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REVIEW

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Synaptic Integration in Cortical Inhibitory Neuron Dendrites

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Abstract—Cortical inhibitory interneurons have a wide range of important functions, including balancing network excitation, enhancing spike-time precision of principal neurons, and synchronizing neural activity within and across brain regions. All these functions critically depend on the integration of synaptic inputs in their dendrites. But the sparse number of inhibitory cells, their small caliber dendrites, and the problem of cell-type identification, have prevented fast progress in analyzing their dendritic properties. Despite these challenges, recent advancements in electrophysiological, optical and molecular tools have opened the door for studying synaptic integration and dendritic computations in molecularly defined inhibitory interneurons. Accumulating evidence indicates that the biophysical properties of inhibitory neuron dendrites differ substantially from those of pyramidal neurons. In addition to the supralinear dendritic integration commonly observed in pyramidal neurons, interneuron dendrites can also integrate synaptic inputs in a linear or sublinear fashion. In this comprehensive review, we compare the dendritic biophysical properties of the three major classes of cortical inhibitory neurons and discuss how these cell type-specific properties may support their functions in the cortex.

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Key words: dendritic integration, inhibitory neurons, synaptic inhibition, dendritic patch-clamp recording.

INTRODUCTION

Cortical neural networks are composed of glutamatergic principal neurons and γ-aminobutyric acid (GABA)-releasing inhibitory interneurons. Although inhibitory interneurons only represent 10–20% of the total neuronal population, they serve important functions in the network (Freund and Buzsáki, 1996; Fishell and Rudy, 2011). By establishing GABA-releasing synapses onto principal neurons, they mediate fast synaptic inhibition and control the level of neural network excitation. It is now clear that besides dampening excitation, inhibitory neurons also have more sophisticated functions such as organizing the spatial and temporal structure of excitation flowing through cortical networks (Pouille and Scanziani, 2001; Adesnik et al., 2012; Stefanelli et al., 2016), and gain modulation of neural responses (Borg-Graham et al., 1998; Mitchell and Silver, 2003; Pouille et al., 2009). Another notable example is the key role that inhibitory interneurons play in generating network oscillations that may function as a temporal reference for neural coding (Buzsáki and Draguhn, 2004; Klausberger and Somogyi, 2008). All these important functions rely on the synaptic activation of GABAergic interneurons by the ongoing cortical network activity.

How are inhibitory neurons recruited by the cortical network? To address this question, it is important to determine the biophysical mechanisms by which inhibitory neurons integrate synaptic inputs and translate them into action potential outputs. Like all cortical neurons, inhibitory cells consist of three distinct subcellular compartments: the dendrites, the soma and the axon. When examined by light microscopy, inhibitory neuron dendrites are often devoid of spines and appear to lack distinct synaptic contact sites (Markram et al., 2004). When examined by electron microscopy, these smooth dendrites display a much higher density of excitatory and inhibitory synapses than the soma and axon initial segment, providing clear evidence that dendrites are the main input structure (Gulyás et al., 1999; Martina et al., 2000). Functional analysis of inhibitory neuron dendrites and axons with patch-clamp electrodes and optical techniques further demonstrate that excitatory synaptic potentials are first integrated in the dendrites and then translated into spikes at the axon initial segment (typically 20–50 μm from the soma) (Martina et al., 2000; Hu et al., 2010; Vervaeke et al., 2012; Hu and Jonas, 2014; Li et al., 2014; Casale et al., 2015). Interestingly, axons of cortical inhibitory neurons arise most often from their dendrites.

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Abbreviations: AHP, afterhyperpolarization; CGE, caudal ganglionic eminence; Cx36, connexin-36; MGE, medial ganglionic eminence; O-LM, oriens-lacunosum moleculare; PV, parvalbumin; SOM, somatostatin; VIP, vasoactive intestinal peptide.

