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REVIEW

Dendritic integration: 60 years of progress

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Understanding how individual neurons integrate the thousands of synaptic inputs they receive is critical to understanding how the brain works. Modeling studies *in silico* and experimental work *in vitro*, dating back more than half a century, have revealed that neurons can perform a variety of different passive and active forms of synaptic integration on their inputs. But how are synaptic inputs integrated in the intact brain? With the development of new techniques, this question has recently received substantial attention, with new findings suggesting that many of the forms of synaptic integration observed *in vitro* also occur *in vivo*, including in awake animals. Here we review six decades of progress, which collectively highlights the complex ways that single neurons integrate their inputs, emphasizing the critical role of dendrites in information processing in the brain.

Dendrites are the main receiving elements of neurons. They act like antennas picking up information from thousands of presynaptic inputs (sometimes tens or even hundreds of thousands), which are often made onto small dendritic processes called dendritic spines. The complex geometry of the dendritic tree, combined with its active and passive properties, enables neurons to perform a wide range of computations on their inputs. Although discovered over a century ago by Santiago Ramón y Cajal, the role of dendrites in neuronal processing was largely unexplored until the 1950s. Around this time, neurophysiologists began to interpret their findings in the context of dendritic properties, initially driven by theoretical considerations on how dendrites influence experimental observations.

A number of important concepts emerged. First, evidence accumulated that action potentials (APs) are initiated near the soma of neurons in the axon initial segment[1,2], which was later confirmed by direct axonal recordings[3–9]. This observation indicates that the capacity of synaptic input to influence AP output depends on how effectively it modulates the membrane potential at this location (**Fig. 1a**). Second, mathematical modeling, pioneered by Wilfrid Rall, quantitatively explored the effect of dendrites on synaptic input, showing that dendrites attenuate and filter synaptic potentials as they propagate to the soma[10], influencing their effect on AP output via the axon. In addition, Rall and others found that the passive membrane properties of dendrites, that is, their resistance and capacitance as well as their geometry, influence the way neurons integrate synaptic inputs in complex ways, enabling a wide range of nonlinear operations[10,11]. Third, a variety of experimental studies using a range of techniques suggested that dendrites contain voltage-dependent channels and therefore have active electrical properties that are similar to axons. These active dendritic properties can boost the effectiveness of distal synaptic inputs through the generation of 'dendritic spikes' (**Fig. 1b**) and support active 'backpropagation' of action potentials into the dendritic tree (**Fig. 1c**). These concepts are at the forefront of research into the integrative properties of neurons. Here we review the progress that has been made over the last 60 years using a variety of techniques and preparations, with a focus on recent insights obtained by studying dendritic integration in the intact brain.

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Early recordings from dendrites

Early extracellular recordings from spinal motoneurons suggested that APs propagate into the dendritic tree as a result of passive spread from the axon initial segment[12]. Extracellular recordings from mitral cells in the olfactory blub supported this idea, but it was suggested this may be an active process in these neurons[13]. Other early work focused on the hippocampus. Because of the laminar organization of this structure, extracellular field potentials could be recorded from locations corresponding to different positions along the dendrites of pyramidal neurons. Using this approach, a number of studies suggested that APs could be generated and/or propagated along the apical dendrites of these neurons. The idea that dendrites can generate active responses was fueled by intracellular recordings from hippocampal pyramidal neurons, where small, spike-like events known as fast pre-potentials were interpreted as being generated in the dendritic tree[14]. The notion that dendrites can generate local voltage-dependent changes in membrane potential was also supported by extracellular recordings in the cerebellum[15].

With the development of acute brain slice preparations[16], progress on understanding the properties of dendrites was substantially advanced. The principal advantage of this approach is that intracellular recordings can be obtained reliably at defined dendritic locations and drugs can be applied rapidly and reversibly. In the cerebellum, this approach provided direct evidence that the dendrites of cerebellar Purkinje neurons can generate active events[17]. Similarly, experiments in the hippocampus using intracellular recording from the dendrites of pyramidal neurons, sometimes under conditions in which dendrites were physically separated from the soma, also supported the notion that active events can be generated in dendrites[18,19] (that is, they don't just propagate there from the axon and soma). However, determining the normal sequence of events was difficult. For example, although a dendrite separated from the soma may generate a spike-like response, AP initiation in the axon initial segment may predominate when dendrites are connected to the soma. Subsequent

work using field potential recordings in the hippocampus found that, at low stimulus intensities, AP initiation occurred in the axon initial segment followed by propagation back into the dendrites, whereas at higher stimulus intensities localized dendritic spikes could precede AP initiation in the axon[20,21].

