Pyramidal neurons: dendritic structure and synaptic integration

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Abstract | Pyramidal neurons are characterized by their distinct apical and basal dendritic trees and the pyramidal shape of their soma. They are found in several regions of the CNS and, although the reasons for their abundance remain unclear, functional studies — especially of CA1 hippocampal and layer V neocortical pyramidal neurons — have offered insights into the functions of their unique cellular architecture. Pyramidal neurons are not all identical, but some shared functional principles can be identified. In particular, the existence of dendritic domains with distinct synaptic inputs, excitability, modulation and plasticity appears to be a common feature that allows synapses throughout the dendritic tree to contribute to action-potential generation. These properties support a variety of coincidence-detection mechanisms, which are likely to be crucial for synaptic integration and plasticity.

Pyramidal neurons are abundant in the cerebral cortex of virtually every mammal that has ever been studied[1], as well as in those of birds, fish and reptiles, but not amphibians[2]. This indicates that their existence in the nervous system has an adaptive value for the organism and that their core functions have been preserved even as they evolved to take on specialized and diverse functions. Pyramidal neurons are found in most mammalian forebrain structures, including the cerebral cortex, the hippocampus and the amygdala, but not the olfactory bulb, the striatum, the midbrain, the hindbrain or the spinal cord[3]. Thus, they are found primarily in structures that are associated with advanced cognitive functions, and an understanding of these neurons is necessary to elucidate the neural bases of such sophisticated functions.

Decades of research have yielded a wealth of information about pyramidal neurons. The lone axon of each pyramidal neuron typically emanates from the base of the soma and branches profusely, making many excitatory glutamatergic synaptic contacts along its length. Critical to the function of each pyramidal neuron is how it responds to its synaptic inputs to produce an action potential that excites its postsynaptic targets. Indeed, this process of synaptic integration lies at the heart of neuronal function and computation. The purpose of this Review is to distill the vast literature on pyramidal neurons down to a manageable summary, and to formulate some key questions that, when answered, will lead to a deeper understanding of pyramidal-neuron function. In particular, the article focuses on recent functional studies that reveal the features of pyramidal neurons that are imposed by excitatory and inhibitory synapses that target different dendritic locations in dendrites that contain voltage-gated channels.

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Dendritic structure: characteristics and variability

The dendritic tree of a pyramidal neuron has two distinct domains: the basal and the apical dendrites, which descend from the base and the apex of the soma, respectively (FIG. 1a). All pyramidal neurons have several relatively short basal dendrites. Usually, one large apical dendrite connects the soma to a tuft of dendrites. This main apical dendrite bifurcates before giving rise to the tuft at a variable distance from the soma. In some cases the resulting 'twin' apical dendrites each bifurcate again[4–6]. Oblique apical dendrites emanate from the main apical dendrite at various angles.

Although these features are characteristic of pyramidal neurons, they can vary considerably between different layers, cortical regions and species[7,8] (FIG. 1a). For example, the basal dendrites of layer II/III pyramidal neurons of macaque monkeys are smaller, simpler and have a lower spine density in the primary visual cortex than in higher visual cortical areas[1]. Basal dendrites are especially large, complex and spiny in the macaque prefrontal cortex. Furthermore, distinct species differences have been observed among prefrontal cortical neurons in different primates, with humans having the most elaborate and spine-rich basal dendritic trees[1].

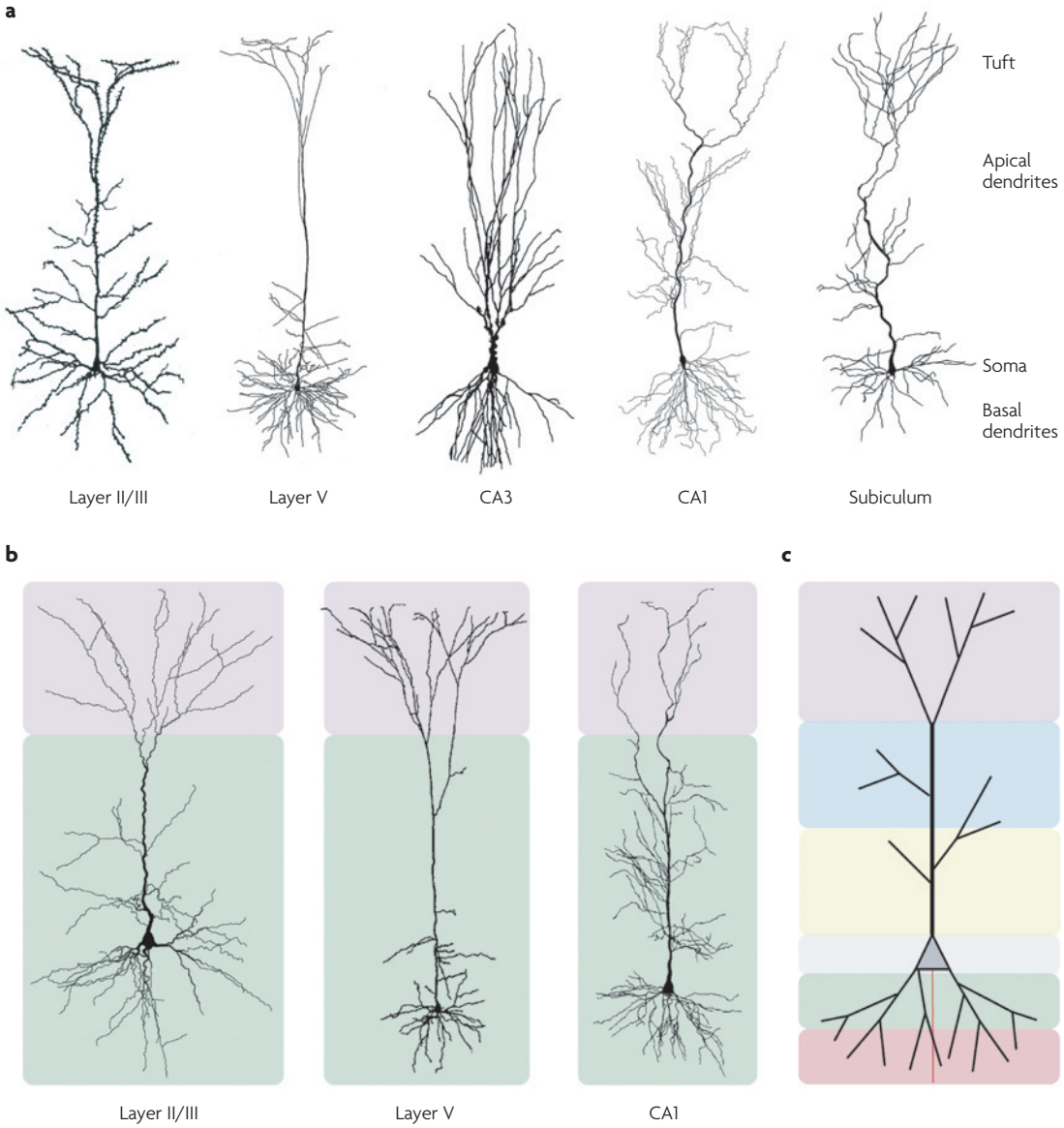


Figure 1 | **Pyramidal-neuron structure and domains of synaptic input. a** | The structures of pyramidal neurons from different cortical areas. Each type of pyramidal neuron has basal and apical dendrites and an apical tuft, but there are considerable differences between the pyramidal neurons shown. Layer V pyramidal neurons have longer apical dendrites and fewer oblique apical dendrites than layer II/III pyramidal neurons. The apical dendrites of hippocampal CA3 pyramidal neurons branch closer to the soma than those of CA1 pyramidal neurons, which typically have a more distinctive main apical dendrite and tuft. CA3 pyramidal neurons also have a cluster of large spines in the first 100 µm of the apical dendrite. The full vertical length of each cell, from left to right, is: unknown; 1,180 µm; 580 µm; 730 µm; 790 µm. All cells are from the rat, except for the layer II/III cell, which is from the rabbit. **b** | The apical tuft (highlighted with a purple background) of pyramidal neurons receives excitatory synaptic inputs that have different presynaptic origins to those that form synapses onto more proximal apical dendrites or basal dendrites (highlighted by a green background). The basal and proximal apical dendrites of layer II/III cells receive inputs from layer IV cells and also receive local-circuit excitation. The apical tuft of layer II/III cells receives inputs from other cortical areas and also receives nonspecific thalamic inputs. A similar arrangement can be identified in layer V pyramidal cells[2,199,200]. The basal and proximal apical dendrites of CA1 pyramidal cells receive input primarily from CA3 cells, whereas the apical tuft receives input from the entorhinal cortex and the thalamic nucleus reuniens[70]. **c** | A schematic drawing of a pyramidal neuron, illustrating various dendritic domains that could receive unique synaptic inputs. Some evidence supports the division of pyramidal cell dendritic trees into at least this many domains, which correspond to regions that receive distinct synaptic inputs and/or have synapses with distinct properties (see main text). Neurons in part **a** reproduced, with permission, from the following references: layer II/III neuron, REF. 3 © (1995) Oxford University Press; layer V neuron, REF. 24 © (1992) Oxford Academic Press; CA3 neuron, REF. 68 © (2001) Wiley-Liss; CA1 neuron, REF. 61 © (2005) Cambridge University Press; subiculum neuron, REF. 86 © (2000) American Physiological Society. Neurons in part **b** reproduced, with permission, from the following references: layer II/III neuron, REF. 125 © (2003) Society for Neuroscience; layer V neuron, REF. 62 © (1998) Society for Neuroscience; CA1 neuron, REF. 141 © (1999) Society for Neuroscience.

