

A cellular mechanism for cortical associations: an organizing principle for the cerebral cortex

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A basic feature of intelligent systems such as the cerebral cortex is the ability to freely associate aspects of perceived experience with an internal representation of the world and make predictions about the future. Here, a hypothesis is presented that the extraordinary performance of the cortex derives from an associative mechanism built in at the cellular level to the basic cortical neuronal unit: the pyramidal cell. The mechanism is robustly triggered by coincident input to opposite poles of the neuron, is exquisitely matched to the large- and fine-scale architecture of the cortex, and is tightly controlled by local microcircuits of inhibitory neurons targeting subcellular compartments. This article explores the experimental evidence and the implications for how the cortex operates.

Introduction

The cortex remains an enigmatic structure, at once beautifully simple and yet mysterious. After more than a century of concerted investigation, both the purpose and operating principles of the cerebral cortex are hotly debated [1–4]. It is still deeply puzzling how neurons in different regions, sometimes many centimeters apart, can be linked with each other and act in concert to form single conscious percepts [5]. But even basic questions such as why the cortex is layered [6] or made up of 70–80% pyramidal neurons [7] remain unanswered. Most computational models of cortical function still treat neurons as simple single-compartment units even though the potential power of single neurons in information processing has long been understood [8]. Here, the view is presented that both the cellular properties and architecture of the cortex are tightly coupled, suggesting a powerful operating principle of the cortex.

At first glance, the architecture of the cortex seems bizarre. Long-range connectivity in the cortex follows the basic rule that sensory input (i.e., the feed-forward stream) terminates in the middle cortical layers, whereas information from other parts of the cortex (i.e., the feedback stream) tends to project to the outer layers [9–13] (Figure 1). This also applies to projections from the thalamus, a structure that serves as both a gateway for feed-forward sensory information to the cortex and as a hub for feedback interactions between cortical regions (Box 1)

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[14–16]. This wiring feature is mysterious because the principal targets for such feedback connections in L1 are a handful of interneurons [17] and the very distal tuft dendrites of pyramidal neurons. Referred to as the ‘crowning mystery’ of the cortex by David Hubel [18], only ~10% of the synaptic inputs to L1 come from nearby neurons and the missing 90% from long-range feedback connections [19,20].

A naïve interpretation of this architecture would lead to the conclusion that feedback information is relatively inconsequential compared to the feed-forward stream. However, it is clear from multiple lines of research that the feedback information stream is in fact vitally important for cognition [21–25] and conscious perception [26–29]. This has led to the suggestion that the cortex operates via an interaction between feed-forward and feedback information [30–32]. In this scenario, feedback provides context or predictive information for modulating neural activity in a given area [33–35], and also provides a mechanism for the cortex to attend to particular features [36].

Because feedback targets the apical dendrites of cortical pyramidal neurons in L1, several authors have proposed an important role for these dendrites [16,37–47]. However, all these theories must contend with the fact that the bulk of cortical feedback inputs arrive at the most electrically remote region of the pyramidal neuron distal tuft dendrites, where they have the least influence on spike generation in the axon [48,49]. Thus, understanding the properties of these dendrites becomes central to explaining the influence of feedback connectivity in the brain. The aim of this article is to set out the evidence for considering the pyramidal neuron to be an associative element and how this property relates to cortical function.

The calcium-spike initiation zone in L5 pyramidal neurons

With regard to the remoteness of the tuft dendrite in L1, a key finding was the discovery of a second initiation zone for broad calcium action potentials (‘Ca²⁺ spikes’) near the apical tuft of layer 5 (L5) pyramidal neurons [50–54]. Feedback inputs to the tuft are therefore much closer to this action-potential initiation zone than to the one in the axon at the other end of the cell. Moreover, the calcium spike is a tremendously explosive engine, driving the L5 pyramidal cell to fire repetitively when ignited [53]. Because it produces long (up to 50 ms *in vitro*) plateau-type

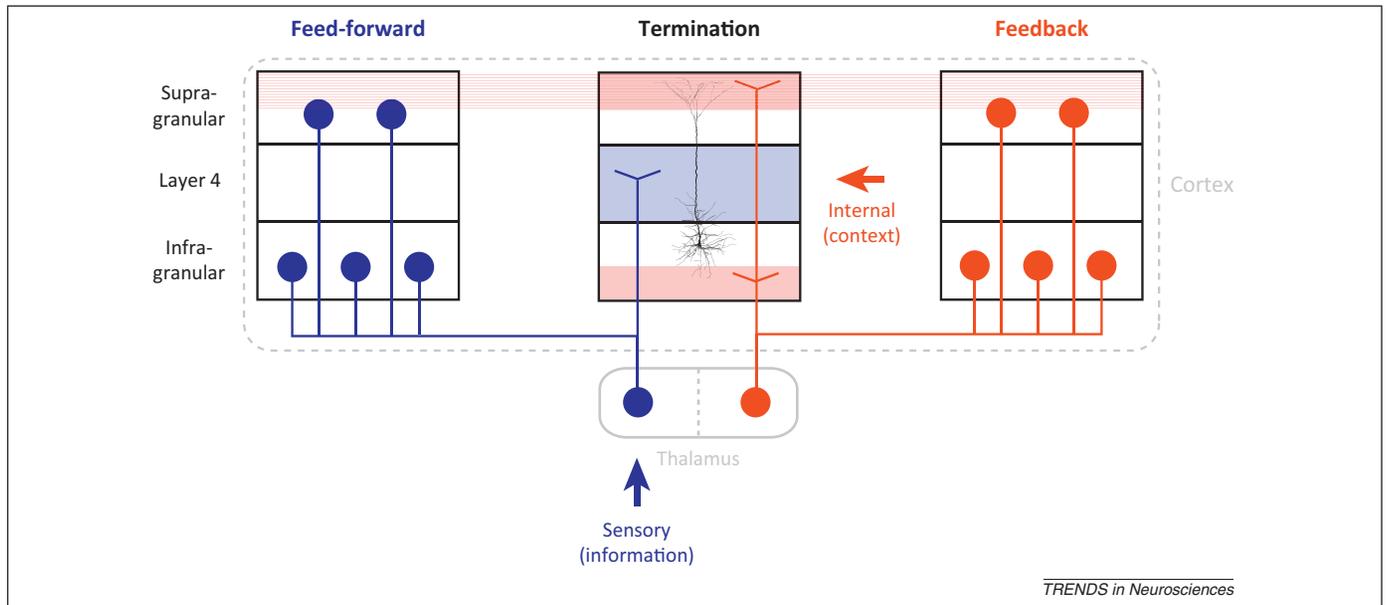


Figure 1. Long-range architecture of the cortex. A general scheme for feed-forward and feedback connectivity between cortical areas proposed by Felleman and van Essen [10] that applies equally to thalamo-cortical interconnections (Box 1). The feed-forward stream is driven by external information influencing the sensory apparatus. The feedback stream is driven by an internal representation built from previous experiences. A layer 5 pyramidal neuron has been superimposed on the middle panel to highlight the location of the dendrites relative to the large-scale wiring of the cortex. Adapted, with permission, from [10].

