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# The single dendritic branch as a fundamental functional unit in the nervous system

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The conventional view of dendritic function is that dendrites collect synaptic input and deliver it to the soma. This view has been challenged in recent years by new results demonstrating that dendrites can act as independent processing and signalling units, performing local computations that are then broadcast to the rest of the neuron, or to other neurons via dendritic transmitter and neuromodulator release. Here we describe these findings and discuss the notion that the single dendritic branch may represent a fundamental unit of signalling in the mammalian nervous system. This view proposes that the dendritic branch is a basic organizational unit for integrating synaptic input, implementing synaptic and homeostatic plasticity, and controlling local cellular processes such as protein translation.

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## Introduction

In his classic *Histology of the Nervous System*, Ramon y Cajal asked “Why do dendritic trees even exist?” and concluded that “Dendrites exist solely to allow the cell to receive, and then transmit to the axon, the greatest variety of information from the most diverse sources.” [1]. This pioneering notion of dendrites as receivers of synaptic information was formalized as Cajal’s ‘law of dynamic polarization’, postulating a unidirectional flow of information within the neuron. This view has been extensively characterized and has become widely established over the years. Experimental and modeling work in a variety of systems has provided strong evidence supporting the view that a major function of dendrites is to collect information from all connected input cells and transmit it to the site of action potential generation. However, it is now becoming

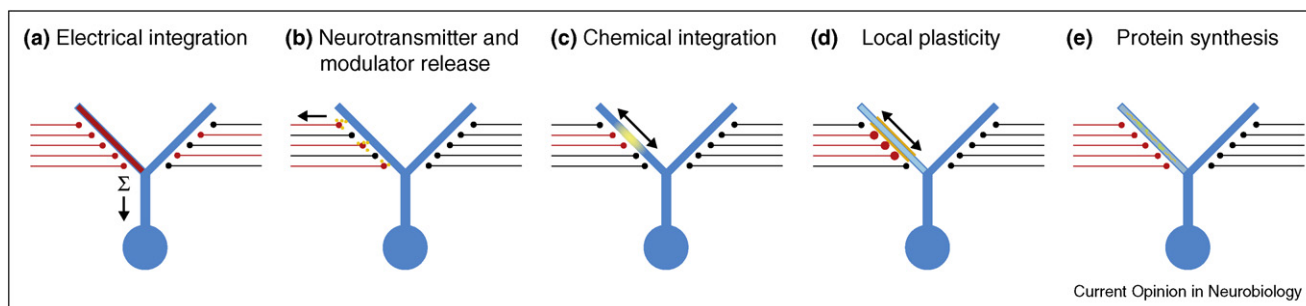
increasingly clear that on top of their role as input receivers, dendrites orchestrate a variety of other processes – electrical, biochemical and cellular – that are fundamental to neuron physiology and circuit function. Furthermore, many of these processes seem to be highly compartmentalized at the level of individual dendritic branches, and the ‘variety of information’ alluded to by Cajal can already be locally processed within a single dendrite. Here we review recent work that supports the emerging notion that the single dendritic branch represents a major signalling unit—one that integrates electrical and chemical inputs, and can send independent output signals to a variety of targets.

## Local electrical integration: signalling to the soma the result of a computation

Dendrites deliver electrical signals to the soma, but they are not just simple conductors of information. The passive and active properties of the dendritic tree are crucial for determining how electrical signals propagate, and define their compartmentalization and their interaction across different dendritic regions. Passive properties alone can act as a compartmentalizing force that acts in concert with the morphology to create electrical compartments on the level of dendritic branches, thanks to the strong attenuation of voltage across dendritic branchpoints. On top of this, the active properties of the dendrite can tune local signals within a branch, either to amplify them or to dampen them, with such non-linear processing again being kept local by the unfavourable impedance matches at branchpoints. Emblematic of this active local processing are dendritic spikes—regenerative potentials initiated locally in dendritic branches when input is sufficiently clustered in space and time (see [2] for review). Such spikes, which appear to be relatively ubiquitous across different cell types [2,3], effectively compute a threshold for the local spatiotemporal distribution of synaptic input. Dendritic spikes can then either be kept within the branch, by failure of active propagation at the branchpoint, or they can spread regeneratively to the soma to influence axonal output (Figure 1a). Thus, there exist both passive and active mechanisms for branch-specific integration of synaptic input. What remains unclear is what exactly is being computed with such mechanisms under physiological patterns of input, and what is the functional role of such computations within specific neuronal circuits. There has been substantial recent progress in exploring these issues both *in vitro* and *in vivo*.