Imaging approaches to studying dendritic integration

The development of calcium-sensitive dyes in the 1980s presented the possibility of monitoring dendritic calcium at high spatial resolution and at multiple locations simultaneously. The method was first applied *in vitro*, using intracellular recordings from neurons in brain slices from the hippocampus and cerebellum. By loading individual cells with dye-containing microelectrodes, early studies in cerebellar Purkinje neurons demonstrated that spontaneous oscillations in electrical activity results in dendritic calcium influx via voltage-gated calcium (Ca_v) channels[22]. Other work in hippocampal pyramidal neurons found that dendritic calcium responses during APs were spatially non-uniform, exhibiting components dependent on both voltage-gated sodium (Na_v) and Ca_v channels[23]. This early work provided direct evidence for the presence of voltage-gated channels in dendrites.

Although these studies were performed using CCD cameras[24], subsequent studies using two-photon microscopy provided improved spatial resolution, making it possible to image individual dendritic spines[25]. These studies led to the conclusion that synaptic activation generates calcium influx that is largely isolated to dendritic spines[25], providing experimental evidence for the idea that dendritic spines can function as isolated chemical compartments[26]. More recent data suggest that dendritic spines also compartmentalize electrical signals during synaptic input[27–29]. In addition to the increased spatial resolution offered by two-photon microscopy, this method allowed changes in dendritic calcium to be imaged *in vivo*[30,31], opening the door to the study of dendritic integration in the intact brain.

Dendritic patch-clamp recording

Another method that has been central to the study of dendritic integration is patch-clamp recording. In the early 1990s, methods were developed to image dendrites in live, unstained brain slices[32], allowing visually guided patch-clamp recording from dendrites[33]. This method, which can be used in combination with two-photon microscopy[34,35], has led to a wealth of information on dendrites, from which several important concepts have emerged. This work, which has been described in detail in previous reviews[36–38], is summarized below.

First, dual somatic and dendritic recordings have revealed that voltage attenuation along dendrites is considerable[34,35,39–44]. These experimental results confirmed predictions based on earlier mathematical modeling that distal synaptic events undergo substantial attenuation as they propagate to the soma and axon initial segment. Dual somatic and dendritic recordings also provided quantitative data on dendritic properties that allowed the development of more accurate, morphologically realistic models of different neuronal cell types.

Second, dendritic patch-clamp recordings allowed the properties and density of voltage-activated channels at different locations to be systematically mapped[45]. A variety of voltage-gated channels, including Na_v, Ca_v, voltage-gated potassium (K_v) and hyperpolarization-activated cation (HCN) channels have been found in dendrites, with differences in channel types, properties and distribution depending on both cell type and dendritic location. For example, Na_v channels are present in the dendrites of neocortical and hippocampal pyramidal neurons[9,46], but virtually absent from the dendrites of cerebellar Purkinje cells[7]. Other evidence indicated that the density of A-type K_v channels is substantially higher in the distal apical dendrites of hippocampal pyramidal neurons compared to the soma[47]. Similarly, HCN channels are expressed at higher densities in the distal apical dendrites of pyramidal neurons in both the hippocampus and cortex[39–42], but are uniformly distributed in cerebellar Purkinje neurons[48]. These data suggest that there are location and cell type–specific differences in the active electrical properties of dendrites.

Third, simultaneous somatic and dendritic recordings indicated that APs are normally observed first in the soma and later in the dendrites[7,9,49], with combined somatic and axonal recordings confirming earlier, less direct, evidence that the axon is the normal site of AP initiation[7,9,50]. These studies also provided direct evidence that, in many neuronal cell types, APs actively propagate into the dendritic tree, albeit usually in a decremental manner[51]. Multiple factors, such as the density of available Na_v and K_v channels, as well as the branching structure of the dendritic tree, work together to determine how well (or poorly) APs propagate into dendrites[47,52–54].

Fourth, as described above, localized electrical events, dendritic spikes, can be generated in the dendrites of many types of neurons.