potentials, the resulting sustained depolarization that spreads to the axon initiation zone causes high-frequency bursting of axonal action potentials [55–58]. In fact, it turns out that triggering a dendritic Ca^{2+} spike produces more output action potentials in the axon than suprathreshold input to the cell body does [53,57,59]. Therefore, counter-intuitively, far from being a minor influence on pyramidal cell firing, distal feedback input to the tuft dendrite could potentially dominate the input/output function of the cell. Furthermore, the presence of distal dendritic Ca^{2+} spikes can be readily detected by the characteristic burst pattern of 2–4 spikes at ~ 200 Hz at the cell body [57]. It is therefore possible that this serves as a means to signal the presence of dendritic spikes to subsequent neurons, and that bursts are a fundamental cortical coding mechanism [60,61].

The active properties of L5 pyramidal neurons so far uncovered display an astonishing degree of complexity [62–64], including the possibility to perform local computations via NMDA receptors (reviewed elsewhere [65]). Local NMDA spikes have been shown to occur in L4 spiny stellate cells *in vivo* [66], and *in vitro* data in L5 neurons suggest that NMDA spikes in the tuft dendrites only significantly affect the output of the neuron if they can first bring the apical dendritic Ca^{2+} initiation zone to threshold. However, regardless of the possible importance of NMDA spikes, the Ca^{2+} and Na^+ initiation zones at either end of the apical dendrite remain pivotal in determining the input/output properties of the cell [57,59,63,67,68].

Backpropagation-activated coupling: an associative mechanism within each cell

The discovery of the dendritic Ca^{2+} spike did not immediately solve the problem of remote input to the tuft. It still remained to be explained how distal synaptic input could

overcome the threshold for evoking such dendritic spikes because even input directly to the tuft has little effect on the apical Ca^{2+} initiation zone [49,63]. The conceptual breakthrough emerged from the demonstration that the Na^+ and Ca^{2+} spike initiation zones can influence each other [59,69] (Figure 2). This occurs via the apical dendrite that is studded with voltage-gated Na^+ channels that support signal propagation [70,71]. The consequence is that although small (sub-threshold) signals contribute only to their respective spike initiation zones, the fact that input has reached threshold in one zone is quickly signaled to the other zone. This provides the possibility for associative interactions within the neuron by which the activity of one region of the cell can lower the threshold for initiation of activity in the other region. Originally, coined ‘backpropagation-activated Ca^{2+} spike firing’ (or ‘BAC firing’), the coincidence of synaptic input to the tuft dendrite with a single ‘backpropagating’ spike at the cell body halves the current threshold for a dendritic Ca^{2+} spike, thereby triggering a burst of multiple action potentials [69] (Figure 2a). This feature can be readily formalized [59] (Figure 2b) and substituted for the more usual ‘integrate-and-fire’ units normally used in neural networks. Unlike in typical neural networks, this architecture allows individual units to process the two information streams separately and then combine them using the intrinsic properties of the cell, reducing the burden on the network complexity.

The biophysical properties shown in Figure 2a were ascertained with stereotypically shaped current injection to the two main action-potential initiation zones of the cell within a time window of 30 ms [69]. However, typical synaptic input comes in barrages of noisy, continuous streams. With this kind of input, the associative mechanism in pyramidal neurons behaves analogously. That is, the response to feed-forward input to the soma compartment can be dramatically increased by relatively weak

Box 1. Thalamo-cortical interaction with an associative cortical mechanism

Understanding cortical function is impossible without reference to its interaction with the thalamus. Although the associative mechanism addressed in this article lies in pyramidal neurons, which are not found in the thalamus, connections from the thalamus to the cortex follow the same principles as cortico-cortical connections (i.e., feed-forward to middle layers, and feedback to outer layer) (Figure 1a) [14]. The thalamus is often referred to in its role of relaying sensory input to the cortex. Relay regions of the thalamus project to relatively specific regions of the cortex and are therefore often referred to as ‘specific’ nuclei. In fact, most areas of thalamus receive inputs predominantly from the

cortex and project back to the cortex in a relatively ‘non-specific’ fashion, thereby serving as a connection hub for different cortical areas. These thalamic nuclei have dense projections to L1 of the cortex, underscoring again the particular emphasis on associative connections to this layer (Figure 1b). The column of the cortex interacting with the two types of thalamic nuclei forms a module, and taken as a whole, the cortex can be viewed as a chain of such thalamo-cortical modules [108] (Figure 1c). Rodolfo Llinás has been a major proponent of the idea that these modules are crucial to conscious perception, relying on the associative properties of pyramidal neurons [100].