This raises two interesting questions: do neurons with more dendrites (and therefore more synaptic inputs) fire more than those with fewer dendrites? If not, how is firing maintained at the same rate? Several studies indicate that homeostatic plasticity maintains firing rates in a fixed range[9], but it is reasonable to postulate that pyramidal neurons with different structural features are also likely to differ functionally.

The functional properties of two types of pyramidal neurons — CA1 pyramidal neurons in the hippocampus and layer V pyramidal neurons in the neocortex — have been studied extensively, primarily in the rat. These two cell types are the focus of most of this Review, although there are also references to CA3 neurons in the hippocampus and layer II/III neurons in the neocortex. It is hoped that a complete theory of pyramidal-neuron function will eventually be developed that will explain why these neurons have their characteristic structural features and how variations in pyramidal-neuron structure and molecular composition allow different types of pyramidal neurons to perform specialized functions.

Methods for studying pyramidal-cell firing *in vivo*

It is important to understand what drives pyramidal-neuron firing in living animals. The classical approach to this problem is to describe the receptive-field properties of neurons by obtaining single-unit recordings in anaesthetized or awake animals. The limitations to this approach are uncertainties about the type of cell that is firing and about the underlying synaptic activity. Two techniques have helped to overcome these limitations: juxtacellular labelling techniques[10,11] and intracellular microelectrode and patch-clamp recording *in vivo*[12–15]. Both techniques can yield information about the firing properties, dendritic morphology and axonal projections of pyramidal neurons. For example, a recent patch-clamp study demonstrated that excitatory postsynaptic potentials (EPSPs) and sparse firing were evoked in layer II/III pyramidal neurons of the barrel cortex in response to activation of the principal whisker and several surrounding whiskers[16]. The dendrites of these neurons were restricted to a single barrel column, whereas their axons extended to surrounding columns, implying that the receptive-field properties could be explained by a combination of primary innervation for the principal whisker and secondary innervation from surrounding columns.

As this example illustrates, one approach to understanding pyramidal-cell firing *in vivo* is to correlate response properties with activity in cortical circuits. Several recently developed methods might assist in this endeavour. These include cell stimulation using glutamate uncaging or optically activated channels and pumps[17–19], and simultaneous patch-clamp recording from several cells in a brain slice[20,21]. These methods have helped to clarify some of the details of connectivity between pyramidal neurons and local inhibitory circuitry; long-range connectivity will be more difficult to establish. A detailed description of the dendritic location of synaptic inputs and how these inputs are integrated is needed to determine what combinations of inputs will cause a pyramidal neuron to fire. The development of new transgenic methods for activating, inactivating and labelling activated neurons and synapses[22,23] will undoubtedly facilitate progress in this area.

Synaptic inputs onto distinct domains

Pyramidal neurons receive synaptic input at the soma, the axon and the dendrites. The soma and the axon receive inhibitory GABA (γ-aminobutyric acid)-ergic inputs, whereas most of the excitatory synaptic drive arrives through the dendrites from multiple sources. Usually, proximal dendrites receive excitatory inputs from local sources (collaterals in the same area or from an adjacent area) whereas the distal apical tuft receives inputs from more distant cortical and thalamic locations (FIG. 1b). This raises interesting questions about how inputs to different domains are integrated. Pyramidal neurons might be designed to respond to coincident input to the tuft and the more proximal dendritic domains[24,25]. Alternatively, the input at the tuft might control responsiveness to more proximal inputs[26]. These possibilities are not mutually exclusive, as the two mechanisms could potentially dominate in different behavioural conditions.

The distinct morphologies of basal and apical dendrites suggest that inputs to these domains might be integrated differently. Furthermore, different dendritic domains receive distinct synaptic inputs. For example, CA1 neurons receive input to the distal tuft from the entorhinal cortex through the perforant path and from the thalamus, whereas the remainder of the dendrites receive input from CA3 through the Schaffer collaterals. Furthermore, CA3 neurons that are distant from CA1 project primarily to apical dendrites, whereas CA3 neurons that are closer to CA1 project more heavily to basal dendrites[27,28]. The functional significance of this arrangement remains mysterious.

Several structural and functional studies of CA1 hippocampal and layer V pyramidal neurons provide the rationale for subdividing the pyramidal-neuron dendritic tree as shown in FIG. 1c. The diagram represents only one possibility, which could justifiably be revised based on other data. For example, inputs to the main apical dendrite and the oblique apical dendrites might be integrated differently[29,30], but it is not known whether synaptic inputs to these domains are identical or different. More details about such arrangements must be identified if we are to better understand how neural activity causes pyramidal cells to fire *in vivo*.

Structure and function of dendritic spines

Pyramidal neurons are covered with thousands of dendritic spines (FIG. 2a) that constitute the postsynaptic site for most excitatory glutamatergic synapses. The number of spines represents a minimum estimate of the number of excitatory synaptic inputs onto a neuron, which varies considerably in different regions and species[31,32]. The function of dendritic spines remains enigmatic (BOX 1).

Receptive field
The area of the sensory space in which stimulus presentation leads to a response from a particular sensory neuron. Other stimulus properties, such as the optimal orientation of a bar of light, might further define the receptive-field properties of a neuron. These properties can be described in increasingly complex terms as more is learned about the conditions that are required for a particular neuron to fire.

Single-unit recording
A method that is used to measure the activity of individual neurons in awake, behaving animals.

Glutamate uncaging
The release of free glutamate by the activation of a 'caged' (chelated) glutamate compound using light.

Spines vary considerably in their size and shape[33], and are highly plastic. In culture and in slice preparations spines are dynamic[34] (FIG. 2b), but little is known about how and why such changes occur *in vivo*. Although technical considerations make it difficult to study spine dynamics under normal conditions[35,36], evidence indicates that there are separate populations of stable and more plastic spines *in vivo*[37], and that these populations can change with experience[38]. It has been suggested that thin, dynamic spines might be available to contribute to learning, whereas larger, more stable spines might be involved in the storage of established memories[39,40]. Repeated activation of small spines can lead to a sustained increase in spine size and glutamate

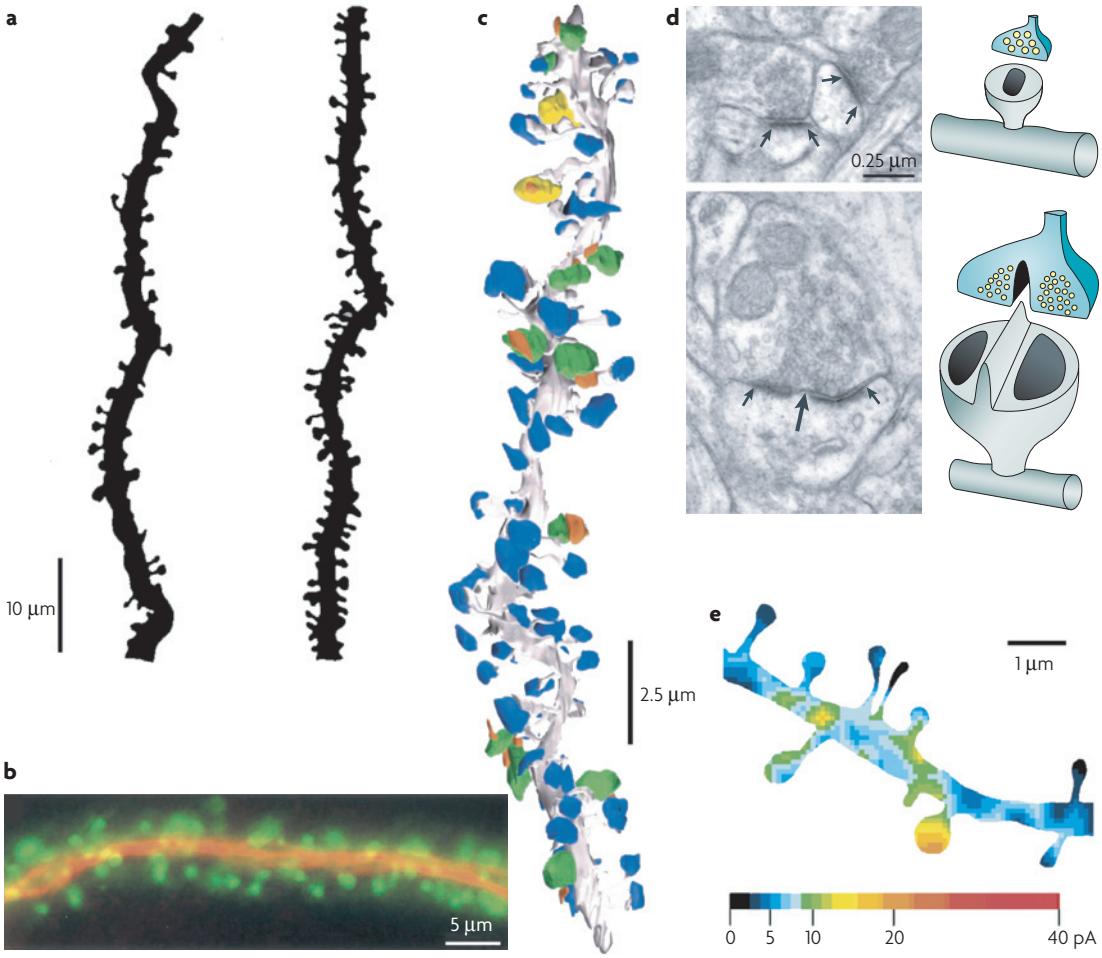
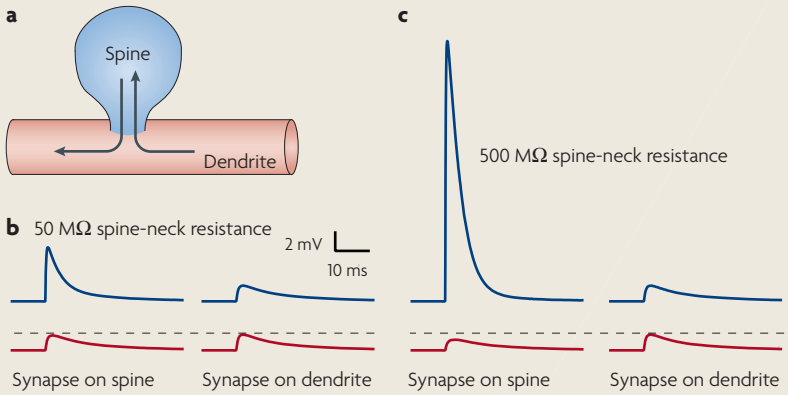