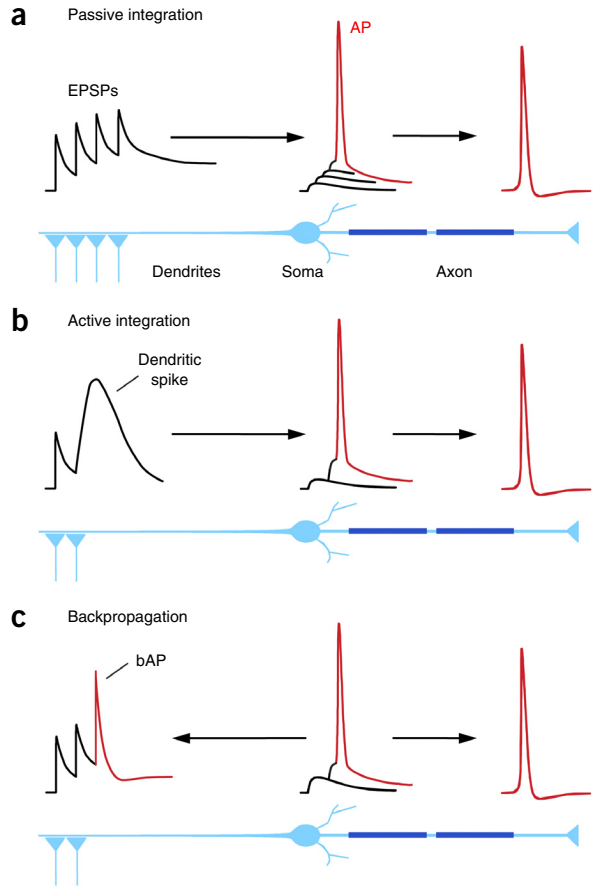

Figure 1 AP initiation, dendritic spikes and backpropagation. (**a**) Passive integration. Dendritic synaptic input generates fast local excitatory postsynaptic potentials (EPSPs) that are filtered and attenuated as they spread to the soma, where they summate to initiate an action potential (AP, red) in the axon initial segment. This AP then propagates down the axon[1,4,10]. (**b**) Active integration. Dendritic synaptic input initiates a local dendritic spike, which spreads to the soma facilitating AP generation[8,55–57]. (**c**) Backpropagation. In some cells, once initiated, APs (red) actively propagate both down the axon and back into the dendritic tree, where they interact with synaptic input[51].

As a result of the electrical properties of the dendritic tree, these dendritic spikes often propagate poorly and usually do not actively spread to the soma and axon. Despite this, dendritic spikes can have a substantial effect on the somatic membrane potential and AP generation, enhancing the capacity of distal dendritic inputs to influence both the timing and probability of neuronal output.

Local dendritic spikes are generated by different mechanisms and mediated by a variety of channel types (**Fig. 2**). Dendritic spikes with relatively narrow widths (<5 ms) are usually mediated primarily by Na_v channels, and are therefore referred to as dendritic sodium spikes[8,55–57]. As with all dendritic spikes, dendritic sodium spikes can occur in the absence of axonal action potentials and are therefore distinct from backpropagating APs (bAPs). A second type of dendritic spike, which is broader (>10 ms) and usually evoked by more prolonged dendritic depolarization, is mediated primarily by Ca_v channels and are called dendritic calcium spikes. These events, which were first described in cerebellar Purkinje neurons by Llinás and colleagues[17,58] and were later also observed in hippocampal and neocortical pyramidal neurons[18,19,59–62], are often mediated by L-type calcium channels[63]. A third type of dendritic spike is mediated primarily by NMDA receptor channels and is referred to as an NMDA spike[64]. These events can be even longer in duration and tend to be initiated in small-diameter dendritic branches such as basal and tuft dendrites of pyramidal neurons[34,35].

All three types of dendritic spikes, sodium, calcium and NMDA spikes, exhibit functional compartmentalization; that is, they are often spatially restricted to the compartment in which they are generated (**Fig. 2**). Dendritic sodium spikes tend to be initiated most readily in small-diameter dendrites, where input impedance is relatively high[56,65], although they can also be evoked in the main apical dendrites of cortical and hippocampal pyramidal neurons[8,55]. Because dendrites are only weakly excitable[66], dendritic sodium spikes tend to fail as they propagate from small, high input-impedance dendrites into larger dendrites with a lower input impedance[65]. Nevertheless, dendritic sodium spikes can deliver a substantial amount of charge to the soma, thereby influencing AP output in the axon[8,55–57]. Dendritic calcium spikes are larger and broader, and thus deliver even more charge to the soma and axon. As a result, dendritic calcium spikes are often associated with high-frequency AP burst firing[17,19,61,67–69]. A number of studies have suggested that dendritic K_v channels are important for restricting the generation and spread of dendritic calcium spikes[43,47,61,70]. Unlike dendritic sodium and calcium spikes, dendritic NMDA spikes cannot propagate beyond the region of glutamate release where they are generated, as NMDA receptor activation requires both glutamate and depolarization[71]. Nevertheless, the extra charge entry associated with NMDA spike generation can exert a substantial effect on AP initiation in the axon[72]. As a result of the longer duration of both dendritic calcium and NMDA spikes, these events can lead to 'plateau potentials' at the soma, which have recently been implicated in sensory tuning[73], synaptic plasticity[74] and feature selectivity[75].

Because all three types of dendritic spikes are functionally compartmentalized to some extent, they cannot be viewed in the same manner as axonal APs, which can propagate over long distances without decrement. As noted above, dendritic spikes can increase the probability of AP firing in the axon, but they do not assure it. bAPs and dendritic spikes can also interact. Pairing weak synaptic stimulation with bAPs can lower the threshold for the generation of dendritic calcium spikes[76], leading to AP burst firing. Conversely, propagation of bAPs into the dendritic tree can reduce the probability of subsequent dendritic sodium spike generation[55,77].