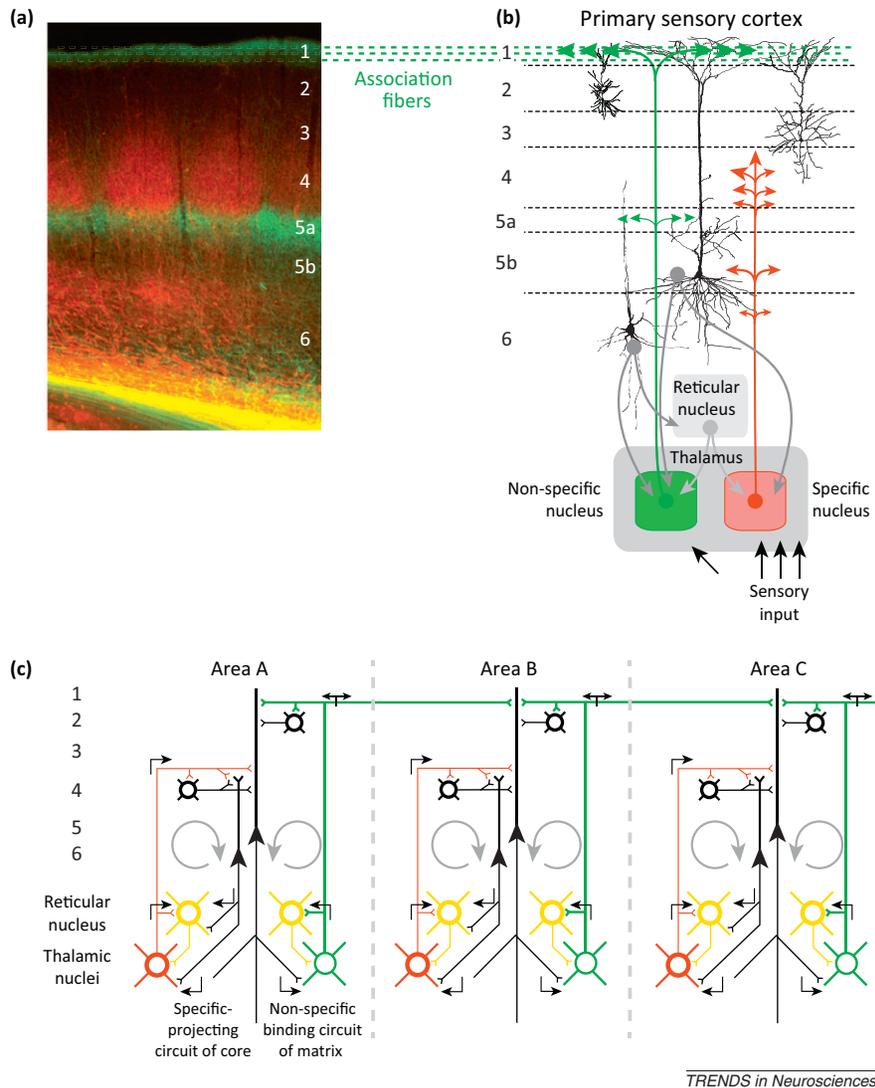


Figure 1. (a) Axons from the primary, specific (ventral posterior medial, red) and secondary, non-specific (posterior medial, green) thalamic nuclei, visualized via injection of an adeno-associated virus (AAV) conjugated with green and red fluorescent proteins to the respective thalamic regions [14]. (b) Schematic representation of the long-range input to the primary sensory cortex in rats. The color scheme follows the fluorescent protein colors in (a) for easy comparison (and not the scheme in the other figures in this article). Association fibers carrying feedback information from other cortical areas are shown overlapping with thalamic, non-specific input in layer 1. (c) A schematic representation of a chain of cortical modules. ‘Core’, specific-projecting neurons (red), and ‘matrix’, non-specific binding circuit neurons (green), interact with the cortex in different lamina via the dendrites of pyramidal and local inhibitory neurons (black). Inhibitory neurons of the reticular nucleus (yellow) control the mode of firing of thalamic cortico-projecting neurons promoting oscillatory behavior (arrows). This architecture forms repeating modules synchronizing cell assemblies across the cortex and thalamus. Adapted, with permission, from [14] (a) and [100,108] (c).

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input to the tuft compartment triggering the BAC firing mechanism [59,72] (Figure 2c). This implies that, once the cell is brought to fire (e.g., with feed-forward input), the cell becomes exquisitely sensitive to feedback input. In fact, these studies demonstrated that, even in the absence of

obvious dendritic plateau potentials, the distal dendritic calcium channels still contribute significantly to the firing rate of the neurons during associative pairing of distal and proximal input [72]. In these cases, the phenomenon might be better termed ‘backpropagation-activated coupling’,