Figure 2 | **Dendritic spines and synapses on pyramidal neurons. a** | Two spine-studded dendrites of a stained CA1 pyramidal neuron. The higher density of spines in the right-hand dendritic segment resulted from estrogen treatment[45], suggesting that spines and synapses might respond dynamically to changes in circulating hormones. **b** | A dendrite that has been labelled for microtubule-associated protein 2 (MAP2; red) and actin (green). MAP2 is concentrated in the dendritic shafts. Actin filaments in the spine head mediate spine motility. **c** | A three-dimensional reconstruction of spines and synapses in a typical pyramidal cell, based on electron micrographs of a single stretch of dendrite from a filled cell. Every spine is contacted by at least one synapse. The dendrite and its spines are shown in grey; synaptic boutons forming single synapses are shown in blue; boutons forming multiple synapses onto more than one cell are shown in green; boutons forming multiple synapses onto the same cell are shown in yellow; spines from other dendrites are shown in orange. **d** | The left-hand panels show electron micrographs of two non-perforated postsynaptic densities (PSDs; top panel, indicated by arrows) and a perforated PSD (bottom panel, the perforation is indicated by the large arrow). The right-hand panel contains schematic diagrams of a non-perforated synapse (top) and a perforated synapse (bottom). **e** | Two-photon glutamate uncaging at various locations on a dendritic segment. The colours indicate the somatically recorded current amplitude that was measured when uncaging was carried out at each location. Note that the largest response (yellow/orange) occurred when the glutamate was uncaged on a large spine head. Part **a** reproduced, with permission, from REF. 45 © (1996) Wiley-Liss. Part **b** reproduced, with permission, from REF. 42 © (2000) American Association for the Advancement of Science. Part **c** reproduced, with permission, from REF. 43 © (2001) National Academy of Sciences. Electron micrographs in part **d** reproduced, with permission, from REF. 65 © (2000) Oxford University Press. Schematic in part **d** reproduced, with permission, from REF. 58 © (2006) Elsevier Science. Part **e** reproduced, with permission, from REF. 55 © (2001) Macmillan Publishers Ltd.

Box 1 | **Possible functions of dendritic spines**



Although dendritic spines (see figure, part **a**) are a striking feature of pyramidal neurons, their functional significance is not clearly understood. They might increase the dendritic surface area in order to optimize the packing of a large number of synapses onto a given length of dendrite[186–188]. Alternatively, they might serve as biochemical compartments that restrict the diffusion of important molecules away from the synapse[49,186,189]. Spines might also have a role in regulating the electrical properties of the neuron[190].

The small size of spines makes their input impedance significantly larger than that of the dendrite. Synaptic currents that originate on the dendrite produce a small voltage in the dendrite, with almost no voltage drop as the current flows into the spine (current flow is represented by the arrows in part **a** of the figure). The same synaptic conductance originating in a spine (computer simulations of a current originating in a passive dendrite and a spine are shown in parts **b** and **c** of the figure) produces a large voltage in the spine head, which drops as the current flows into the dendrite. This occurs for two reasons: first, the larger voltage change in the spine reduces the driving force at the synapse; second, some charge is lost as current flows from the spine into the dendrite. The magnitude of both effects depends on the resistance of the spine neck.

Although the voltage drops significantly as the current flows from the spine to the dendrite, charge attenuation is considerably less. Charge attenuation from the spine to the dendrite is proportional to the steady-state voltage drop from the dendrite to the spine[191], which is small. In order for charge attenuation from the spine to the dendrite or voltage attenuation from the dendrite to the spine to be significant, as suggested in recent reports[192,193], the resistance of the spine neck must be very high. Various methods have been used to estimate spine-neck resistances, with results ranging from 1 MΩ to more than 1 GΩ[49,194,195]. This might reflect biological variability and plasticity, but might also reflect the inherent difficulty in estimating this value from experimental measures. Parts **b** and **c** of the figure compare the effects of spine-neck resistances of 50 MΩ (**b**) and 500 MΩ (**c**). Spine-neck resistance has its greatest effect on the local voltage in the spine, which can significantly affect the activation of voltage-activated channels in the spine head[192,193,196]. In addition, however, a higher spine-neck resistance results in a considerable reduction of the excitatory postsynaptic potential in the dendrite, because of the reduced driving force and some charge loss that occurs. Thus, improved estimates of spine-neck resistance will provide valuable information about the electrical functions of dendritic spines.

responsiveness[41]. By contrast, low-level activation of α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA)-type glutamate receptors (AMPARs) stabilizes spines, suggesting a dual role for glutamate-receptor activation in promoting structural plasticity[42].

Although most spines contain a single synapse, some contain multiple synapses[43–45] (FIG. 2c). A perforation is present in 10–30% of spine postsynaptic densities (PSDs)[46–51] (FIG. 2d). The functional significance of the perforation is unclear, but perforated PSDs are large, are contacted by multiple release zones and have a high density of AMPARs, suggesting that the strength of their synapse is increased[52–54]. Functional studies also indicate that the largest spines also have the most AMPARs[55] (FIG. 2e). These observations suggest that many spines might contain small, weak synapses (many non-perforated synapses might even be silent synapses), whereas a minority of spines contain larger, stronger synapses[56,57]. Activity-dependent plasticity might convert small, silent synapses to larger, fully functional synapses[58]. Thus, there is significant diversity in the size and structure of spines and their synapses. As detailed below, these properties also vary across different dendritic domains.

Postsynaptic density (PSD). An electron-dense thickening underneath the postsynaptic membrane at excitatory synapses. PSDs contain receptors, other signalling molecules and structural proteins linked to the actin cytoskeleton.

Distance-dependent synaptic integration

The integration of excitatory synaptic inputs is greatly influenced by their location on the dendrite (BOX 2). Synapses distant from the soma are expected to have less influence over action-potential initiation in the axon, owing to the loss of charge as current flows from the dendrites to the soma and axon[59–62]. Synapses might be able to compensate for their distance from the soma by scaling their conductance in order to normalize their somatic influence[63]. Evidence for such 'synaptic scaling' has been identified at some but not all synapses in CA1 pyramidal neurons[64,65] and not in layer V pyramidal neurons[66]. Synaptic scaling might be limited because it is biophysically inefficient. Small-diameter dendrites have high input impedance; therefore, distal synapses cause large local synaptic potentials and reduce the driving force for synaptic current. If the conductance of distal synapses is increased to compensate for distance, the gain in terms of synaptic charge entry is limited by this driving-force reduction (BOX 2).

Distal synapses might also exert significant influence over action-potential initiation through the activation of dendritic voltage-gated channels, which can enhance charge entry at distal synapses and might even lead to dendritic spike initiation (see below). The high input impedance of small-diameter dendrites is expected to enhance this effect, with the large local depolarization causing significant activation of voltage-gated conductances.

Neurons might take advantage of the location dependence of synaptic efficacy to perform more complex integrative processing[67]. Several observations suggest that synapses at different dendritic locations are specialized to perform different functions. One striking example is the mossy fibre synapses that are formed by dentate gyrus neurons on CA3 pyramidal neurons[68]. At these synapses, large synaptic boutons contact large dendritic spines (FIG. 1a), forming several synapses with each spine[69]. The large size and proximal location of these synapses suggest that they are specialized to provide powerful excitation to CA3 neurons. These inputs are certain to be integrated differently from those from the entorhinal cortex, which are restricted to the distal apical dendrites[70].

In CA1 pyramidal neurons, perforated synapses are more abundant and there are higher AMPAR densities in mid apical dendrites than in proximal apical dendrites. The distal apical tuft also has a large number

of perforated synapses, but these synapses have lower AMPAR densities[65]. The apical tuft also has a relatively large number of synapses on the dendritic shaft[71]. These differences suggest that these various dendritic regions (FIG. 1c) receive synaptic inputs that have distinct properties. Synaptic plasticity is also different for the various synapses on pyramidal neurons (see below), providing further justification for distinguishing between different populations of synapses on the basis of their location.