First, the involvement of dendritic mechanisms in elementary computations is supported by modeling studies that propose a role for dendritic computation in

Figure 1



Different forms of functional compartmentalization in single dendritic branches.

Schematic representation of a simplified dendritic tree showing how single dendrites exhibit local integration and transmission of information on different levels. **(a)** Electrical integration of synaptic inputs to a single branch is then passed on to the rest of the neuron. **(b)** Feedback signalling restricted to a small cluster of spines. **(c)** Chemical signalling restricted to the neighbourhood of activated inputs along the branch. **(d)** Plasticity signalling extending across the whole branch. **(e)** Signalling local protein synthesis in response to branch activation.

complex operations, such as feature detection in the hippocampus [4] or detecting the order of input arrival [5]. Recent experimental *in vitro* work has demonstrated directly that single dendrites can carry out simple computations, showing that the combination of local impedance gradients and NMDA receptors allows dendrites to discriminate multiple temporal input sequences [81<sup>••</sup>]. Experiments in hippocampal neurons have also revealed that single dendrites can directly process the spatiotemporal relationship of excitation and inhibition [6]. That computations may be implemented on the level of single branches is further supported by the elegant work of Katz *et al.* [7], who showed that in apical oblique dendrites of CA1 pyramidal cells, excitatory synaptic strength decreases towards the tip of the branch, which is consistent with an optimization for local electrical integration within dendritic branches.

Second, dendritic spikes have been suggested to be a hallmark of local computations in dendrites [74,82]. Determining the conditions for their generation may therefore tell us something about their functional role in different circuits. A beautiful example illustrating the importance of dendritic spikes in a neural circuit is provided by the retina, where in directionally selective retinal ganglion cells somatic spikes are primarily triggered by locally generated dendritic sodium spikes, which amplify the direction selectivity of the input [8]. Such a direct link between a behaviourally relevant computation and local dendritic electrogenesis has been more difficult to find elsewhere in the brain. Recently, in CA1 pyramidal neurons, Takahashi and Magee [9] showed that simultaneous burst stimulation of perforant path and Schaffer collateral inputs generates large NMDA-gated and voltage-gated  $\text{Ca}^{2+}$  channel-dependent plateau potentials that are converted into action potential bursts at the soma, suggesting that dendritic spikes might be used to compare information carried by

these two different inputs. A similar scenario was described in basal dendrites of layer 5 pyramidal neurons, where high frequency input delivered to a single branch generates large NMDA spikes that lead to somatic burst firing [10], the size of the NMDA spike decreasing with distance from the soma due to dendritic filtering [11]. In these neurons, NMDA-dependent regenerative potentials have also been recently described in distal tuft dendrites, where dual dendritic recordings have shown that such events can be used to signal to the soma the localized activation of feedback inputs from the thalamus and other cortical regions [12], placing local dendritic mechanisms in a network context.