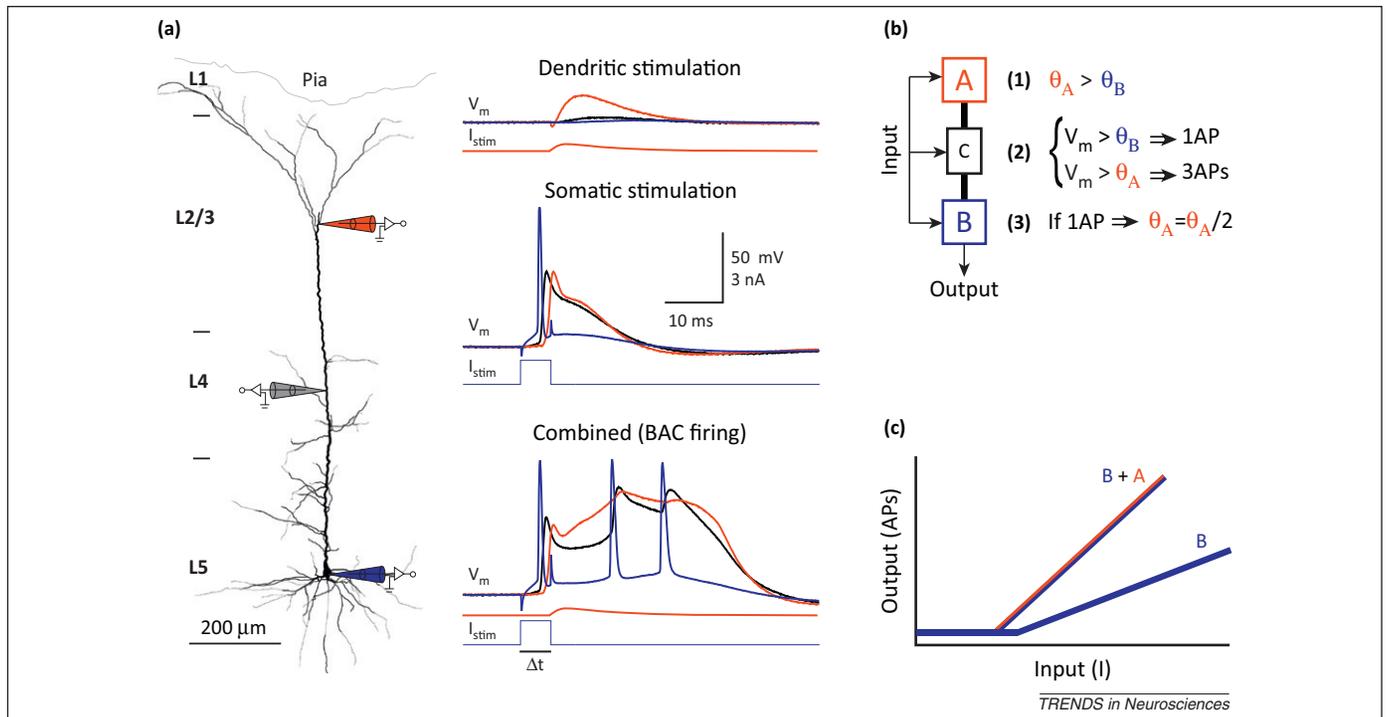


Figure 2. Backpropagation activated calcium spike firing (BAC firing). **(a)** (Left) Schematic depiction of an *in vitro* experiment from a layer 5 (L5) pyramidal neuron with triple recordings from soma (blue) and dendritic tree (black and red). (Right, top) Simulated distal excitatory postsynaptic potential (EPSP) with dendritic current injection (I_{stim} , red) causes no dendritic spike (red) and has virtually no impact at the cell body (blue). (Right, middle) A somatic action potential evoked with somatic current injection (I_{stim} , blue) invades the dendritic tree but still causes no dendritic spike. (Right, bottom) Combined injection of the same dendritic and somatic currents as in the upper panels reaches threshold for a dendritic calcium spike which triggers burst firing [69]. **(b)** (Left) Simplified model of BAC firing with a three compartment pyramidal neuron [57]. Compartments A and B are sites of action potential initiation (with thresholds θ_A and θ_B) that integrate predominantly synaptic inputs to the apical tuft and basal dendrites, respectively. Compartment C couples compartments A and B, integrating predominantly inputs to the oblique dendrites [109] and influences signal propagation in both directions. (Right) The rules for stereotypical inputs and outputs. For rules 2 and 3, ‘APs’ refers to output action potentials in the axon that exits from compartment B. **(c)** The rules for stereotypical inputs shown in (a) and (b) can be generalized for any input (for example, random, noisy input similar to that seen during *in vivo* recordings). Here the slope of the curve – or the output as a function of the input to compartment B (blue) – is dramatically increased by only very small additional input to compartment A (red and blue) [59]. Adapted, with permission, from [69] (a).

although even without Ca^{2+} spikes it still involves activation of Ca^{2+} channels and additional spiking. In any case, it is now clear that the intrinsic properties of pyramidal neurons play a huge role in determining the number of output action potentials and that models of the cortex that do not take this into account are likely to be inaccurate. In summary, because of the shape and orientation of pyramidal neurons combined with the architecture of the cortex, the BAC firing mechanism is ideally suited to associating feed-forward and feedback cortical pathways.

Inhibitory control of BAC firing

It is now abundantly clear that associative pairing can be very effectively blocked by specific inhibitory neurons in the cortical microcircuit, placing special significance on dendrite targeting inhibition [73]. This powerful suppression of dendritic plateau potentials has been observed *in vitro* [69,74–77] and *in vivo* [72,78]. Anesthesia – which is associated with elevated inhibition [79] – also dampens dendritic calcium spikes *in vivo* [80]. Although the activation of both $GABA_A$ and $GABA_B$ receptors has a powerful effect on the generation of dendritic calcium spikes, this occurs on very different timescales (10s versus 100s of ms) and via very different mechanisms. This gives the cortex the capability of exquisite control of dendritic plateau potentials and their contribution to the generation of output spikes. Some inhibitory neurons, such as Martinotti

neurons [81] and neurogliaform neurons [82], specifically target the dendrites of pyramidal neurons. There are also indications that some of the molecular machinery for suppressing dendritic calcium channels is located specifically in the apical dendrite [77]. This specificity implies that the control of dendritic calcium activity is of great importance to the normal functioning of the cortex. It also provides the means for possible tools for future research to target specifically associative pairing to test its significance for behavior.

BAC firing and cortical information processing

To this point, this article has dealt with the biophysical evidence for the existence of an associative firing mechanism in pyramidal neurons and its influence on the input/output function. This degree of integration between the micro- and macroarchitecture, as well as inbuilt complexity at the cellular level, invites speculation about whether and how the whole system utilizes this feature. The importance of this mechanism conceptually is that the pyramidal neuron is able to detect coincident input to proximal and distal dendritic regions, investing the cortex with an inbuilt associative mechanism at the cellular level for combining feed-forward and feedback information [59,69]. Feedback, in this scheme, serves as the ‘prediction’ [34] of the cortex as to whether a particular pyramidal neuron (or microcolumn of pyramidal neurons) could or

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should be firing (Figure 3b). But only if that neuron receives enough feed-forward input to fire in the first place is the dendritic threshold lowered sufficiently to trigger the BAC firing mechanism. Seen in these terms, the internal representation of the world by the brain can be matched at every level with ongoing external evidence via a cellular mechanism (Figure 3a). The fact that it occurs at the cellular rather than network level is important because it allows the cortex to perform essentially the same operation (i.e., internal versus external) with massively parallel

processing power. Here, information with an external (e.g., sensory) origin feeds forward to establish a baseline frequency of firing that can then interact with feedback information of internal origin arriving at the dendrites to dramatically alter the firing of the neuron (Figure 3a).