Targeted inhibition

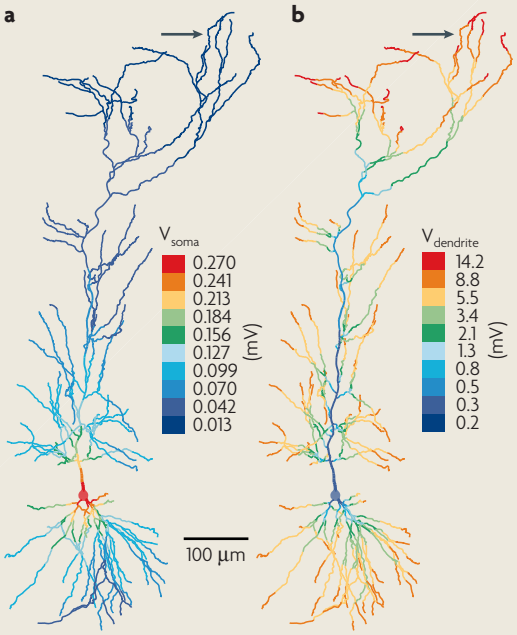
Distinct populations of GABAergic interneurons target specific cellular domains on pyramidal neurons[72–74] (FIG. 3). Basket cells, which target perisomatic regions, are likely to reduce the probability of firing during the activation of all excitatory synapses, whereas hippocampal OLM interneurons and neocortical Martinotti cells, which target the apical tuft, are likely to selectively affect the activation of distal apical synapses[75]. Other interneurons have different targeting features but are generally selective for the axon, the soma or specific dendritic domains.

It is important to understand how each of these interneurons influences synaptic integration. Central to any framework of interneuron action is whether the interneurons are activated in a feedforward manner (by the same synapses that excite the pyramidal neuron) or in a feedback manner (by firing pyramidal neurons). Feedforward inhibition of pyramidal neurons (resulting from feedforward activation of interneurons) can limit the duration of pyramidal-neuron synaptic excitation, even when pyramidal neurons do not fire action potentials. This is an important determinant of the time window for temporal summation of excitatory inputs. By contrast, feedback inhibition (resulting from feedback activation of interneurons) is only activated when pyramidal neurons in the network fire action potentials, and thus it limits sustained pyramidal-neuron firing. Two types of feedback inhibition have been identified in the hippocampus: onset-transient inhibition, which responds quickly to firing of the CA1 neuron but ceases rapidly, and late-persistent inhibition, which takes longer to develop but is sustained[77]. Onset-transient neurons target the soma and proximal dendrites, whereas late-persistent neurons target the distal dendrites (FIG. 3). The significance

Box 2 | Attenuation of synaptic inputs on pyramidal neurons

Because synapses are formed at different distances from the soma, the resulting excitatory postsynaptic potentials (EPSPs) are dependent on the dendritic location of each synapse, as predicted by cable theory[197]. Part **a** of the figure shows the amplitude of the somatic EPSP for an excitatory synapse of fixed synaptic conductance (0.3 nS) simulated at each dendritic location in a model of a CA1 pyramidal neuron with passive dendrites[65]. Synapses proximal to the soma produce somatic EPSP amplitudes of 0.2–0.3 mV (yellow–red on the linear colour scale)[64], but the amplitude falls off sharply as a function of distance. Synapses approximately 150 micrometres from the soma produce somatic EPSPs of approximately half of this unitary amplitude (0.1 mV; light blue on the scale), whereas synapses in distal dendrites produce somatic EPSPs of less than one-tenth of this unitary amplitude (less than 0.02 mV; dark blue on the scale).

Part **b** of the figure shows the amplitude of the local EPSP in the same simulations. The amplitude in the main apical dendrite and in the soma is 0.2–0.3 mV (dark blue on the logarithmic colour scale), but the local amplitude for synapses on smaller dendrites is considerably larger. Proximal basal, apical oblique and tuft branches depolarize by a few millivolts (green–yellow on the scale), whereas the most distal branches depolarize by more than 10 mV (red on the scale).



At the location marked by the arrow in parts **a** and **b** of the figure, the local synaptic potential is approximately 13 mV and the resultant somatic EPSP is approximately 0.014 mV (>900-fold attenuation). This voltage attenuation is largely a consequence of the small diameter, and thus the high impedance, of the distal dendrites, which causes large local EPSPs (almost 50-fold larger than the 0.27 mV EPSP for the somatic synapse).

On the other hand, the somatic EPSP produced by the distal synapse is only approximately 20-fold smaller than the EPSP produced by a somatic synapse. Biophysically, this attenuation is caused mostly by charge loss between the synapse and the soma, which is proportional to the steady-state voltage attenuation in the opposite direction[191,198]. In addition, the relatively large local EPSPs on distal synapses reduce the synaptic driving force and thus decrease charge entry. Large dendritic EPSPs can also increase the activation (or deactivation) of voltage-gated channels in the dendrites.

Increases in synaptic conductances can compensate for the reduced somatic impact of distal synapses. This mechanism has limits, however, as increasing synaptic conductance also increases the local voltage change, further reducing the driving force and increasing the likelihood of generating local dendritic spikes.

Silent synapse
A synapse that produces no detectable EPSP in the soma. Distal synapses might produce some local dendritic depolarization, but nevertheless be difficult to detect in the soma.

Input impedance
The resistance to the flow of current provided as an input to a neuron. This property depends on the resistance and capacitance of the structure (for example, the cell body or the dendritic spine) into which the input current is applied.

Dendritic spike
A spike initiated in the dendrites.

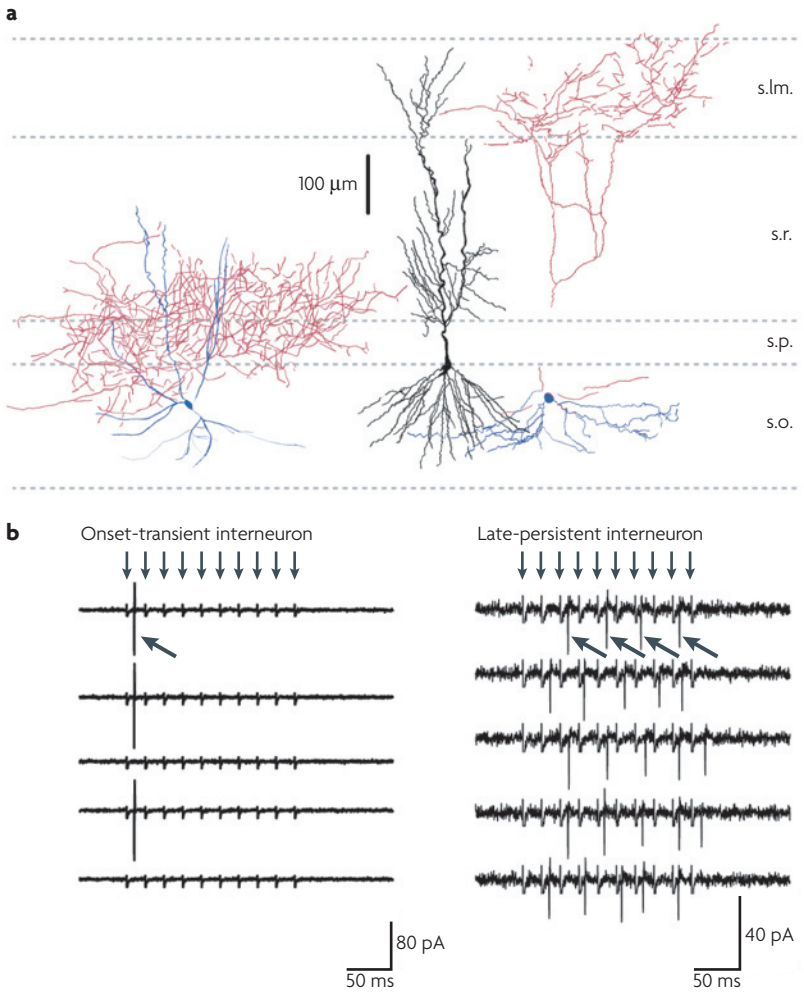


Figure 3 | **Dendritic-domain-specific targeting by inhibitory synapses on pyramidal neurons. a** | A trilaminar interneuron (left), a CA1 pyramidal neuron (middle) and an OLM interneuron (right). Interneuron dendrites and axons are blue and red, respectively; CA1 dendrites are black. Note the twin apical dendrites on this CA1 pyramidal neuron. The axon of the trilaminar interneuron is restricted to the stratum radiatum (SR), the stratum pyramidale (SP) and the proximal stratum oriens (SO). The main axonal arborization of the OLM interneuron is restricted to the stratum lacunosum-moleculare (SLM). **b** | Cell-attached responses from an onset-transient interneuron (the trilaminar cell in part **a**) and a late-persistent interneuron (the OLM cell in part **a**). Current deflections (indicated by the diagonal arrows) indicate action-potential firing in response to the stimulation of CA1 axons in the alveus (indicated by the vertical arrows). A combination of synaptic and intrinsic properties is responsible for these different firing responses[77]. Figure reproduced, with permission, from REF. 77 © (2004) Macmillan Publishers Ltd.

Action-potential threshold
The membrane potential at which an action potential is generated — usually approximately 20 mV above the resting potential.