Part of the problem in assigning a functional role to dendritic spikes is that in order for them to be exploited by neural circuits, the subcellular input distribution over the dendritic tree and the relative timing of their activation during a behavioural task needs to meet the conditions for dendritic spike generation. This can only be studied in the intact brain, and new approaches for measuring dendritic calcium signals *in vivo* are providing information not only about the spatial localization of synaptic input, but also about the engagement of dendritic mechanisms during sensory processing. Using a microendoscope to image bulk dendritic activity in awake and anesthetized rats, Murayama *et al.* [13,14<sup>•</sup>] provided evidence consistent with the idea that sensory stimulation of the hindlimb is represented by dendritic calcium spikes in layer 5 pyramidal cells. However, to precisely localize sensory-driven synaptic input it is necessary to image individual dendritic branches *in vivo*, and several groups have recently taken up this challenge. In the cricket cercal system, Ogawa *et al.* [15] performed simultaneous presynaptic and postsynaptic calcium imaging to reveal that interneuron dendrites can directly extract the direction of air currents. Two recent studies in the visual systems of *Xenopus* tadpoles [16<sup>••</sup>] and locust [17]

indicate that in these circuits the subcellular topographical organization of sensory inputs favours dendritic computations. Finally, in the mouse visual cortex Jia *et al.* [18\*\*] found dendritic NMDA-dependent calcium hotspots driven by visual stimulation, showing that local dendritic non-linearities are engaged *in vivo*. While they did not find a direct relationship between orientation selectivity and the distribution of the dendritic calcium transients, these signals were measured while hyperpolarizing the soma, which decreases the probability of triggering dendritic spikes, and only a subset of all branches could be imaged. Nevertheless, such experiments represent a breakthrough in that they demonstrate that it is possible to map sensory input on the dendritic tree of a mammalian neuron, a prerequisite for understanding how single dendrites compute information.

### Local dendritic release of neurotransmitters and neuromodulators—retrograde signalling of postsynaptic activity

The results of dendritic computations can be passed on to the soma, where they are integrated to produce a pattern of action potential firing and neurotransmitter release by the axon, thus transmitting the local computations to other partners in the network. However, even this output step can be performed by dendritic branches alone, bypassing the soma and axon. Dendrites can release either classical neurotransmitters such as glutamate and GABA [19,20], as well as neuromodulators like endocannabinoids and BDNF [21] that can act in a retrograde manner and in some cases activate autocrine receptors (Figure 1b). How does dendritic release work, how local can it be and what is it signalling to the presynaptic neuron?

Dendritic release of neurotransmitters is now well-established and appears to be a primarily calcium-dependent process that relies on vesicle exocytosis machinery. Recent work supports this view, with postsynaptic depolarization of Purkinje cells triggering SNARE-dependent dendritic release of glutamate [22] that can retrogradely activate presynaptic NMDARs in interneurons to increase GABA release, as well as calcium-dependent dopamine release that leads to autocrine activation of mGluRs [23]. In substantia nigra dopamine neurons, calcium release from intracellular stores facilitates dendritic dopamine release [24], a process that can be regulated by stress hormones [25], and in the thalamus, interneurons in the lateral geniculate nucleus can provide feedforward inhibition to thalamo-cortical neurons via dendritic GABA release that follows activation of dendritic L-type calcium channels and calcium spikes [26].

While most of the studies on dendritic release of neurotransmitter have characterized release following global and widespread activation of the dendritic tree, the dependence on voltage-gated calcium channels and calcium entry suggests that neurotransmitter release