Dendritic computation

The passive and active properties of dendrites allow them to perform basic logical operations such as AND, OR and AND-NOT, enabling dendrites to perform complex computations on their inputs. For example, AND operations can occur when sufficient synchronized synaptic input occurs on a single dendritic branch to generate a dendritic spike[44,56,78]. This form of computation acts as a simple coincidence detector. Other examples include the capacity of proximal input to enhance the propagation of distal dendritic spikes to the soma and thereby their effect on AP output[79,80], which has recently been suggested to underlie feature selectivity[75]. The coincidence of bAPs with distal dendritic input has also been shown to enhance AP output by promoting dendritic spike generation[80]. Another example of an AND operation is where AP generation only occurs if dendritic spikes are generated in more than one of many dendritic branches[81]. Synaptic integration in dendrites may also give rise to OR operations in which different sets of presynaptic inputs, perhaps localized onto specific dendrites, are alone sufficient to generate AP firing. Neurons can also use inhibition to implement AND-NOT operations, where on-path inhibition can veto more distal excitatory input[11]. More distal (off-path) inhibition can also be effective in excitable dendrites by reducing dendritic spikes[82]. Although each one of these logical operations is relatively simple, dendrites allow them to be combined in different ways, resulting in the potential for a single neuron to perform more complex operations on its inputs.

Dendritic integration in the intact brain

Studying dendritic integration *in vitro* offers many advantages, including ease of access, allowing direct recordings from dendrites under visual control as well as high signal to noise during fluorescence imaging. These technical advantages come at a cost, however, with one

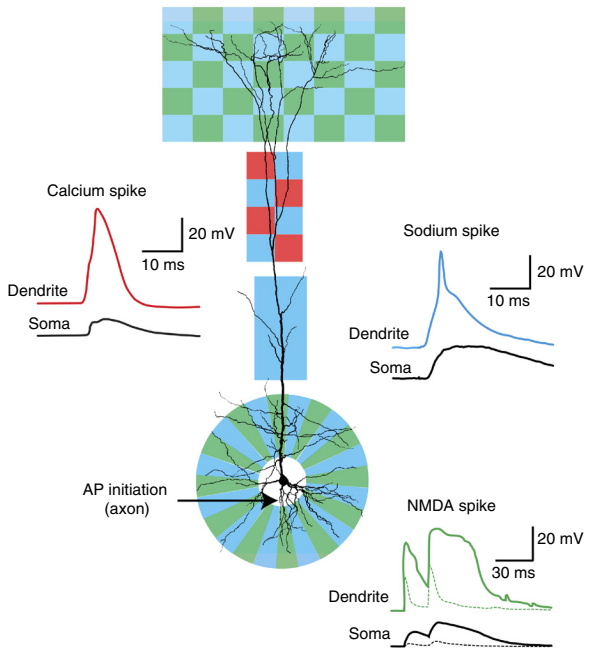

Figure 2 Location dependence of dendritic spike generation. Examples are shown of dendritic sodium (blue), calcium (red) and NMDA (green) spikes evoked by synaptic stimulation during simultaneous recordings from the soma (black), apical (blue, red) and basal (green) dendrites of a layer 5 pyramidal neuron[8,34,62]. Dotted lines indicate the effect of blocking NMDA receptors. Colored boxes and circles superimposed onto the morphology of a cortical layer 5 pyramidal neuron indicate the dendritic regions in which these different spikes are usually generated[8,34,35,43,62,148].

of the main disadvantages being that selective activation of known presynaptic inputs can be difficult to achieve. To some extent, this issue can be overcome by activation of specific pathways in some brain regions using extracellular stimulation (for example in the hippocampus, owing to its highly laminated projection pathways) or through the use of paired recordings in the case of local circuit interactions. The recent development of optogenetics has improved this situation, making it possible to activate defined pathways in a controlled manner[83]. In addition, glutamate uncaging allows activation of inputs at specific dendritic locations with sub-micron resolution[84].

Although these new methods have substantially increased the capacity to selectively activate specific inputs to neurons *in vitro*, activation is nonetheless artificial and, as a result, the relevance of the different types of synaptic integration observed to neuronal function in the intact brain is unclear. Furthermore, as the vast majority of synaptic input to neurons in brain slice preparations is silent, activation occurs in the absence of the normal background network activity found in the intact brain. This background activity includes the effect of neuromodulatory pathways, which can have a marked influence on cellular properties and network activity *in vivo*[85]. As a result, *in vitro* studies can only provide a description of the possible types of computations dendrites can perform. They are well suited for studying the physical 'machinery' and integrative capabilities of dendrites, but determining which of the many forms of synaptic integration described *in vitro* are used by the brain under more natural conditions requires investigation in the intact brain.