Afterhyperpolarization
Membrane hyperpolarization following an action potential.

Afterdepolarization
Membrane depolarization following an action potential.

of this arrangement is unknown, but it is probably important for the function of hippocampal circuits. Whether similar functional arrangements exist in other pyramidal neurons is also unknown.

The impact of inhibitory synapses in the soma is not scaled to normalize for dendritic location[78], suggesting that the action of inhibitory synapses might be primarily local. Dendritically targeted inhibition limits dendritic Ca^{2+} spikes in both hippocampal and neocortical pyramidal neurons[79–81]. In neocortical neurons, this inhibition occurs through G-protein-coupled inhibition of dendritic Ca^{2+} channels[81].

A surprising discovery is that axonally targeted, GABAergic chandelier cells might not be inhibitory[82]. These cells excite the axons of pyramidal cells because there is a depolarized Cl^- reversal potential in the axon initial segment, suggesting that the principle role of some interneurons might be to determine the timing of action-potential firing during rhythmic activity[83,84]. Much remains to be learned about how different interneurons regulate pyramidal-neuron activity, but the domain-specific targeting of various interneurons supports the hypothesis of domain-specific synaptic integration in pyramidal neurons.

Intrinsic firing properties of pyramidal neurons

It is also important to understand how voltage-gated channels contribute to action-potential firing. These channels influence intrinsic properties of the neuron, such as the action-potential threshold, spike afterhyperpolarization (AHP) and afterdepolarization (ADP), and action-potential firing mode. Some pyramidal neurons respond to somatic current injections with a regular-spiking pattern that has spike-frequency adaptation, whereas others exhibit intrinsic burst firing[85,86]. Variability in these properties reflects diversity in pyramidal-neuron function.

Action potentials in pyramidal neurons are typically followed by an ADP[87–89], which is mediated by voltage-gated Na^+ and/or Ca^{2+} channels but also requires K^+ channels to close quickly to limit repolarization. Variation in the size of the ADP contributes to differences between regular-spiking and intrinsically bursting neurons[89]. Because the conductances that underlie the ADP and the action potential are affected by prior activity and modulatory neurotransmitters, the firing properties of neurons are highly dynamic[90,91].

Dendritic channels can also contribute to intrinsic bursting by providing additional current to the spike initiation zone[92–97]. Furthermore, dendritic structure can affect how a neuron responds to somatic current injection[8,98–101]. Dendritic channels are recruited more heavily by excitatory synaptic input than during current injection in the soma. Thus, dentritic channels are likely to have a greater effect on burst firing in response to natural stimuli, as dendritic Ca^{2+} spikes can trigger a burst of action potentials in the axon and soma[102–104].

Dendritic excitability and dendritic spikes

Voltage-gated channels in pyramidal-cell dendrites have important influences on synaptic integration[105,106]. The distribution of these channels can be uniform, as is approximately the case for Na^+ channels[107], or non-uniform and can differ between various types of pyramidal neurons. A-type K^+ channels are expressed in a somatodendritic gradient in CA1 pyramidal neurons[108], but are expressed uniformly in the dendrites of layer V pyramidal neurons[109,110]. Hyperpolarization-activated cation channels (HCN channels) are expressed in a somatodendritic gradient along the apical dendrites of both of these cell types[111–114], but are virtually absent from layer II/III and CA3 pyramidal neurons[114].

Voltage-gated channels can affect the integration of synaptic potentials. For example, deactivation of HCN channels reduces EPSP duration and results in a slight hyperpolarization following the EPSP[112,115]. Conversely, activation of HCN channels reduces inhibitory post-synaptic potential (IPSP) duration and produces a slight depolarization following the IPSP[116]. This effect is strongest at distal synapses and thus it limits the expected distance-dependence of EPSP temporal summation in the soma[115]. Surprisingly, the effect does not appear to require a somatodendritic gradient of the channels[117].

Activation of Na^+ and Ca^{2+} channels below the threshold for spiking can enhance synaptic efficacy[118,119], but this effect is limited by the activation of low-threshold K^+ channels[120–122]. Activation of Na^+ channels in the axon can also amplify EPSPs under some conditions[123].

The most important function of dendritic Na^+, Ca^{2+} and K^+ channels might be to support backpropagating action potentials and dendritic spikes[59,106,124,125]. In apical pyramidal dendrites, backpropagating action potentials decrease in amplitude as they reach progressively distal locations (FIG. 4a,b). Recently, this has also been observed in the basal dendrites of layer V pyramidal cells[126,127] (but see also REF. 128). Dendritic recordings have not yet been obtained from oblique apical dendrites, but Ca^{2+}-imaging experiments suggest that action potentials also attenuate as they backpropagate into these dendrites[129,130].

In CA1 pyramidal neurons, the decrement of backpropagating action potentials is largely due to the increasing density of dendritic A-type K^+ channels[108,131,132]; in layer V pyramidal neurons, other types of K^+ channels might contribute. Dendritic morphology also affects backpropagation, as branching promotes the attenuation and failure of backpropagating action potentials[133]. Furthermore, depolarization promotes backpropagation by facilitating Na^+-channel activation and/or K^+-channel inactivation[130,131,134]. Inactivation of dendritic Na^+ channels can lead to an activity-dependent reduction in action-potential backpropagation in CA1 and layer V pyramidal neurons[135–137] but not in layer II/III pyramidal neurons[138].

Activation of both Na^+ and Ca^{2+} channels can also lead to dendritic spikes[106,137,139] (FIG. 4c,d). The briefest spikes are called Na^+ spikes, even though there is some Ca^{2+} influx associated with these events; larger, broader dendritic spikes are usually called Ca^{2+} spikes[104,124,140,141]. In some cases, attenuation of a spike from its initiation site to the dendritic recording site can lead to ambiguity about whether it should be called a Na^+ spike or a Ca^{2+} spike. NMDA (*N*-methyl-D-aspartate) spikes are another type of dendritic spike. These are mediated by regenerative activation of NMDA receptors as a result of voltage-dependent relief of Mg^{2+} block[142,143]. However, NMDA spikes cannot propagate beyond dendritic regions where glutamate release has occurred[144]. NMDA spikes have been observed in basal dendrites but not apical dendrites. Dendritically initiated Na^+ spikes, but not Ca^{2+} spikes, have also been observed in basal dendrites[127,145,127], which suggests that the excitability of basal dendrites might be different from that of apical dendrites. Direct application of glutamate to pyramidal-neuron dendrites can produce both fast spikes and large, long-lasting plateau potentials, both of which are probably mediated by a combination of dendritic Na^+ and Ca^{2+} channels and NMDA receptors[146–151].

Locally generated dendritic spikes could eliminate the problem of distance-dependent synaptic efficacy, by allowing voltage-gated current to amplify the depolarization that is produced by distal synapses. However, dendritic spikes actually complicate (or enrich) synaptic integration rather than simplify it.

Whether or not a synapse contributes to dendritic spike initiation depends on several factors. Strong, synchronous activation of several synapses promotes dendritic spike initiation[137,145,152,153]. Once initiated, dendritic spikes propagate towards the soma[137,153] where, in some cases, they can initiate an action potential. However, failure of dendritic spike propagation[29] is frequently observed in slice experiments (FIG. 4c,d). Forward propagation of spikes is less reliable than backpropagation, because the currents that are required to produce a spike in small dendritic branches are too small to depolarize larger dendrites above the threshold for action-potential propagation[133]. Branch points are also problematic for backpropagating action potentials, although less so than for forward propagation because the large currents that generate an action potential in the main apical dendrite can more easily depolarize the smaller, more distal dendrites to threshold levels.

Dendritic excitability *in vivo*

The details given above regarding synaptic integration and plasticity in pyramidal neurons are based on experiments performed in slices. Dendritic spikes do appear to occur *in vivo*, but how often they occur and under what conditions remain open questions. Dendritic current injection in layer II/III pyramidal neurons *in vivo* evokes backpropagating action potentials[125] (FIG. 4b). Dendritic recordings from hippocampal pyramidal neurons *in vivo* have demonstrated that dendritic spikes arise in response to strong current injection and synaptic activation, as well as during sharp waves[154]. The recordings were obtained in anaesthetized animals, but hippocampal sharp waves also occur in unanesthetized animals, suggesting that dendritic spikes might occur naturally.

It is important to consider the strength of inputs that are required to induce axonal action potentials or dendritic spikes. Although the stimulus strength for detecting dendritic spikes in slices is often higher than that which is required to elicit axonal action potentials, dendritic spikes are harder to detect because they decrement so strongly. In slices, uncaging of glutamate onto just a few dendritic spines produces dendritic spikes, but the voltage changes in the soma are barely detectable[30] (FIG. 4d). Similarly, synaptic stimulation can trigger dendritic spikes that fail to propagate to the soma[153]. Synaptic stimulation of basal dendrites triggers nonlinear responses that are probably dendritic NMDA or Na^+ spikes[145,155]. Computational modelling indicates that it might be difficult to detect dendritic spikes that occur in response to the activation of small numbers of

Hyperpolarization-activated cation channels
(HCN channels). Membrane cation channels that carry a current called Ih. The current is activated by hyperpolarization but causes depolarization. Some Ih is activated at rest, thus reducing input impedance and depolarizing the resting potential.

Backpropagating action potential
An action potential that is initiated in the axon and then propagates back into the dendrites.