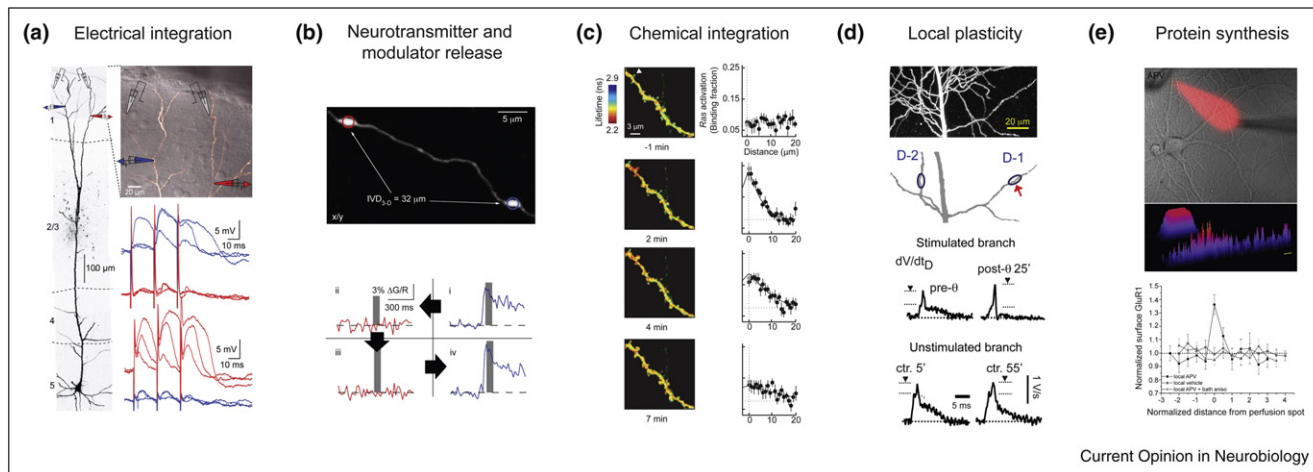
can in some cases be highly compartmentalized. Dendritic spikes can be restricted to single branches [2], and calcium diffusion can be even more limited [27], raising the possibility that local dendritic integration might be directly converted into a spatially confined output signal. Interestingly, in the mammalian olfactory bulb, Castro and Urban [28] have shown that subthreshold depolarizations delivered to the soma of mitral/tufted cells are capable of eliciting calcium transients and subsequent dendritic glutamate release in the apical dendrite, implying that similar depolarization levels restricted to a subset of the dendritic tree might achieve localized neurotransmitter release. More recently, an elegant study by Grimes *et al.* [29\*\*] has provided evidence for subcompartmentalization of transmitter release in dendrites of A17 amacrine cells in the retina (Figure 2b). These dendrites provide direct feedback inhibition to rod bipolar cells, and within a single branch, activation of L-type calcium channels that supports GABA release is restricted to  $\sim 10 \mu\text{m}$ , allowing fast synapse-specific and independent feedback, a process partially regulated by BK potassium channels [30].

Apart from neurotransmitters, dendrites are also capable of releasing a variety of neuromodulating substances. This has been described in response to different types of stimuli in almost every neuron type studied (see [21] for review), and the list continues to grow. For example, Best and Regehr have recently shown that dendrites of neurons in the inferior olive have 5-HT receptors that respond to endogenous serotonin by releasing endocannabinoids, which in turn act retrogradely on presynaptic CB1 receptors to decrease glutamate release probability [31]. Also, in cultured hippocampal neurons, Matsuda *et al.* [32] used a GFP-pHluorin fused with BDNF to directly visualize full collapse of BDNF-containing dendritic vesicles in response to action potential backpropagation, a phenomenon that appears to be calcium-dependent and able to trigger phosphorylation of nCREB in nearby neurons [33]. Similarly to dendritic neurotransmitter release, most studies have not directly addressed the spatial regulation of neuromodulator secretion. However, Branco *et al.* [34\*] showed that dendritic depolarization negatively regulates presynaptic release probability, possibly via release of an (unknown) retrograde neuromodulator, and that this regulation is implemented at the level of single dendritic branches, as evidenced by the resulting spatial distribution of release probabilities over a dendritic tree. Thus, the current data seem to suggest that dendritic release can follow local integration and be spatially restricted, and that in most cases it provides a form of local and input-specific negative feedback regulation (see [35] for discussion).

### Local chemical integration: biochemical signalling within the branch

Synaptic input can initiate complex cellular events and be effectively converted into and integrated as a biochemical

Figure 2



Examples of local functional compartments in single dendrites.