Thus the main function of the cortex – to associate external data with an internal representation of the world – could in theory be achieved without the need for complex circuitry, and instead use a single, essentially 2D sheet of vertically aligned pyramidal neurons. Moreover, with this

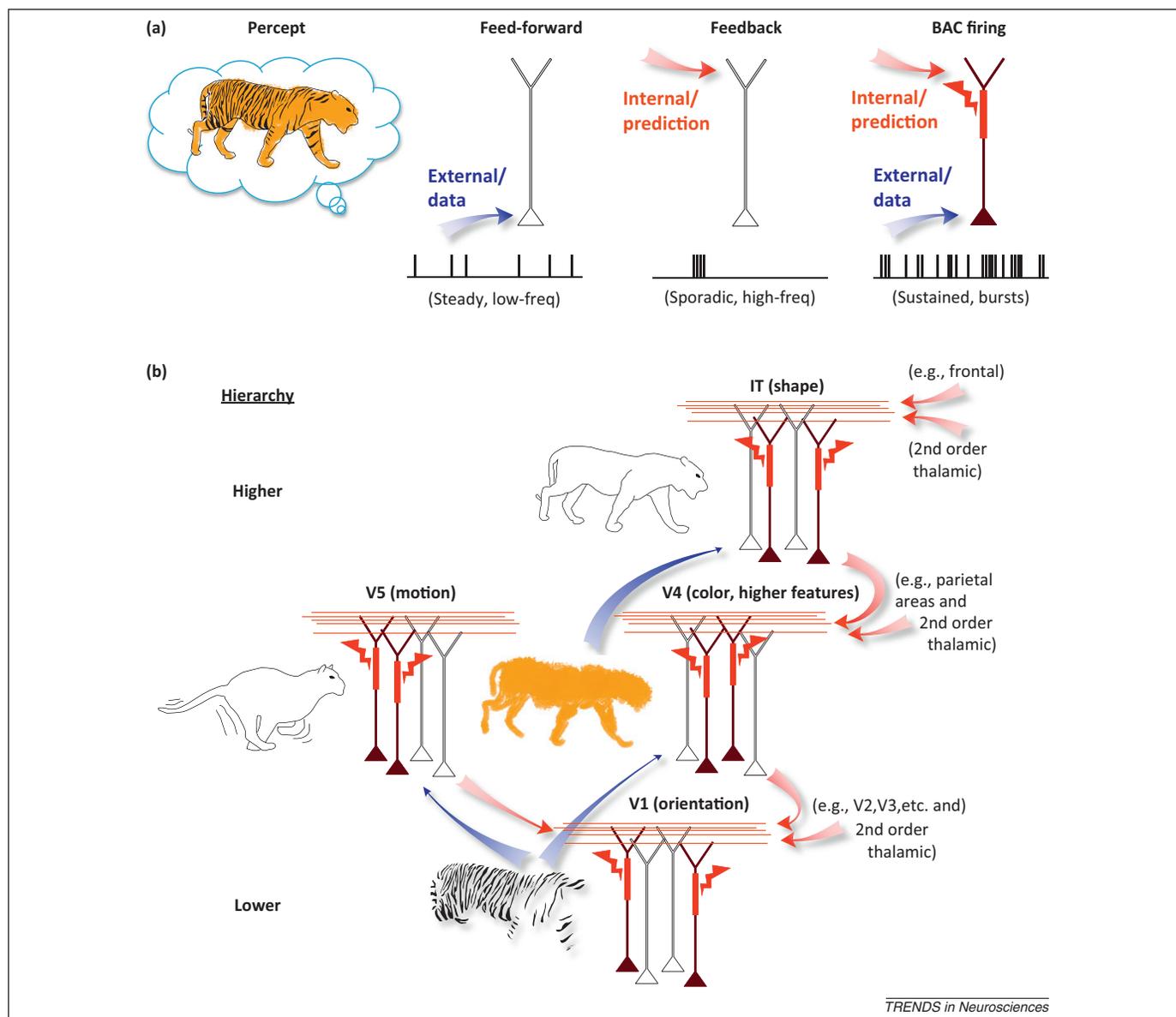


Figure 3. Conceptual representation of the backpropagation activated calcium (BAC) firing hypothesis for feature binding and recognition. **(a)** Any given percept (such as a tiger in the visual receptive field) is represented internally via a cortical ‘engram’ of neurons receiving feed-forward (blue) and feedback (red) information. This engram is encapsulated by pyramidal neurons because these are the only neurons that project to other areas within and outside the cortex. Based on the properties of the pyramidal neuron from *in vitro* experiments, neurons receiving predominantly feed-forward information are likely to fire steadily at low rates, whereas feedback input to the distal dendrite is predicted to reach threshold occasionally and produce a short burst of APs. The BAC firing hypothesis predicts that the combination of both streams simultaneously will result in sustained firing and possibly a change in the mode of firing to bursts [59]. **(b)** Illustration of how a cellular mechanism for associating feed-forward and feedback signals can serve the recognition process. In this simplified view of the visual cortex (not including all areas and cell types), low-level features are encoded in primary sensory regions and this signal propagates up the visual hierarchy. Feedback inputs come not only from regions immediately above in the hierarchy but also from many other higher-level cortical and thalamic regions (red arrows), and are carried by horizontal fibers along L1 that synapse on to the distal tuft dendrites. Particular assemblies of neurons can thereby be associated with each other and their output greatly enhanced. For this conceptual representation, only four regions are shown and are arranged according to the visual hierarchy [10]: striate cortex (V1) sensitive to orientation, V4 sensitive to color, V5 sensitive to motion, and inferior temporal (IT) cortex sensitive to shapes and objects. However, it is assumed that many more regions and modalities interact, for instance regions encoding emotional responses or movement planning, etc. In this way, the feedback information provides context or expectation informing lower areas about higher-level representations manifesting elsewhere in the cortex. The representation manifests as an engram of BAC firing neurons.

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design, cortical associations could be manifested in the firing of neurons that requires no downstream read-out mechanism or homunculus. In other words, rather than requiring an additional mechanism to detect and group neurons of interest, those neurons matching the feedback prediction simply have the most influence on the rest of the brain because of their increased firing and/or bursting. Their activity in turn provides additional feed-forward influence to further hone the feedback prediction and so forth [13]. This does not rule out the possibility that other mechanisms, such as synchrony between ensembles of neurons, might contribute simultaneously with the associative pairing mechanism [83]. In fact, the timing-dependence of BAC firing would both increase the importance of synchronous input and also serve to entrain neurons increasing synchronous output.