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The axon can emerge from first-, second- or even third-order dendritic branches, typically only a few tens of μm from the soma, but larger distances (100–200 μm) are not uncommon (Martina et al., 2000; Markram et al., 2004; Prönneke et al., 2015). In these inhibitory neurons, synaptic inputs may bypass the soma to evoke action potentials in the axon (Martina et al., 2000; Hu et al., 2010). Collectively, these studies indicate that the flow of information in individual inhibitory neurons follows the direction that was originally proposed by Cajal more than a century ago; i.e. synaptic input → dendrites → axon → synaptic output. By sampling and integrating synaptic inputs, dendrites are a key determinant of the input–output relationship. Thus, studying how interneuron dendrites integrate synaptic input is critical for understanding how these cells contribute to cortical processing.

Dendritic research over the past few decades has made a tremendous advance. More than 50 years ago, Wilfrid Rall established the theoretical framework for dendritic integration. By modeling the spread of voltage signals in dendrites as a function of space and time with the cable equation, Rall's work describes how dendritic filtering attenuates synaptic potentials as they propagate from the dendrites to the soma (Rall et al., 1967; Redman, 1973; Spruston et al., 1994). The three passive cable parameters, the membrane resistance (R_m), membrane capacitance (C_m) and axial resistance (R_i), in conjunction with the morphology of the cell, are the most basic determinants of synaptic integration. Experimental measurements of these cable properties have largely been obtained from excitatory principal neurons, in particular pyramidal cells with a large dendritic tree (Spruston et al., 1994; Stuart and Spruston, 1998; Golding et al., 2005). These studies have shown that the cable theory is indeed a successful conceptual framework to describe synaptic integration in dendrites. But it was too basic. We know now that pyramidal cells in the cortex have dendrites bestowed with a complex repertoire of voltage-gated ion channels. The complex interplay among synaptic inputs, dendrite morphology and dendritic biophysical properties, allow principal neurons to perform an incredibly diverse set of nonlinear dendritic operations (Häusser et al., 2000; London and Häusser, 2005; Stuart and Spruston, 2015).

In sharp contrast to the wealth of information about pyramidal neuron dendrites, we know very little about the dendrites of cortical inhibitory neurons. This is due to a number of conceptual and technical challenges: First, inhibitory cells are heavily outnumbered by principal neurons. There are at least four times more glutamatergic principal neurons in the cortex than inhibitory cells. In the early days of 'blind' electrophysiology without the guidance of a microscope, it was technically difficult to obtain electrophysiological recordings from inhibitory neurons, let alone targeting their dendrites. Second, cortical inhibitory neurons display a high degree of morphological, functional and molecular heterogeneity, and their classification is still an ongoing debate (Rudy et al., 2011; Defelipe et al., 2013; Kepecs and Fishell, 2014; Tremblay et al., 2016). Third, and most importantly, electron microscopy revealed that inhibitory neuron dendrites are typically less than 1 μm in diameter (Emri et al., 2001). This is in contrast to the large pyramidal neurons that often have apical dendrites that taper from 3 to 4 μm close to the soma, to about 2 μm several hundred micrometers away from the soma (Trommald et al., 1995). Thus, it is technically difficult to directly analyze the functional properties of interneuron dendrites with the patch-clamp method, which is still the gold standard for characterizing ion channels and electrical signaling in dendrites (Major et al., 2013).