Despite their limitations, *in vitro* studies have led to an explosion of knowledge regarding the integrative properties of dendrites. A key benefit of these studies is that they provide an interpretive framework for understanding dendritic integration in the intact brain. For example, understanding the properties of bAPs from dendritic recordings *in vitro* has made it possible to understand AP backpropagation from less direct measurements obtained *in vivo*. Recordings from neocortical pyramidal neurons *in vivo* with calcium-sensitive dyes support the idea that APs actively propagate back into the dendritic tree[30,31,86]. Furthermore, extracellular recordings using multi-site silicon probes aligned to hippocampal dendrites revealed that AP backpropagation *in vivo* is activity dependent, as observed *in vitro*[87–89]. Intracellular recordings from the dendrites of neocortical and hippocampal pyramidal neurons also indicate that decremental and activity-dependent AP backpropagation occurs *in vivo*[30,86,90,91].

These descriptions of bAPs *in vivo* are not merely confirmatory; they resolve an important debate that arose following the initial description of bAPs *in vitro*. The concern raised was that background activity *in vivo* could make AP backpropagation ineffective as a result of shunting by ongoing synaptic activity[66]. *In vivo* work has demonstrated, however, that bAPs are just as large or larger during active network states[87,92]. This fact can be attributed to the finding that background synaptic activity *in vivo* is sparse[93] and that the dendritic depolarization that occurs during periods of intense network activity boosts the amplitude of bAPs[70,92].

Early work by Llinás and colleagues in cerebellar Purkinje cells revealed that local dendritic spikes can be generated in dendrites *in vivo*[58,94]. More recent work using patch-clamp recording supports this idea[73,74,86,91,95–97]. Notably, these studies indicate that dendritic spikes observed *in vivo* have properties consistent with dendritic sodium spikes, calcium spikes and NMDA spikes observed *in vitro*. Calcium imaging from dendrites *in vivo* provides further support for the idea that dendrites generate dendritic spikes in the intact brain[72,96,98–102].

Establishing that bAPs and dendritic spikes can occur *in vivo* is an important step. More critical, however, is to determine when these regenerative events occur (and when they don't). Recent studies have addressed this question using whole-cell patch-clamp recording, often combined with calcium imaging, in both anesthetized and awake animals *in vivo*. Some of these studies have concluded that sensory stimuli (visual, auditory, somatosensory) are integrated in a linear or sub-linear manner[103–111], as originally suggested by early work in motoneurons[112]. Other studies have concluded that supra-linear responses involving dendritic spikes contribute to neuronal processing *in vivo*[72–75,96–101]. These findings indicate that *in vivo* neurons are likely to perform both sub- and supra-linear forms of dendritic integration. Below we highlight recent work on this topic.

Experiments in somatosensory cortex *in vivo* have provided evidence for regenerative activity in the distal apical dendrites of layer 5 pyramidal neurons. In awake rats, an air puff to the hindlimb produces a large and sustained increase in dendritic calcium in the apical tuft of these neurons[113]. In anesthetized animals, this distal dendritic calcium signal is increased, rather than decreased, by blocking Na_v channels near the soma, indicating that it is unlikely to be mediated by bAPs; rather, it presumably represents dendritic calcium or NMDA spikes[98]. Other experiments show that these distal dendritic events can be regulated by dendritically targeted inhibition, as well as inter-hemispheric inhibition via $GABA_B$ receptors[98,99]. In separate work in awake, but head-restrained, animals, global increases in dendritic calcium in the distal tuft dendrites of layer 5 pyramidal neurons were associated with dendritic spikes (plateau potentials) and were maximal during integration of sensory and motor signals in the whisker system[96] (**Fig. 3a–c**). Spontaneous global calcium signals have also been observed in both the distal apical and basal dendrites in motor cortex in anesthetized animals[105], although in these experiments they required bAPs and are therefore unlikely to represent dendritic spikes. Together, these studies provide strong evidence for active dendritic signaling in the distal apical dendrites of layer 5 pyramidal neurons and show that these events are correlated with particular aspects of behavior.

Similar observations have been made in of layer 2/3 pyramidal neurons using both calcium imaging and direct dendritic recording in anesthetized and awake animals. These studies indicate that during sensory input the dendrites of layer 2/3 pyramidal neurons in somatosensory and visual cortex can generate NMDA spikes[72] as well as putative dendritic sodium spikes[97]. In contrast, somatic recordings from layer 2/3 neurons in binocular visual cortex indicates linear or sub-linear integration in both anesthetized and awake (head-fixed) animals[109,111]. Together, these studies indicate that a range of integration modes (linear, supra-linear and sub-linear) can occur in the dendrites of layer 2/3 neurons during sensory input. Both linear and supra-linear integration has also been observed in layer 4 neurons in somatosensory cortex[73,107].