Evidence for BAC firing *in vivo* and the relationship to conscious perception

By their nature, the distal dendrites of pyramidal neurons are extremely difficult to investigate in living animals. However, advances with fiber-optic approaches and two-photon microscopy are starting to reveal evidence for the existence of the BAC firing mechanism *in vivo*. Dendritic calcium spikes have been recorded *in vivo* [57,84,85] that correlate to behavior [78,86]. Using a fiber-optic imaging technique, which enabled recordings specifically from populations of tuft dendrites of L5 pyramidal neurons, it was demonstrated that dendritic calcium activity can increase by an order of magnitude in awake versus anesthetized rats (Figure 4a), and was correlated to the movement of the limbs of the animal. Notably, this effect occurred only in the dendrites of L5 cells while the activity of nearby L2/3

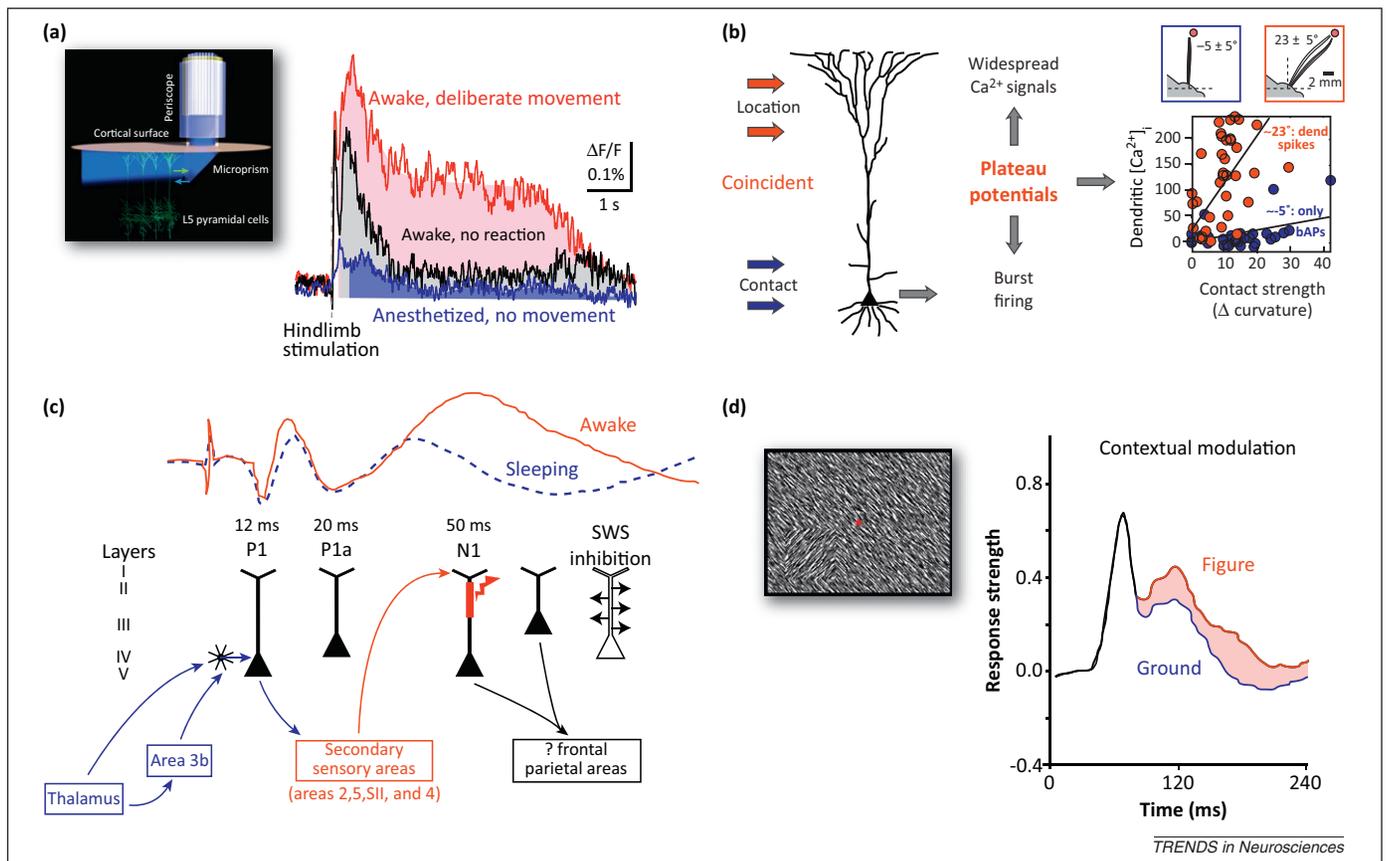


Figure 4. Recordings of brain activity consistent with the backpropagation activated calcium (BAC) firing hypothesis. **(a)** (Left) Schematic diagram illustrating the 'periscope' technique used for optical recordings of calcium activity specifically from the dendrites of layer 5 (L5) pyramidal neurons in the sensorimotor cortex of a rat [102]. (Right) Such recordings show an order of magnitude increase in dendritic activity in awake animals during deliberate movement (red). Trials in awake animals without reaction (black) were still fourfold larger than in anesthetized animals (blue) [87]. **(b)** Information about whisker location is hypothesized to arrive at the distal dendrites of L5 pyramidal neurons through long-range cortico-cortical feedback inputs (red) to L1, whereas direct feed-forward sensory input from the whiskers (blue) arrives close to the cell body. In this *in vivo* study, which utilized two-photon imaging from L5 pyramidal tuft dendrites in awake mice, dendritic Ca^{2+} activity was measured as a function of the strength of contact between the whisker and a post (insets; -5° , blue box; -23° , red box). The findings led to the conclusion that, at the preferred position, whisker location dependent input to the tuft coincident with whisker contact sensory input perisomatic regions caused dendritic plateau potentials in the tuft. These dendritic events are predicted to lead to increased burst firing activity whereas contact at non-preferred positions are associated with only single backpropagating APs or short duration trunk spikes [86]. **(c)** The hypothesized events underlying the consciousness-dependent surface negativity (N1 component) of the somatosensory-evoked potential in the primary somatosensory cortex (S1) in monkeys during a tactile task. (Top) Averaged somatosensory-evoked potentials shown for sleeping and awake states [90]. (Bottom) Hypothesized sequence of events outlined by the authors [90] with the additionally-inserted BAC firing hypothesis (red) for the N1 component at 50 ms. On the right-hand side is indicated diagrammatically that slow-wave sleep inhibition (SWS) is expected to be generated in the sleep state. **(d)** Extracellular recordings from monkey primary visual cortex (V1) detecting an object (Figure) on a very similar background image (Ground). The monkey indicated whether it saw the figure (red) and these trials were compared to trials with no object (blue). The difference (gray) occurred after ~ 50 ms and was shown to be dependent on feedback connections to V1 [90]. Adapted, with permission, from [87] (a), [86] (b), [90] (c), and [93] (d).

neurons was unaltered [87]. More recently, using two-photon imaging, input to the tuft was demonstrated to be integral to the processing of sensory input from the whiskers in awake mice [86] (Figure 4b). Here, the position of the whisker was encoded in L5 pyramidal neurons by plateau potentials (Ca^{2+} spikes) in the tuft dendrites. The Ca^{2+} spikes were greatly increased for the preferred whisker position of the neuron. Input from motor cortex to L1 [88,89] was clearly crucial because blocking neuronal activity in the motor area abolished dendritic Ca^{2+} spikes. The authors suggested that dendritic Ca^{2+} spikes were activated via the BAC firing mechanism [86].