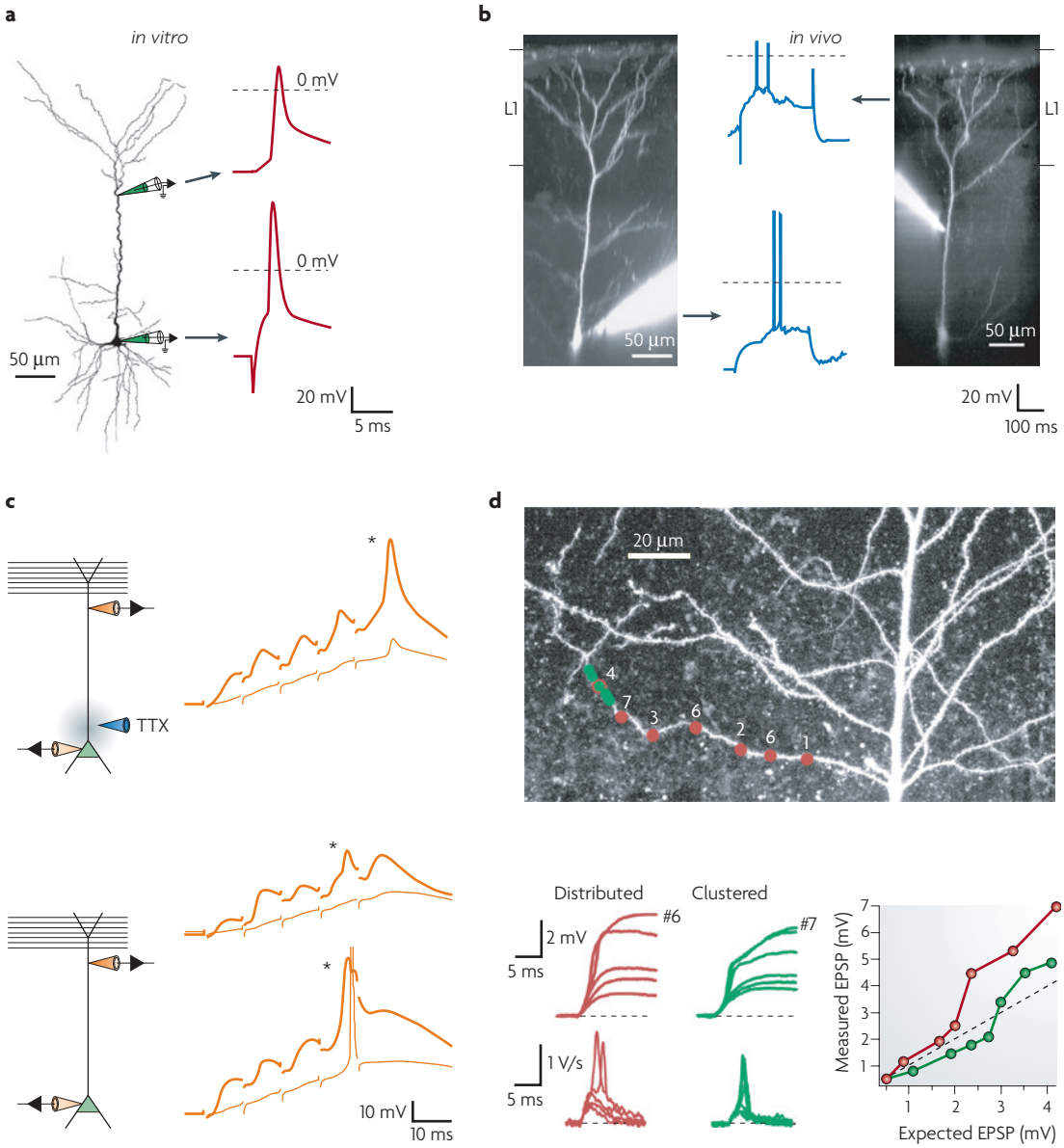


Figure 4 | **Dendritic excitability of pyramidal neurons. a** | A backpropagating action potential recorded simultaneously from the soma and dendrite of a layer II/III pyramidal neuron in a slice from rat somatosensory cortex. Note the attenuation of the dendritically recorded action potential. **b** | Somatic and dendritic action potentials (left-hand image and lower plot; right-hand image and upper plot, respectively) recorded from rat somatosensory cortex *in vivo*. The images are two-dimensional projections of two-photon scans through the neurons. Note that the dendritically recorded action potentials have smaller amplitudes, suggestive of the attenuated backpropagating action potentials that are observed *in vitro*. **c** | Dendritically initiated spikes observed in a CA1 pyramidal neuron in response to stimulation of the perforant path. In the top pair of traces (thick trace, dendritic membrane voltage; thin trace, somatic membrane voltage) the dendritic spike (*) fails to evoke a somatic action potential: it evokes only a spikelet. Usually the spikelet (an attenuated dendritic spike) would trigger an action potential in the axon, but in this case action-potential initiation was prevented by local application of tetrodotoxin (TTX) to the soma, the axon and the proximal dendrites. In the middle and bottom pairs of traces, which were recorded without TTX application, a small dendritic spike is virtually undetectable in the soma (middle pair) but a larger dendritic spike evokes a full-sized action potential (bottom pair; the action potential is truncated). **d** | Glutamate uncaging evokes local dendritic spikes in a CA1 pyramidal neuron. Uncaging was performed at several spots that were either distributed along the dendritic branch (red circles and lines) or clustered in one spot (green circles and lines). The voltage responses recorded in the soma exhibited a nonlinear increase when multiple spots were activated in rapid succession. Associated with this nonlinear increase in voltage was a spike-like increase in dV/dt, which suggests that a dendritic spike was generated. At the soma, however, the spike increased the response by only approximately 2 mV. The threshold for evoking a dendritic spike was lower for the distributed input than for the clustered input. EPSP, excitatory postsynaptic potential; L1, layer 1. Parts **a** and **b** reproduced, with permission, from REF. 125 © (2003) Society for Neuroscience. Part **c** reproduced, with permission, from REF. 166 © (2002) Macmillan Publishers Ltd. Part **d** reproduced, with permission, from REF. 30 © (2006) Elsevier Science.

synapses[156,157] (see below). These observations suggest that synaptic inputs that are sufficiently restricted in time and space might readily result in dendritic spikes, but that these events might not be easily detected using somatic recordings.

Larger dendritic spikes require the activation of many synapses. Estimates suggest that several tens of synapses must be activated to produce a single action potential[158] or to evoke local dendritic spikes[29]. Even if double this number of synapses were needed (as is the case, for example, for a burst to be evoked by a dendritic Ca^{2+} spike), this would still be less than 1% of the 30,000 excitatory synapses on a typical CA1 neuron[71]. GABAergic inhibition must increase the number of excitatory synapses required; however, large dendritic spikes clearly do occur *in vivo*, and so the numbers of synapses that are activated by stimulating electrodes when producing comparable events *in vitro* are likely to be biologically relevant.

It will also be important to determine the distribution of active synaptic inputs *in vivo*. Clustered inputs onto individual branches might evoke dendritic spikes more effectively than inputs that are distributed across multiple dendritic branches[159,160].

Dendritic coincidence detection

Distance-dependent synaptic efficacy is a feature of pyramidal neurons, at least during asynchronous activation, which tends not to produce dendritic spikes. Under these conditions, it seems inevitable that distal synapses must cooperate with more proximal synaptic inputs to contribute to action-potential initiation. During more synchronous activation, distal synapses can trigger local dendritic spikes[29,145,152]. The propagation of dendritic spikes to the soma is unreliable and depends on the size of the spikes. Whereas large dendritic Na^+ or Ca^{2+} spikes propagate effectively, smaller dendritic spikes, such as those that originate in a single branch, propagate less effectively[59,140,145,153]. Thus, small dendritic spikes from individual branches might need to sum with other inputs to evoke action-potential firing. Pyramidal neurons therefore operate as coincidence detectors. Traditionally, this implies simply the coincident activation of a sufficiently large number of inputs to reach the action-potential threshold. However, dendritic excitability introduces other forms of coincidence detection, such as coincident spiking in multiple dendritic branches or coincident activation or spiking of multiple dendritic domains. Two examples highlight how dendritic excitability can lead to dendritic coincidence detection.

In CA1 pyramidal neurons, apical tuft synapses do not exhibit synaptic scaling and probably influence action-potential firing either by summing with synaptic inputs from Schaffer collaterals or by triggering dendritic spikes[65]. Simulations and experiments suggest that the distally generated dendritic spikes do not propagate reliably from the apical tuft into the main apical dendrite[153,156] (FIG. 5a). This failure of dendritic spike propagation occurs because of the large drop in input impedance at points where small branches are connected to larger dendrites. When the Schaffer-collateral and perforant-path synapses are activated together, dendritic spikes can propagate reliably[156] (FIG. 5a, bottom). Conversely, inhibition targeted to the apical dendrite prevents propagation of the dendritic spike[156]. Thus, synaptic input to the apical dendrite can open or close a 'gate' that governs the influence of distally generated dendritic spikes on axonal action-potential initiation.

