer [61]. This latter facet of the documented changes in inhibitory system may also have a profound effect on the rhythmicity seen in brains of patients with schizophrenia. Studies have shown that the EEG response to 40 Hz auditory clicks elicit a 40 Hz, gamma, response in normal individuals but elicit both a 20 Hz, beta, and a 40 Hz response in patients with schizophrenia. Computational modeling by Vierling-Claassen *et al.* [62] suggests this deficit in gamma and increase in beta could be the result solely of increasing the decay time constant of cortical GABAergic synapses — as seen with GAT dysfunction (above). As the time constant is increased, the excitatory cells, which are believed to carry the EEG signal, cannot always respond to every 40 Hz pulse but instead responded mainly to every other pulse, thus creating a prominent 20 Hz component in the EEG signal (Figure 3).

General anesthesia and states of reduced arousal

General anesthesia — the pharmacologically induced state of reversible coma — provides powerful evidence that changes to intrinsic membrane and synaptic currents within networks, devoid of structural abnormalities, can elicit highly pathological brain dynamics. Historically, the study of anesthetic drugs has focused on their effects at the molecular level. Such descriptions do not completely explain the diversity of anesthetic effects, which can range from the profound (a state akin to brain death) to the paradoxical (excitation, delirium, hallucinations). Recent research has shifted the focus from the molecular targets of anesthesia to effects in larger networks, treating the anesthetic drugs as perturbations to the dynamics of an underlying but intact network [63••]. Such an approach has revealed how seemingly local neuromodulatory effects can lead to vast changes in behavior. Moreover, understanding anesthesia at a network level has exposed novel connections to related pathologies such as coma [63••,64•], suggesting interesting ways to investigate fundamental properties of the brain's arousal mechanisms and new treatments in disorders of consciousness.

To date, the clearest example of the network effects of general anesthesia is through propofol, a common clinical drug that is thought to act primarily through an increase in GABAergic inhibition [63]. At subanesthetic dose levels, the drug causes 'paradoxical' excitation, a delirium-like state that is associated with beta (16–25 Hz) frequency oscillations in the EEG [66]. When viewed only through the lens of inhibition, such oscillations are difficult to explain. However, when network elements are considered, a clear mechanism emerges. Indeed, it has been shown that a subset of cortical interneurons — LTS cells — can interact with elevated GABA kinetics (decay-time) and increased conductance in order to pattern pyramidal cell spiking into a beta rhythm. Potentiation of the GABA synaptic currents causes a reduction in the M-current (a slow potassium membrane current), leading to an increase in LTS cell excitability and, eventually, rebound spiking [65]. A similar mechanism has been proposed in the context of Parkinson's disease, where a GABA — M-current interactions are thought to provide the basis for aberrant beta oscillations in striatal networks [13••]. The connection to striatal networks is particularly intriguing given recent evidence of another type of paradoxical 'excitation,' involving zolpidem. That drug, also a GABA agonist, has been shown to promote behavioral improvement in patients in minimally conscious states. The purported mechanism involves cortex, striatum, globus palladus and thalamus [67]. When considered in this broad network setting, it is

(Figure 3 Legend Continued) transition from low to high dose behavior, that is, from (b) to (c) (adapted from [72]). During the low dose regime, cortical beta oscillations are mediated by LTS and FS cells with minimal thalamic participation. In the high dose regime, cortical oscillations decrease in frequency concurrently with an increase in thalamic participation, resulting in a thalamocortical alpha rhythm.

suggested that the GABAergic actions of zolpidem may act selectively on the GPi, leading to a disinhibition of thalamic neurons and subsequently restoring the thalamocortical network to a basal dynamic regime [68,69•].

Thalamocortical networks are particularly relevant in the mechanisms of anesthesia at higher dose levels. At such levels, the paradoxical effects give way to reduced arousal, awareness and, as defined clinically, unconsciousness [63,70•,71]. When this happens, the EEG displays a 9–12 Hz alpha rhythm that is broadly coherent over frontal cortices [72,73•,70•,71]. Modeling has shown that such a phenomenon can arise through altered time-scales of inhibition in thalamic relay and reticular neurons [73•]. Increased decay-time and conductance of inhibition from reticular cells causes relay cells to enter a hyperpolarized state. This engages hyperpolarization-activated currents that render the relay cells more susceptible to rebound excitation and intensify existing mechanisms of thalamic alpha such as the well-known spindle oscillation [74]. In cortical networks, larger and longer IPSPs lead to rhythmic activity in the alpha range. Thus, neural activity may coalesce into a state of alpha 'hypersynchrony,' impeding function within the thalamocortical loop [73,71]. Here, again, it is intriguing to consider a connection with a pathological condition of similar phenomenology: 'alpha coma' [75]. Although structural lesions are involved in the pathophysiology, the possibility of mechanistic overlap with anesthesia raises a complementary network-oriented interpretation that — as in aforementioned case of zolpidem — may lead to novel therapeutic strategies. For instance, emerging research suggests that methylphenidate (Ritalin) may serve to counteract the efficacy of isoflurane [76•], suggesting a nuanced network interplay between inhibition, dopamine and the anesthetic state.

Other network effects associated with deep general anesthesia, such as slow and delta-band oscillations, have been studied in the context of drugs such as enflurane [77], isoflurane [78], etomidate [79] and nitrous oxide [80]. The mechanisms suggested in these studies involve a general increase in cortical inhibition, leading to slowing of network activity [81,82] and impaired functional connectivity between cortical regions [83]. In contrast, the anesthetic drug ketamine, whose site of action is thought to be the NMDA receptor, is known to create higher-frequency patterns of activity in cortical field potential [84,85]. Such patterns correlate with the well-known dissociative effects of the drug. The fact that reversible neuromodulatory changes can lead to such a range of network and behavioral changes establishes the role of neuronal kinetics in governing larger-scale brain function.

Conclusion

Here we have argued that alterations in the amplitudes and kinetics of neuronal intrinsic and synaptic currents play an important role in changes to network dynamics, even in the absence of structural changes (anesthesia), and may provide a substrate for compensatory anatomical changes in neurological disease processes. Viewing pathological dynamics as an aberrant state of an underlying normal network or the source of structural deviations has broad implications for treatment of these disorders. In future work, anesthesia can serve as partial model of the network changes due to alterations in the amplitudes and kinetics of neuronal currents that occur in underlying disease processes. For example, proposed network changes at low doses of anesthesia have been shown to relate to a source of the pathological beta oscillations in Parkinson's disease. Changes in brain rhythms that occur in anesthesia are likely to shed light on network pathology associated with minimally conscious states. An important question for neurological diseases including schizophrenia is to what extent correction of pathologies of rhythms can have a beneficial effect on symptoms and progression of these diseases; DBS can be considered such an example for Parkinson's disease.

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- • of special interest
- •• of outstanding interest

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