Experimental data illustrating the different forms of functional compartmentalization in dendrites. **(a)** Double dendritic recording in apical dendritic branches of layer 5 pyramidal cells showing that NMDA spikes are restricted to the stimulated branch (from Ref. [12]). **(b)** Local synaptic stimulation elicits a calcium transient in only the stimulated varicosity of an A17 amacrine cell dendrite, which leads to localized dendritic release of GABA (from Ref. [29<sup>••</sup>]). **(c)** Fluorescence lifetime imaging of a *Ras* activity reporter reveals that potentiation of a single spine produces spread of *Ras* activation along the dendritic branch (from Ref. [45<sup>•</sup>]). **(d)** Delivering a theta-burst protocol to individual branches of CA1 pyramidal neurons results in potentiation of the coupling between the branch and the soma only in the stimulated branch (from Ref. [39<sup>••</sup>]). **(e)** In cultured hippocampal neurons, local protein synthesis at the dendrite maintains and regulates the homeostatic scaling of surface GluR1 receptors (from Ref. [67]).

signal (Figure 1c). A classic hallmark of this process is elevation of the local calcium concentration in the dendrite, with calcium either entering directly via the stimulated synapses or following activation of voltage-gated calcium channels, or a number of other possible second messenger pathways (see [27] for review). Calcium triggers a wide range of biochemical cascades, and the extent of its spatial spread depends on its source, the chemical pathways activated, as well as local geometry and calcium buffering [27]. Recent work has taken advantage of techniques that permit high spatial resolution imaging and synaptic activation, such as simultaneous 2-photon calcium imaging and glutamate uncaging. While activation of single synapses in hippocampal pyramidal cells has been shown to give rise to calcium signals via NMDARs and VGCCs that can be restricted to the spine head [36–38], it is also clear that spine calcium signals can invade the dendritic shaft. One major source of calcium entry and spread into dendrites is via VGCCs and NMDARs following dendritic spikes [9,11,39<sup>••</sup>], which due to the strong voltage attenuation at branchpoints favours individual dendritic branches as a functional unit for calcium signalling. This link between local dendritic voltage and calcium elevation has been nicely demonstrated in Purkinje cells using simultaneous calcium and voltage-sensitive dye imaging [40]. Other sources of calcium can give rise to signals that do not spread throughout the entire dendritic branch, either because they represent diffusion from a small source, or their spread is actively restricted. In the hippocampus, spontaneous release from internal calcium stores in pyramidal

cells diffuses up to 10  $\mu\text{m}$  [41] and calcium entry following mGluR5 activation in interneurons is limited to  $\sim 15 \mu\text{m}$  [42]. In A17 amacrine cells, synaptic stimulation results in calcium transients that do not spread beyond  $\sim 10 \mu\text{m}$  due to the interaction between electrical propagation in these dendrites and the threshold for VGCC activation [29<sup>••</sup>]. Compartmentalized sensory-evoked dendritic calcium signals have also been reported in response to visual stimulation *in vivo*, in the *Xenopus* tadpole [16<sup>••</sup>] and in the mouse visual cortex [18<sup>••</sup>]. NMDARs are involved in both cases, and while in the former study this seems to result from activation of several clustered synaptic inputs, in the latter the authors suggest that this follows activation of single synapses (though no direct evidence was provided to support this claim).

Other studies have analysed the compartmentalization of biochemical signals other than calcium. Rose *et al.* [43] used GFP-tagged CaMKII in cultured hippocampal neurons to show that localized glutamate puffing induces CaMKII translocation into dendritic spines, a process that was often seen to spread over the whole dendritic tree. Interestingly, CaMKII translocation requires NMDAR and VGCCs activation, and in their conditions calcium transients invaded all dendrites upon stimulation, suggesting that if the calcium signal is more localized as seen in other preparations, so will be CaMKII entry in spines. Such highly local biochemical compartmentalization has indeed been nicely demonstrated after LTP induction at single spines, where CaMKII activation was restricted to the stimulated sites [44]. Another