Calcium imaging in the hippocampus of awake animals has revealed heterogeneous calcium signals resulting from putative dendritic spikes in different basal dendrites of CA1 pyramidal neurons, showing that this correlates with the stability of place fields during navigation in a virtual reality environment[101] (**Fig. 3d,e**). Task-related, branch-specific calcium spikes have recently been seen in the distal tuft dendrites of cortical layer 5 pyramidal neurons[102]. In contrast, as described above, multi-branch dendritic calcium signaling has been observed in tuft dendrites of cortical layer 5 pyramidal during active touch[96] and in basal dendrites of CA1 pyramidal neurons during complex spike bursts[100]. Thus, both isolated and multi-branch dendritic activity is seen in anesthetized and awake animals, indicating that in the intact brain different dendritic branches can work alone or together.

Both calcium imaging and direct dendritic recording also support the idea that active dendritic integration is important for information processing in the intact retina. Dendritic recordings from ganglion cells indicate that dendritic sodium spikes contribute to directional selectivity in these cells[114], consistent with earlier conclusions based on somatic recordings[115,116]. In another study, calcium imaging indicates that dendritic signaling in individual dendrites of starburst amacrine cells contributes to directional selectivity[117].

Dendrites and synaptic plasticity

Given the predominant dendritic location of the vast majority of synapses, it is perhaps not surprising that dendritic integration also has a key role in synaptic plasticity. Although first described in *in vivo* preparations in the early 1970s[118], the use of *in vitro* preparations has been essential for determining the underlying cellular mechanisms. This work indicates a critical role of bAPs in a form of synaptic plasticity called spike timing–dependent synaptic plasticity (STDP)[119–121], whereas other work has shown that, under some conditions, synaptic plasticity requires the generation of dendritic spikes[122–126]. Recent work *in vivo* has confirmed both of these findings, showing that STDP has similar properties *in vivo* and *in vitro*[127], and that, during sensory input, NMDA spikes are important for the induction of synaptic plasticity *in vivo*[74]. Another recent study *in vivo* found a key role for dendritic calcium spikes in specific dendritic branches in learning in motor cortex[102]. Finally, it is important to realize that the intrinsic properties of dendrites are also subject to plasticity[128,129], providing an additional mechanism by which synaptic plasticity can influence the effect of synaptic input on neuronal output.

Requirements for dendritic spike generation

Despite the progress made in understanding dendritic integration *in vivo*, one issue stands out. To what extent and under what conditions do dendrites generate local dendritic spikes? Although this issue is not easy to address, one strategy is to consider the conditions necessary for dendrites to generate spikes *in vitro* and to compare these conditions to what we know from anatomical studies and *in vivo* physiological studies.

Work *in vitro* indicates that dendritic spikes typically require activation of multiple synaptic inputs, usually in a synchronized manner[8,44,56,78,130]. Although the precise number of inputs required is difficult to estimate during extracellular stimulation, this has been addressed using two-photon glutamate uncaging during sequential activation of dendritic spines[56]. These experiments suggest that, in hippocampal and cortical pyramidal neurons, anywhere from a handful to dozens of inputs need to be activated in a localized dendritic region in a few milliseconds to generate a dendritic spike, suggesting that synaptic input needs to be spatially colocalized and temporally synchronous. Under what conditions will this happen in the intact brain? Furthermore, can dendritic spikes be generated with less synchronized and localized synaptic input *in vivo* as a result of the presence of background synaptic input or neuromodulators? With respect to the latter question, a number of *in vitro* experiments indicate that neuromodulators can have a direct effect on the active properties of dendrites[131].

As a starting point to addressing these issues, it is important to know whether inputs are activated in a clustered or dispersed manner during synaptic activity under physiological conditions *in vivo* (**Fig. 4a**). Functional studies suggest that both dispersed and clustered input occurs. Calcium imaging experiments in visual, somatosensory and auditory cortex indicate that single spine responses evoked by similar sensory information are dispersed across multiple dendritic branches[103,106,110] (**Fig. 4b**). However, dendritic recordings *in vivo* in visual cortex indicate that dendritic spikes can contribute to the orientation selectivity[97], and other experiments on hippocampal