With hindsight, it is possible to speculate on whether evidence from conventional recording-studies might be consistent with the presence of dendritic electrogenesis. For instance, extracellular recordings from monkey somatosensory cortex have indicated a current sink in the upper layers of the cortex that is specific to the conscious perception of touch by the monkey [90] (Figure 4c). This sink is consistent with the presence of excitatory synaptic input to the distal dendrites of pyramidal neuron that would likely enhance dendritic electrogenesis. It is also possible that the extracellularly recorded signal itself would be influenced by dendritic spikes [91,92]. Importantly, the sink corresponded to a component of the sensory-evoked potential that was absent in anesthetized and sleeping monkeys (Figure 4c). At a minimum, these data showed that some activity in a primary sensory region correlates to a component of conscious experience but, in the absence of more precise data, it was not possible to know for sure how this relatively small change could account for such a profound shift in perception or whether it was indeed causally related. For the time being this remains speculative, but it is now possible to return to these experiments with modern methods and assess the current hypothesis.

Extracellular recordings have demonstrated that a similarly subtle change in activity in primary visual cortex also correlates to a decisive shift in visual perception in monkeys [93] (Figure 4d). Here the foreground object to which the monkey is trained to respond is only visible because of the context of the background image. Termed 'contextual modulation', the 'object' is made up of statistically identical components to the background and therefore requires feedback connections from higher cortical areas to be identified [24,94–96]. Contextual modulation (and feedback information) has consistently been shown to be a fundamental aspect of cognition [31,97,98]. Another example of such feedback connections is the influence of motion in cortical area V5 on the primary visual area (V1) [23,26,99]. All these examples demonstrate that feedback is able to influence activity in primary sensory regions and that such activity correlates to conscious perception in some mysterious way. Although this is entirely consistent with the hypothesis outlined here, it remains to be shown definitively.

A valid question that one may ask at this point is why the huge effects of dendritic electrogenesis seen *in vitro* and *in vivo* should lead to such subtle influences when using more conventional recordings? Such qualitatively decisive shifts in perception seem to demand a large change in the

firing activity of neurons. However, in the BAC firing scenario, only a small subset of neurons change their firing behavior significantly (i.e., the neurons receiving both feed-forward and feedback input simultaneously). The problem facing most conventional recording approaches is that by sampling the average activity of the region, the large changes occurring at particular neurons would be missed. Far from being a weak influence, therefore, the BAC firing hypothesis predicts that perception should correspond to an ensemble (or engram) of pyramidal neurons distributed throughout the cortex firing at extremely high rates, and perhaps also distinguished by their firing in bursts. By this mechanism, the cortex could thus entrain all the neurons that need to be bound together for a single percept via a positive feedback loop.

Concluding remarks

The BAC firing hypothesis presented here offers a cellular mechanism that addresses a number of questions about the cortex. It suggests that the pyramidal neuron cell type is an associative element which carries out the same essential task at all cortical stages: that of coupling feed-forward and feedback information at the cellular level. This mechanism succinctly explains the advantage of the cortical hierarchy with its structured terminations in different cortical layers, and also offers a plausible explanation for how cell assemblies across the different areas can be 'bound' instantaneously to represent features across many levels. The mechanism itself has been well-demonstrated in pyramidal neurons of rat primary sensory cortex, and the task remains of investigating this feature in other areas of the cortex and hippocampus (Box 2), as well as in other species.

Postulating a fundamental cellular mechanism for cortical associations leads to a broad range of specific predictions. First and foremost, the hypothesis predicts that large dendritic calcium transients should be correlated to behaviorally relevant cognitive performance such as feature binding [5,16] and conscious perception [30,45,100], and that both the behavior and dendritic calcium should be abolished by events leading to dendritic inhibition [13,23,101]. The first experiments from the apical dendrites of L5 pyramidal neurons in awake rats have so far observed such increases [86,87] (Figure 4c), and recent methodological advances (such as optogenetics) are emerging that promise to enable examination of this phenomenon in freely behaving animals [102,103]. The hypothesis also predicts that activation of specific populations of interneurons known to block dendritic activity, such as Martinotti neurons [78,81,104] and L1 neurogliaform cells [72,82], should be powerful regulators of cognitive functions. As a corollary, it follows that disinhibitory mechanisms [105] are necessary to enable the BAC firing mechanism.

The long-lasting suppression of BAC firing by dendritic GABA_B-receptor activation also raises a few possibilities that are testable. The suppression of dendritic calcium channels has a disproportionately potent effect on spiking output from the neuron [77]. Under particular conditions, more than half the total spikes generated could be attributed to dendritic mechanisms that are shut down by the

Box 2. Does the hippocampus rely on a cellular mechanism for association?

Although the hippocampus is still not completely understood, it is clear that it is necessary for memory consolidation, a task that presumably entails the association of various experiences such that one thought leads to another. The structure of the hippocampus with its trisynaptic pathway and cortical re-entry also lends itself to be described as an associative device. The hippocampus and related structures, even more so than the neocortex, are heavily dominated by pyramidal neurons that form the principal excitatory neurons. Information is passed in a loop in which the axon fiber tracts follow a strict separation in terms of where they synapse on the dendritic

trees of the following pyramidal neurons (Figure 1a). The dendrites of CA1 pyramidal neurons have been shown to have a similar complement of dendritic channels [62,110] that lead to calcium spikes and bursts of action potentials [111,112]. These cells exhibit associative behavior [113,114] via dendritic plateau potentials, with simultaneous stimulation of the proximal and distal dendritic synapsing axons [stratum radiatum (SR) and stratum lacunosum moleculare (SLM)] (Figure 1b). Long-term potentiation of distal synaptic inputs is also dependent on dendritic spikes in the tuft region [115].