beautiful example of compartmentalized chemical signalling in dendritic branches comes from the work of Harvey *et al.* [45<sup>\*</sup>], who engineered a genetically encoded FRET reporter of *Ras* GTPase activation, and used 2-photon lifetime fluorescence imaging and glutamate uncaging to reveal that calcium-dependent *Ras* activity diffuses locally along the branch up to 10  $\mu\text{m}$  (Figure 2c). Biochemical signals can therefore spread from their site of origin to influence the immediate neighbourhood, which is typically limited to the activated branch. As it has been suggested for LTP, for example [46], this is likely to result in small segments of the dendritic tree having similar properties, suggesting that they act as a basic functional unit.

### Local plasticity—storage of local computations

Given the compartmentalization of biochemical signals within dendritic branches and their relationship with synaptic plasticity (especially for calcium), it is expected that single branches might also function as plasticity units (Figure 1d). This would imply that dendrites could be capable not only of performing individual computations, but also of locally storing them. One form of plasticity that was initially suggested to fulfil this prediction is plasticity of dendritic excitability, a phenomenon first demonstrated directly by Frick *et al.* [47] in CA1 pyramidal neurons. In this study, changes were restricted to the stimulated region, suggesting a local loop between excitability and plasticity implementation [2]. The actual restriction to single dendritic branches has now been convincingly demonstrated by recent work from the Magee lab. First, Losonczy *et al.* [39<sup>\*\*</sup>] found that in hippocampal pyramidal neurons, the coupling between local dendritic sodium spikes and the soma is plastic, and that this coupling can be changed in a branch-specific manner by NMDA-dependent potassium channel regulation (Figure 2d). A follow-up study by Makara *et al.* [48] went a step further, and showed that this compartmentalized potentiation of branch excitability is linked to enriched environments, suggesting that it might play a role in learning and memory. Albeit on a much shorter time scale, Remy *et al.* [49] have also shown that the refractoriness of local dendritic sodium spikes can influence dendritic excitability of individual branches, providing them with a history-dependence of activity. More traditional forms of long-term plasticity in hippocampus have also been suggested to benefit from local compartmentalized interactions in dendritic branches. While LTP is usually considered to require backpropagation of action potentials, Hardie and Spruston [50] have shown that local synaptic depolarization as well as local dendritic spikes is more effective in eliciting LTP of inputs that are spatially close (see [51] for discussion). A similar scenario was suggested by Branco *et al.* [34<sup>\*</sup>] for homeostatic plasticity, where release probability appears to be retrogradely controlled by local dendritic depolarization with single branch specificity. The simultaneous operation of

Hebbian plasticity and homeostatic changes at the branch level suggests that a single branch can exhibit the whole repertoire of operations required to act as an independent and stable plasticity unit (see [52] for discussion). More evidence for branch regulation of synaptic strength comes from elegant work in hippocampal neurons showing that Homer-1a, a protein involved in late-phase plasticity, enters spines only in dendritic branches that have been activated [53]. Furthermore, the local balance between inhibitory and excitatory inputs that has previously been described [54] is maintained after LTP induction [55], and dendrites that have been separated from the cell body can still develop L-LTP [56]. As for calcium signalling, plasticity induction can also have a more restricted spread along dendritic branches, either directly linked to calcium diffusion itself [40,42,46,57], or to secretion of regulating factors [45,58].