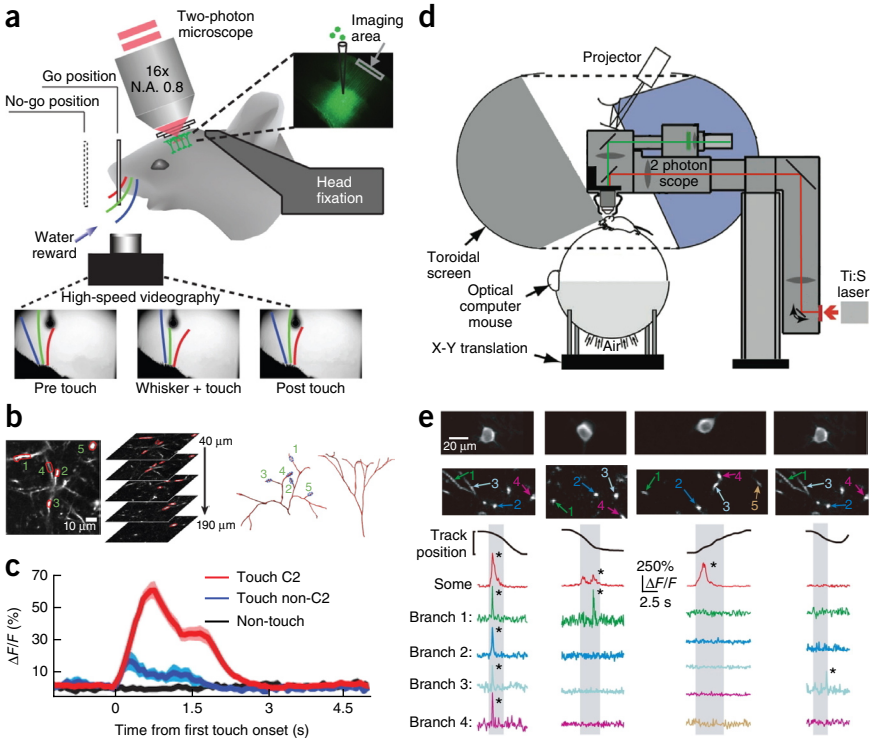

Figure 3 Examples of dendritic integration during behavior. (**a**–**c**) Global dendritic calcium signals in distal apical dendrites of cortical layer 5 pyramidal neurons during a whisker-dependent object-localization task[96]. (**a**) Schematic of the experimental arrangement during two-photon calcium imaging in awake, head-fixed mice. (**b**) Images of different distal apical dendrites (left; 1–5) identified to be from the same cell based on a reconstruction (right) from image stacks (middle). (**c**) Average rise in calcium in distal apical dendrites similar to those shown in **b** versus time on trails in which the whisker corresponding to the imaged barrel (C2) touched the target pole (red), other whiskers touched the target pole (blue) or no whiskers touched the target pole (black). (**d**,**e**) Discrete dendritic calcium signals in basal dendrites of CA1 pyramidal neurons during spatial navigation[101]. (**d**) Schematic of a typical experimental arrangement during two-photon calcium imaging in awake, head-fixed mice navigating in a virtual reality enviroment[149]. (**e**) Cell soma (top) and different basal dendrites (middle; color coded 1–5, cell on the right is the same as the cell on the left). Bottom, calcium response at the soma and different basal dendrites versus track position. Examples show cases in which an increase in calcium (denoted by an asterisk) is seen at all locations (left), the soma and some basal dendrites (second from the left), only the soma (second from the right), and only in one basal dendritic branch (right). Shading in **e** indicates place-field traversals.

neurons both *in vitro* and *in vivo* support the idea that spontaneous synaptic input onto the same dendrite can be activated in a clustered manner[132,133] (**Fig. 4c**). Clustered activation has also been shown to occur during motor learning[134]. There is also anatomical evidence supporting both clustered and dispersed synaptic inputs to dendrites. For example, layer 5 pyramidal neurons typically target their synaptic input to surrounding layer 5 pyramidal neurons in a dispersed manner onto different basal dendritic branches[135]. Such a synaptic arrangement has the advantage that there is minimal effect of the voltage change associated with one input on the driving force of others, thereby maximizing the current flow at individual synapses. On the other hand, recent anatomical evidence in both the neocortex and hippocampus suggests that inputs onto dendrites are not random, but can be clustered onto specific dendritic branches[136,137]. In summary, both functional and anatomical evidence so far supports clustered activation in some cases and dispersed activation in others, possibly even in the same neuron under different conditions.

Conclusions and future directions

As neuroscientists seek to untangle how neural circuits control behavior, we need to understand not only the various cell types and innumerable connections between them, but also how these different cell types integrate their inputs to generate an output. Dendrites have a critical role in this process, not only because of the large number of inputs they receive, but also because of the complex computations they perform. Only by studying dendritic integration in many cell types will we be able to identify the universal principles, as well as the cell type–specific specializations, that neurons use to process their inputs. This knowledge will provide a key piece of the puzzle needed to reveal the relationship between neural activity and behavior.

One issue the field needs to address is the potential effect of anesthetics. Although in many cases dendritic integration is essentially the same in anesthetized and awake animals, apparent differences between some of the studies discussed above may arise as a result of the use of anesthetics. Anesthetics, by their very nature, influence the way the nervous system works. Although studies in visual cortex indicate that anesthetics have little effect on stimulus-response properties[138], they can change spontaneous firing rates and have recently been found to influence the level of inhibition in the cortex[139]. In addition, *in vitro* experiments indicate that the majority of anesthetics have a negative effect on active dendritic membrane properties in cortical pyramidal neurons[140]. Future work is needed to determine how these different effects influences dendritic integration *in vivo*.