Despite these difficulties, great progress has been made in the last decade due to several technical advances. First, the development of new transgenic mouse lines has made it much easier to target specific classes of inhibitory neurons (Oliva et al., 2000; Hippenmeyer et al., 2005; Ma et al., 2006; Taniguchi et al., 2011; Gerfen et al., 2013). Second, advances in subcellular patch-clamp techniques have allowed direct access to the finest processes of neurons (Nevian et al., 2007). This breakthrough opened the door for comprehensive mapping of ion channel distributions and the investigation of synaptic signaling in interneuron dendrites and axons (Hu et al., 2010; Vervaeke et al., 2012; Hu and Jonas, 2014; Li et al., 2014). Third, the development of new optical tools such as organic and genetically encoded Ca^{2+} and voltage indicators have allowed studying dendritic signaling with unprecedented spatial and temporal resolution (Kaiser et al., 2001; Goldberg et al., 2003a; Rózsa et al., 2004; Chen et al., 2013; Casale et al., 2015). Fourth, mimicking synaptic input patterns onto dendrites with two-photon glutamate uncaging has provided a detailed description of the input–output relationship of inhibitory neurons (Vervaeke et al., 2012; Chiovini et al., 2014; Tran-Van-Minh et al., 2016). These techniques, as well as powerful computer modeling tools, have revealed that the dendritic properties of inhibitory interneurons are substantially different from those of pyramidal neurons, and that interneuron dendritic properties may well fit the function that these neurons perform in the network.

Here we review the progress that has been made to reveal the dendritic integration properties of cortical inhibitory neurons. We focus on inhibitory neurons because several excellent reviews have been written about synaptic integration in pyramidal neuron dendrites (Häusser et al., 2000; Magee, 2000; Stuart and Spruston, 2015). We want to convince the reader that the dendritic properties of inhibitory neurons can be remarkably different from those of pyramidal neurons. Furthermore, while the dendrites of pyramidal cells have many integration features in common, the dendrites of inhibitory neurons appear to be more diverse. We will start by discussing briefly the challenges of classifying inhibitory neurons. Then we will describe the properties of chemical and electrical synapses found on inhibitory cells, regardless of cell type. Next, we will review what we know about the dendritic biophysical properties of each of the major classes of inhibitory cells. And finally we review the little we know about dendritic integration in these cells *in vivo*.

A STAGGERING DIVERSITY OF CORTICAL INHIBITORY INTERNEURONS

How to classify cortical inhibitory neurons is complicated and is an ongoing debate (Defelipe et al., 2013). Historically, the classification of inhibitory neurons in the hippocampus was done on the basis of their morphological features including the location of their soma and the layers to which they project their axons and dendrites (Freund and Buzsáki, 1996). This works well in the hippocampus, because of its simpler three-layered structure and its single layer of principal cell somata that allows to functionally discriminate hippocampal interneurons based on the spatial distribution of their dendrites and axons. This classification scheme however does not work well for the neocortex, which has six layers and a more complex circuitry. In recent years, a new classification scheme has emerged that classifies inhibitory neurons on the basis of only three molecular markers (Lee et al., 2010; Miyoshi et al., 2010; Rudy et al., 2011). These three markers are the calcium-binding protein parvalbumin (PV), the neuropeptide somatostatin (SOM) and the ionotropic serotonin receptor 5HT3a (5HT3aR). These three markers are expressed in largely non-overlapping classes of inhibitory neurons, and in the somatosensory cortex, this accounts for nearly 100% of all inhibitory cells (Lee et al., 2010; Rudy et al., 2011). Thus, at least in the neocortex, inhibitory neurons can be divided into three major classes: PV, SOM and 5HT3aR-expressing neurons. There are several arguments why this appears to be a useful classification scheme: (1) Neurons belonging to the same class have the same developmental origin (Miyoshi et al., 2010), (2) they have more similar gene expression patterns (Zeisel et al., 2015; Tasic et al., 2016), and (3) they are more functionally related than cells from different classes (Tremblay et al., 2016). Here, we will review the dendritic properties of inhibitory neurons belonging to these three classes, and ask whether cells of the same class have also similar dendritic properties. For simplicity, we will adhere to the neuronal marker classification scheme, although occasionally we will use morphology-based or firing pattern-based neuronal names because some neurons are still most commonly identified by these criteria (Petilla Interneuron Nomenclature Group et al., 2008).