### Local translation in dendrites—changing local dendritic structure and function

In the classical perspective, translation from mRNA to proteins happens at the soma, and freshly synthesized proteins are then shipped out to the appropriate locations in the dendrites. However, over the past two decades it has been shown that the entire translational machinery—polyribosomes, enzymes and associated membranous cisterns—is also present in dendrites, and that mRNA can be trafficked to dendrites. There is now very compelling evidence that these dendritic mRNAs can be used for local synthesis of the encoded proteins [59,60]. Such local protein synthesis has been shown to be engaged by synaptic stimuli, playing a key role in the durable synaptic changes found during both long-term potentiation and depression [61,62]. While one important consequence of local translation is increased speed of protein delivery to targets, another is the potential for conferring a high degree of compartmentalization to protein production and delivery. One means to achieve this would be via targeted delivery of mRNAs, such that different dendritic branches would have different mRNA populations. This possibility is supported by the observation of differential spatial distribution patterns for different mRNAs in Purkinje cell dendrites [63], as well as by the fact that *Arc* mRNA accumulation in dentate gyrus granule cells after perforant path stimulation is restricted to the dendritic region to which these inputs project [64–66]. Another possibility is that the triggers of mRNA translation activation can be locally restricted. Given that changes in synaptic strength and dendritic excitability can be branch-specific and potentially depend on production of new proteins, it is conceivable that the same proteins are produced on-demand, at different rates in different branches. In fact, given the apparent synapse-specificity of some plasticity processes and the preferential localization of ribosomes at the base of dendritic spines, a popular hypothesis holds that this arrangement allows for synapse-specific delivery of synaptic proteins [61],

though this will depend on how translation activators and final products spread along the branch. Probably the most compelling evidence to support region-specific translation in dendrites comes from the work of Sutton *et al.* [67]. This study elegantly showed that the homeostatic increase in GluR2-lacking AMPARs that occurs in response to synaptic activity block is implemented via increased protein synthesis, which is only evident in areas of the dendrite exposed to NMDAR blockers (Figure 2c).

In addition, local translation in dendrites has been implicated in the regulation of dendritic morphology, both during development and during experience-dependent changes [61]. In developing neurons of the optic tectum in *Xenopus tadpoles*, Bestman and Cline [68] used 2-photon *in vivo* imaging to show that mRNA granules distributed throughout the developing dendritic tree locally regulate branch dynamics, suggesting a model where mRNA is released from the granules and changes local levels of proteins involved in dendritic growth. Similarly, in the *Drosophila* peripheral nervous system, the presence of a transcription repressor in developing processes is essential to the regulation of dendritic branching [69], and in hippocampal neurons, proteins present in mRNA granules control dendritic outgrowth during development as well as spine number in mature neurons [70,71]. One interesting aspect of such local control of dendritic growth is that a highly compartmentalized neuron will tend to grow in an even more compartmentalized way given that growth signals will automatically be kept local [72]. While global coordination of dendrite growth might be necessary, the potential for a positive feedback mechanism that locally directs

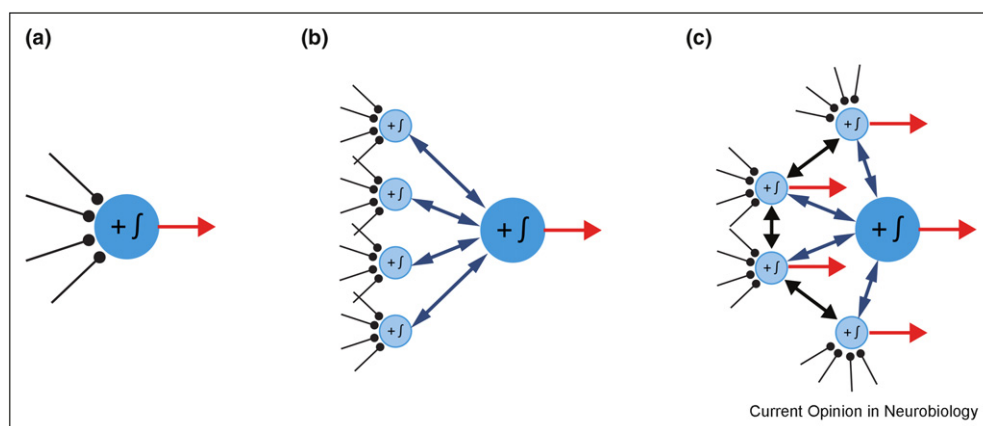
growth supports the view of dendritic branches as basic subcellular units that can act independently of each other.