Another important issue that requires further research is under which conditions neurons generate dendritic spikes *in vivo*. A related issue is whether synaptic input carrying similar information converges onto the same or different dendritic branches. As discussed above, there is evidence both for and against this idea, suggesting that dendritic spikes will occur under some conditions, but not others. It is also worth mentioning that recent modeling suggests that *in vivo*–like background synaptic activity alone is sufficient to promote dendritic spike generation in the absence of clustered activation[141]. In support of this idea, dendritic spikes can be generated spontaneously *in vivo* as a result of background synaptic activity[72]. Although this theoretical and experimental work suggests that dendritic spikes may be more common than previously thought, the notion that dendritic spikes can be generated spontaneously without clustered activation of specific inputs also questions their role in information processing.

Finally, and probably most importantly, is the issue of how the different types of dendritic integration relate to brain function. To date, even the best work has only shown correlations between different forms of dendritic integration and behavior. Future studies will need to address the issue of causality. This issue can only be addressed in unanesthetized, awake animals, which imposes practical limitations. Nevertheless, substantial progress has been made with a number of new techniques, such as fiberoptic systems with GRIN lenses that can be used to image dendrites in freely moving animals[142], miniaturized microscopes that are small enough to mount on the head of freely moving rats or mice[143,144], and the increasing use of awake, head-fixed animals, allowing both two-photon imaging and whole-cell patch-clamp recording to be performed during behavior, including in animals navigating on spherical or linear treadmills[145]. Although we have restricted this review to studies in the vertebrate nervous system, use of invertebrate systems, where experiments in unanesthetized preparations are more common, offer substantial technical advantages and provide an important comparative view. Valuable insights into dendritic integration under natural conditions *in vivo* can also be obtained by imaging the activity of presynaptic inputs to dendrites[146,147]. An important next step using this method will be to determine the dendritic location of activated inputs and how activity in multiple presynaptic pathways is integrated during a variety of behaviors, including learning.

After 60 years of research, we now understand many of the basic biophysical properties of dendrites, but what does the future hold? Although dendrites were originally thought to act as simple receivers of synaptic information, funneling information to the soma and axon, we now know that they have a key role in information processing, owing to their capacity to influence the way neurons integrate their inputs. These computations range from passive interactions, leading

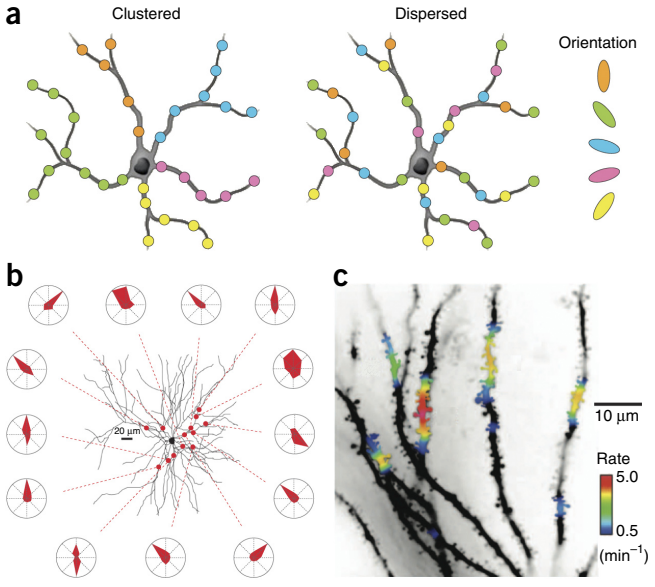

Figure 4 Distribution and timing of synaptic input. (**a**) Schematic representation of two possible distributions of synaptic input, with inputs coding similar information (orientation) color coded and targeted to the same dendritic branch (left) or dispersed across multiple dendritic branches (right)[150]. (**b**) Distributed orientation preference (indicated by surrounding red polar plots) of synaptic input to different spines (red circles) on basal dendrites of a layer 2/3 pyramidal neuron in visual cortex recorded *in vivo*[106]. (**c**) Clustered activation of spontaneous synaptic input to hippocampal pyramidal neuron dendrites (warmer colors) recorded *in vitro*[132].

to sub-linear summation and filtering of synaptic responses as they propagate throughout the dendritic tree, to highly nonlinear, spike-like events resulting from activation of voltage-dependent channels. Heterogeneity in dendritic morphology, as well as passive and active properties of dendrites, results in a wide range of dendritic interactions that are both cell-type and input specific. Continuing work both *in vitro* and *in vivo* will be required to unravel the complex way dendrites process their inputs. Aided by new technological advances, future research will undoubtedly increase our understanding of the complex role of dendrites in information processing in the brain.

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