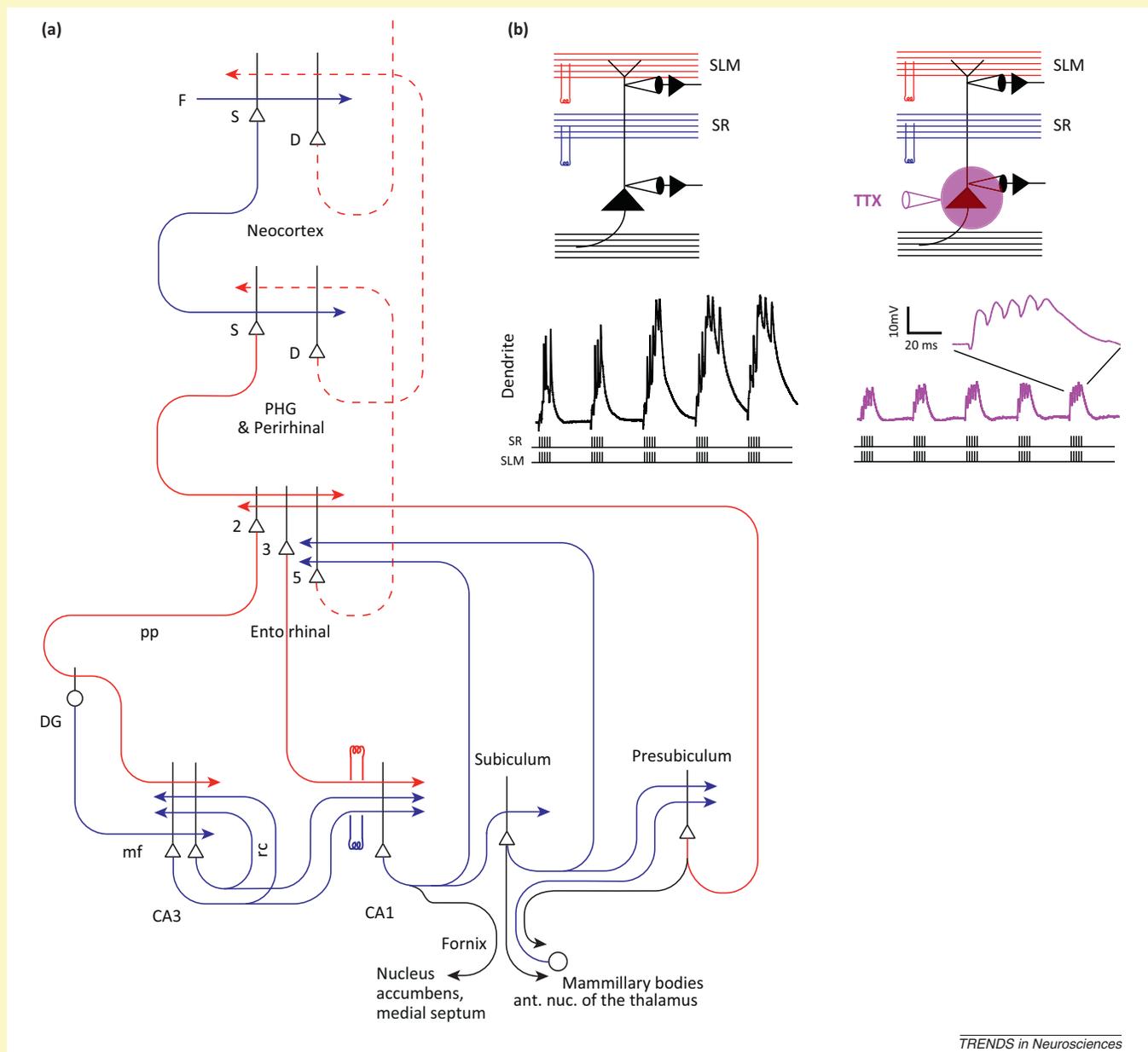


Figure 1. Evidence for a cellular associative mechanism in the hippocampus. **(a)** Schematic diagram of the interconnectivity of the neocortex with the hippocampus showing the conservation of feed-forward/feedback loops involving pyramidal cell dendrites. Feed-forward pathways are labeled in blue, feedback in red [116]. **(b)** (Left) Recordings from CA1 neurons showing coincident proximal and distal input leading to dendritic plateau potentials. (Right) Preventing back-propagating action potentials with local tetrodotoxin (TTX) application at the soma prevented dendritic plateau potentials [114]. Abbreviations: ant. nuc., anterior nucleus; D, deep pyramidal cells; DG, dentate gyrus; F, forward inputs to areas of the association cortex from preceding cortical areas in the hierarchy; mf, mossy fibers; PHG, parahippocampal gyrus and perirhinal cortex; pp, perforant path; rc, recurrent collateral of CA3 pyramidal cells; S, superficial pyramidal cells. Adapted, with permission, from [116] (a) and [114] (b).

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activation of GABA_B receptors [72], demonstrating unequivocally the large role of dendritic conductances in determining output firing. The approximately half-second suppression of dendritic calcium spikes seems disproportionate to the normal timescale of synaptic integration; however, it closely corresponds to the timescale for the build-up of conscious perception – sometimes called the ‘readiness’ or ‘Bereitschafts’ potential [106] and the typical Gestalt-switch timing [107]. Because background inhibition is normally present, according to the BAC firing hypothesis, conscious perception should require the release from dendritic inhibition (via as yet unknown disinhibitory mechanisms) that would take on the order of hundreds of ms. The hypothesis also predicts that overactivation of dendritic activity (i.e., via upregulation of dendritic channels via neuromodulation, channelopathies, downregulation of dendritic inhibition, or overstimulation of feedback) should lead to faulty perception (e.g., hallucinations, dreams) and that underactivation of dendritic activity should inhibit contextualization of perception.

These predictions flow directly from the hypothesis that dendrite Ca²⁺ activity in pyramidal neurons is central to the operation of the neocortex. The techniques and methodology for investigating dendritic activity in conscious, behaving animals is only now emerging and promises to be decisive in evaluating and refining the hypothesis over the next few years.

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