## Conclusion

There is ample and growing evidence that dendritic branches can act as fundamental units of neuronal signalling. We have described how this argument is supported by the compartmentalization of various forms of signalling in dendrites – electrical, chemical, translational – on the scale of single branches. Such compartmentalization can arise simply by focal clustering of active synaptic input to the dendritic tree—which is easily achievable experimentally, but which has not yet been convincingly demonstrated with physiological patterns of synaptic input *in vivo*. Nevertheless, the physical structure of the dendritic tree itself can help ensure this compartmentalization: since electrical signals are attenuated at dendritic branchpoints, this helps keep them local; and all other types of signalling that flow from the original electrical signal will therefore also be compartmentalized. It will now be crucial to examine how these different levels and types of compartmentalization are engaged in the intact animal during behaviour. Addressing this will require imaging methods capable of resolving electrical, chemical and even translational events on the spatial scale of microns, in the awake animal. Preliminary results have shown that dendrites can be imaged in awake animals [73], suggesting that the necessary technical obstacles will soon be surmounted.

What are the functional implications of the view that the single dendritic branch is a fundamental unit of processing? First, it provides a massive increase in the computational power of the single neuron, which should

Figure 3



A new model of hierarchical parallel processing in dendritic trees.

(a) In the ‘point neuron’ representation, all inputs are integrated at the soma, with an output (red arrow) generated when somatic voltage crosses threshold. (b) In the two-layer network representation [74], synaptic inputs are integrated locally in dendritic subunits, each of which computes the sum of its local inputs and applies a local thresholding nonlinearity (e.g. a dendritic spike). The results of multiple dendritic subunits are then summed at the soma, where the final decision to generate output is taken (red arrow, right). (c) Dendritic release of neurotransmitters and neuromodulators allows local integration in dendritic subunits to also be expressed as local output. Furthermore, there is bidirectional communication between individual subunits and between subunits and the soma. Figure modified from Ref. [76].

be proportional to the number of independent processing compartments it contains [74,75]. It is important to note however, that while this can provide advantages for many computational tasks, some computations demand low levels of voltage compartmentalization in the dendritic tree, as recently demonstrated for computations relying on interactions between oscillations in different dendrites of the same neuron [78,79]. These tend to phase-lock after a period of time that depends on the electrotonic structure of the dendrites, suggesting that a single neuron might alternate between local and global processing depending on the integration timescale, and that different neurons might be tuned to different spatial computation scales [80]. A second implication of the view of single branches as individual processing units is that it provides another challenge to Cajal's law of dynamic polarization: since dendrites can act as output structures, and can themselves influence signalling and computations in neighbouring dendrites (both further upstream from the soma as well as downstream towards the soma), this provides further evidence that flow of information can be bidirectional within the single neuron. Third, the ability of single branches to provide output signals via neurotransmitter/modulator release means that a single neuron can acquire the function of an entire network of simple units, providing multiple parallel input–output compartments rather than all computations only being expressed via a single axonal output (see Figure 3; [76,77]). Fourth, these results blur the classical distinction between dendrites and axons as receiving and transmitting elements (which is well-known to be ambiguous in insect neurons), underlining the importance of identifying the distinct molecular identities and determinants of these structures [20]. Finally, given that it is synaptic input that both drives and harnesses the functional specializations provided by each dendritic branch, this highlights the need to understand how the spatial organization of synaptic input to individual dendritic branches is managed, and how local homeostasis between excitatory and inhibitory synaptic inputs is achieved. The prospect that each dendritic branch may have its own unique 'personality', driven by and reflecting the special functional properties of its particular collection of synaptic inputs, should inspire anatomical and physiological work on targeting of circuits to dendrites over the next decade.

## Acknowledgements

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