In neocortical layer V pyramidal neurons, the apical dendrites can generate Na^+ and Ca^{2+} spikes in response to strong synaptic activation[137,140]. High-frequency action-potential firing can also trigger a Ca^{2+} spike in distal apical and basal dendrites[126,161]. These requirements (strong synaptic activation or high-frequency action-potential firing) can be eliminated, however, if a backpropagating action potential occurs together with moderate synaptic input to the apical dendrites[95,134] (FIG. 5b,c). The distal EPSP sums with the backpropagating action potential to trigger a distal dendritic Ca^{2+} spike called a backpropagation-activated Ca^{2+} spike (BAC spike), which in turn causes a burst of action potentials in the soma. *In vivo*, the backpropagating action potential would presumably be induced by activation of proximal synapses. Thus, coincident activation of proximal and distal synapses could lead to action-potential bursting by the BAC spike mechanism.

Dendritic excitability and synaptic plasticity

Dendritic excitability in pyramidal neurons also has a role in the induction of synaptic plasticity. One of the most widely studied forms of long-term potentiation (LTP) and depression (LTD) — spike-timing-dependent plasticity (SDTP) — is dependent on the relative timing of the EPSP and the action potential. For the synapse to detect spike timing, the spike must propagate from its initiation site in the axon back to the synapse. Such backpropagating action potentials could relieve the Mg^{2+} block at glutamate-bound NMDA receptors on synaptically activated spines[162]. Indeed, when small EPSPs are paired with current-evoked action potentials, blocking or inhibiting the backpropagating action potential prevents LTP induction[163–165]. Furthermore, pairing action potentials with small EPSPs in the apical tuft of CA1 pyramidal neurons does not induce LTP, presumably because action potentials do not propagate reliably to this distal location[166]. In neocortical layer V pyramidal neurons, small EPSPs from distal synapses are potentiated by pairing with action potentials only when the backpropagating action potentials are amplified by dendritic depolarization[164]. This demonstrates how dendritic compartmentalization is critical to pyramidal-neuron function. Pairing of EPSPs and action potentials represents an associative interaction between a weak input (small EPSP) and a stronger input (leading to the action potential). Whether or not this associative interaction leads to Hebbian LTP depends on the timing and location of the two inputs[167].

The ability of backpropagating action potentials to potentiate EPSPs during pre- and postsynaptic pairing is limited. Potentiation is only observed when pairings occur at relatively high frequencies or when postsynaptic bursts or large EPSPs are used during low-frequency pairing[168–171]. Furthermore, some forms of LTD do not require action-potential firing[164,172,173], so the role of

Backpropagation-activated Ca^{2+} spike
(BAC spike). A spike that occurs in the distal apical dendrites of layer V pyramidal neurons during coincident synaptic stimulation and action-potential backpropagation.

backpropagating action potentials in synaptic depression remains unclear. These observations point to other forms of dendritic depolarization being necessary for the induction of synaptic plasticity[174].

Dendritically initiated spikes are required for LTP or LTD induction in response to strong synaptic stimulation[158,166,172] or during pairing of EPSPs with postsynaptic bursts[168,169]. In these forms of LTP the

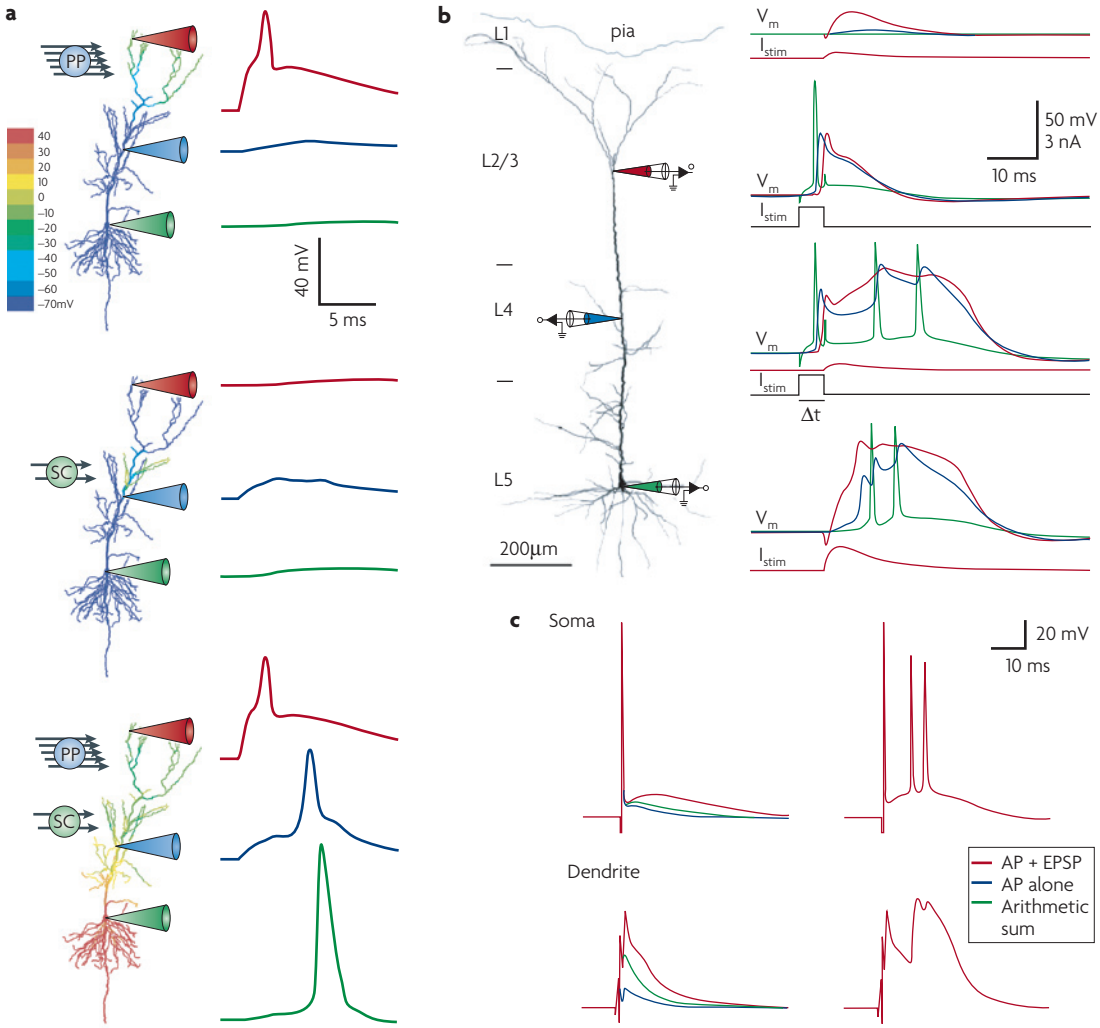


Figure 5 | **Coincidence detection by excitable dendrites in pyramidal neurons. a** | Gating of dendritic spike propagation in a model of a CA1 pyramidal neuron. The top panel illustrates how the simulated activation of 251 perforant-path (PP) synapses results in a spike in the apical tuft that does not successfully invade the apical dendrite proximal to the primary bifurcation. The middle panel illustrates how the simulated activation of 115 Schaffer-collateral (SC) synapses produces spikes in apical oblique branches that do not invade the main apical dendrite. The bottom panel illustrates how the simulated activation of PP and SC synapses together results in the successful propagation of a spike along the main apical dendrite and into the soma and axon. **b** | Backpropagation-activated Ca^{2+} (BAC) spikes in layer V (L5) pyramidal neurons. The diagram of the nerve shows the positions from which recordings were taken: the soma (indicated by the green electrode), the mid-apical dendrite in layer IV (blue electrode) and the upper apical dendrite in layer II/III (red electrode). Membrane-potential responses and current stimuli (all colour-coded to match the electrodes) are shown for four stimuli — from top to bottom: excitatory postsynaptic current (EPSC)-like current injection in the upper apical dendrite produces an EPSP-like response; somatic current injection evokes a backpropagating action potential; a combination of these two stimuli produces a BAC spike in the upper and mid apical dendrites and a burst of action potentials in the soma; a larger EPSC-like current injection in the upper apical dendrite similarly produces a dendritic Ca^{2+} spike and a burst of action potentials. **c** | Amplification of backpropagating action potentials by dendritic EPSPs can lead to bursting. The two left-hand plots show somatic (top) and dendritic (bottom) responses to an antidromic action potential (AP) activated alone (blue trace) or in combination with a dendritic EPSP-like response to dendritic current injection. The combined response (red trace) is larger than the linear sum of the action potential and the EPSP separately (green trace). The two right-hand plots are from another trial in which the EPSP triggered a second action potential that backpropagated even more effectively, leading to a large dendritic spike that triggered another action potential and hence a burst. Part **a** reproduced, with permission, from REF. 156 © (2005) Macmillan Publishers Ltd. Part **b** reproduced, with permission, from REF. 95 © (1999) Macmillan Publishers Ltd. Part **c** reproduced, with permission, from REF. 134 © (2001) Macmillan Publishers Ltd.

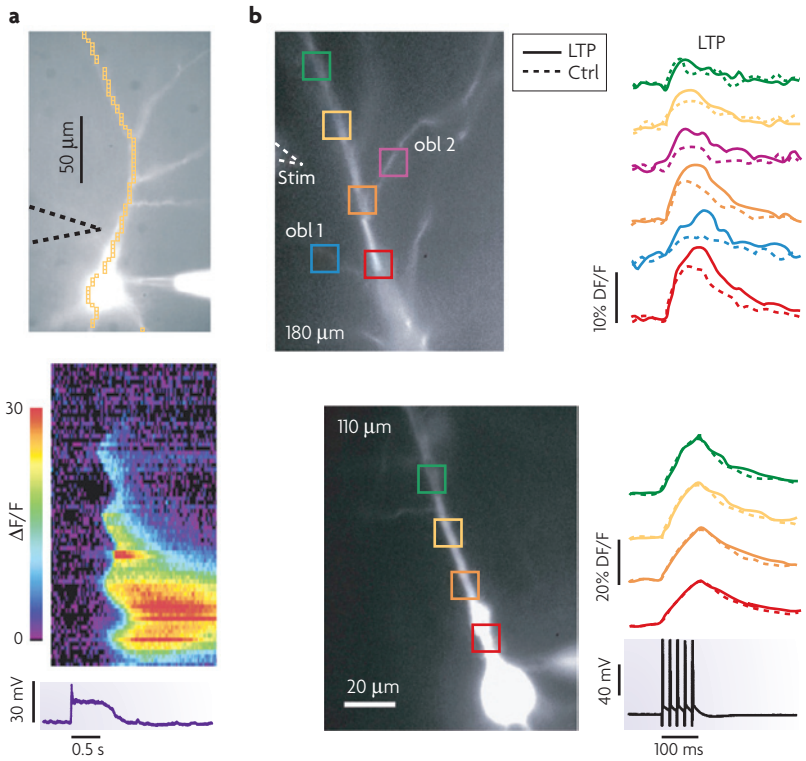


Figure 6 | **Modulation of pyramidal-neuron function by metabotropic-receptor activation or activity-dependent plasticity. a** | Ca^{2+} waves induced by synaptic stimulation in a layer II/III pyramidal neuron. The top panel shows a fluorescence image of the filled cell. The patch electrode is visible and the dashed lines indicate the position of the stimulating electrode. The middle panel shows the Ca^{2+} response along the scanning path as a function of time. The somatically recorded voltage response is shown at the bottom. The cell was activated by 100 Hz synaptic stimulation for 0.5 seconds. The resulting voltage response (bottom panel) produced a small, fast Ca^{2+} response that spread beyond the apical dendritic branch point. The slower Ca^{2+} wave that followed was larger but was restricted to relatively proximal apical dendrites. **b** | Localized enhancement of dendritic excitability following the induction of LTP. The left-hand two panels are a photographic montage of a CA1 pyramidal neuron filled with Ca^{2+}-sensitive dye. The coloured boxes indicate regions of interest for Ca^{2+} imaging. The dashed lines indicate the position of the stimulating electrode. Two imaging regions are on oblique dendrites (labelled obl 1 and obl 2); the remaining areas are on the main apical dendrite. The upper two sets of plots are Ca^{2+}-imaging responses (corresponding to the coloured boxes in the left-hand panels) to a burst of five 50 Hz action potentials (bottom plot). Note the increase in Ca^{2+} concentration near the stimulation electrode (particularly obl 1, obl 2 and the main apical dendrite in between) following the induction of LTP. Part **a** reproduced, with permission, from REF. 176 © (2003) Cambridge University Press. Part **b** reproduced, with permission, from REF. 182 (2004) Macmillan Publishers Ltd.

dendritic spike signals cooperative synaptic activation and provides the necessary postsynaptic depolarization for Hebbian LTP to occur. Dendritic spikes also induce LTP or LTD in response to single presynaptic shocks or a burst[158,172], suggesting that dendritic spikes constitute a particularly powerful signal for the induction of synaptic plasticity.

These findings indicate that a variety of sources of dendritic depolarization can participate in the induction of LTP in pyramidal neurons. More work is needed, however, to establish which types of LTP and LTD predominate during natural synaptic and firing conditions *in vivo*.

Modulation of synaptic integration and firing

Neurotransmitters, such as dopamine, serotonin, noradrenaline and acetylcholine, modulate pyramidal-neuron function. Neuromodulators change various features of pyramidal-neuron function by targeting channels that are gated by voltage, by neurotransmitters or by other intracellular messengers. This in turn can affect various cellular functions, such as synaptic strength, firing rates, firing modes, dendritic excitability, up and down states and intrinsic and network oscillations. One example of this modulation is the activation of muscarinic acetylcholine receptors (mAChRs) in layer V pyramidal neurons of the entorhinal cortex, which leads to a form of persistent firing through the activation of a Ca^{2+}-dependent, nonspecific cation current[175]. Neuromodulation can be spatially restricted as a result of differential innervation, receptor distribution or the presence of different targets of second-messenger systems in different dendritic compartments. An example of domain-specific neuromodulation in both CA1 and layer II/III pyramidal neurons is the Ca^{2+} waves that are evoked by coincident action-potential firing and activation of metabotropic glutamate receptors (mGluRs) or mAChRs. These Ca^{2+} waves propagate along the main apical dendrite of pyramidal neurons but do not extend into smaller dendritic branches[176,177] (FIG. 6a). This constitutes an example of coincidence detection of action potentials and metabotropic-receptor activation. The functional significance of these Ca^{2+} waves remains unknown; however, they could be important for modulating cellular excitability, gene expression and synaptic strength[178].

Another example of a spatially restricted effect of a modulatory neurotransmitter is the action of acetylcholine at mAChRs. This action suppresses synaptic transmission at CA3–CA1 synapses on proximal apical dendrites while having less of an effect on synapses that selectively innervate the apical tuft[179]. Such dendritic-domain-specific effects indicate that pathways that relay different types of presynaptic 'information' might be weighted differently during different behavioural states.

Modulators also affect synaptic plasticity in a dendritic-domain-dependent manner. In neocortical pyramidal neurons, pairing of EPSPs and action potentials leads to the potentiation of synapses on proximal basal dendrites but not on distal basal dendrites. In the distal basal dendrites, synaptic potentiation occurs only when synaptic activation (which is strong enough to evoke an NMDA spike) is paired with BDNF application[180]. This finding serves as a rationale for distinguishing between excitatory synapses on proximal and distal basal dendrites (FIG. 1c).

In addition to effects that are mediated by the activation of modulatory neurotransmitters, synaptic plasticity can also be accompanied by long-lasting changes in cellular excitability[91,181], which can be restricted to particular subcellular domains. Induction of LTP in CA1 pyramidal neurons is accompanied by a long-term increase in excitability due to the modulation of A-type K^+ channels in only those branches near the activated synaptic input[182] (FIG. 6b).

Up and down states
Two distinct cortical states that are defined by relatively depolarized membrane potentials and lots of action-potential firing (the up state) versus hyperpolarized membrane potentials and very little firing (the down state). Although these states are often determined from the membrane potential in individual cells, groups of cells tend to transit between these states synchronously, so the state is a reflection of local cortical activity.

Conclusion

There are some recurring themes in the work described here. For example, it is clear that synaptic integration is dependent on the dendritic domain that is targeted by a synaptic input, and that dendritic excitability might serve to implement a variety of coincidence-detection rules. Coincident synaptic input to individual branches produces local spikes that do not propagate reliably to the soma, whereas coincident input to multiple branches can result in larger dendritic spikes that propagate to the soma more readily and thus trigger an axonal action potential. Coincidence-detection rules have led to the hypothesis that pyramidal-neuron dendrites function in a way that can be compared to a multi-layered network[155,160,183]. It remains to be determined, however, to what extent specific mechanisms, such as the gating of distal dendritic spikes or BAC-spike mediated bursting, represent functions that are shared by all pyramidal neurons or functions that are used only in particular types of pyramidal neurons.

The separation of basal and apical dendrites on all pyramidal neurons implies strongly that these dendrites have distinct functions. However, the degree to which these and other dendritic domains function differently remains unclear. For example, are synapses on apical oblique branches equivalent to those on the main apical trunk? Do the apical oblique synapses on separate branches receive different information, or do presynaptic inputs from a single source randomly target different apical and basal dendritic branches? Consider, for example, a CA1 pyramidal neuron that fires when a rat enters a particular position in space. It would be useful to know which of the thousands of excitatory, inhibitory and modulatory synapses that contact the neuron were active as the cell fired in its place field. Furthermore, it would be useful to know the receptive-field properties of the active presynaptic neurons, as well as the dendritic arrangement of the activated synapses. How does this situation change when the neuron is reactivated during sleep or rest?

Most pyramidal neurons have very complex receptive-field properties that are not static, but rather change as a function of behavioural state and prior activity. For example, CA1 place cells can re-map to represent new locations when the animal explores a novel environment[184,185]. Such effects evoke questions about what causes the firing properties of the cell to change so dramatically. The possibilities are numerous: activity-dependent synaptic plasticity of excitation, inhibition, or both; local changes in dendritic excitability; or changes in modulatory inputs to influence synaptic and intrinsic properties. Such changes could be restricted to CA1 or could be distributed across many brain regions, which would result in changes in the populations of neurons that drive a particular CA1 cell. As questions like these continue to be answered we will move closer to a detailed understanding of the complex and dynamic function of pyramidal neurons, a crucial key to unlocking the mysteries of cortical function.

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FURTHER INFORMATION
Nelson Spruston's homepage: http://www.northwestern.edu/neurobiology/faculty/spruston/
Scholarpedia article on pyramidal neurons: http://www.scholarpedia.org/article/Pyramidal_neuron
Wikipedia article on pyramidal neurons: http://en.wikipedia.org/wiki/Pyramidal_cell
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