CHEMICAL AND ELECTRICAL SYNAPSES IN INTERNEURON DENDRITES

Chemical synapses

Fast synaptic excitation of cortical neurons is mainly mediated by ionotropic glutamate receptors, including AMPA, NMDA and kainate receptors. The combination of glutamate receptor subunits that these receptors are composed of, largely determines their properties and plasticity rules. Interestingly, growing evidence indicate that the expression of glutamate receptors in inhibitory neurons differs substantially from that in principal cells (reviewed in (Akgül and McBain, 2016)), and this cell type-specific expression of glutamate receptors may account for a number of unique synaptic properties in inhibitory interneurons.

AMPA receptors are multimeric channels composed of combinatorial variations of GluR1–4 subunits. Among these, GluR2 subunits determine ion permeability and the sensitivity to intracellular blockade by polyamines. AMPA receptors without GluR2 subunits are permeable to Ca^{2+} ions (Jonas and Burnashev, 1995). While inhibitory neurons can express both GluR2-containing and GluR2-lacking AMPA receptors (Tóth et al., 2000; Lei and McBain, 2002; Sambandan et al., 2010), the relative expression level of Ca^{2+}-permeable and Ca^{2+}-impermeable AMPA receptors is dependent on their embryonic origin (Matta et al., 2013). During development, cortical inhibitory neurons originate mainly from progenitor cells in the medial ganglionic eminence (MGE) and caudal ganglionic eminence (CGE) of the ventral telencephalon (Wonders and Anderson, 2006). MGE-derived inhibitory cells (PV and SOM neurons) abundantly express Ca^{2+}-permeable AMPA receptors, while CGE-derived interneurons (5HT3aR neurons) express higher levels of Ca^{2+}-impermeable AMPA receptors (Matta et al., 2013). Ca^{2+}-permeable AMPA receptors are an important source of Ca^{2+} entry and are implicated in some forms of long-term synaptic plasticity in inhibitory cells (Tóth et al., 2000; Goldberg et al., 2003c; Lamsa et al., 2007; Oren et al., 2009). The Ca^{2+} permeability of these AMPA receptors is voltage-dependent, because intracellular polyamine molecules block these channels and prevent Ca^{2+} entry when the cells are depolarized' (Jonas and Burnashev, 1995). Because of this polyamine blockade, long-term potentiation that is induced by the activation of Ca^{2+}-permeable AMPA receptors is prevented by postsynaptic depolarization (Lamsa et al., 2007; Oren et al., 2009). This type of synaptic plasticity is different from the NMDA receptor-dependent long-term potentiation in pyramidal neurons that requires postsynaptic depolarization. Finally, the molecular composition of AMPA receptors also determines their kinetics. While inhibitory cells express fewer of the slow GluR2 subunits compared to principal neurons, they express the rapidly desensitizing GluR4 subunits more abundantly (Geiger et al., 1995). The presence of GluR4 produces AMPA receptors with rapid gating kinetics and contributes to the fast excitatory synaptic potentials typically seen in fast-spiking interneurons (Geiger et al., 1997).

In addition to Ca^{2+}-permeable AMPA receptors, NMDA receptors in inhibitory neurons can also generate Ca^{2+} influx (Lei and McBain, 2002; Goldberg et al., 2003c; Sambandan et al., 2010). In contrast to Ca^{2+}-permeable AMPA receptors that are blocked during depolarization, NMDA receptors require depolarization to become conductive. NMDA receptors are blocked by Mg^{2+} ions at the resting membrane potential. Activation of NMDA receptors requires the binding of glutamate and membrane potential depolarizing that expels the Mg^{2+} block. Thus, NMDA receptors function as coincidence detectors of pre- and postsynaptic activity during associative learning. NMDA receptors also control the efficacy and temporal precision of EPSP-action potential coupling in specific subpopulations of hippocampal

interneurons (Lei and McBain, 2002; Maccaferri and Dingledine, 2002). Indeed, NMDA receptors contribute a substantial amount of charge that helps to depolarize the cell, but the time course of NMDA receptor-mediated current is very slow. Thus, synaptic potentials with a large NMDA component typically do not trigger temporally precise spikes. Interestingly, the expression level of NMDA receptors in interneurons is often inversely correlated with that of Ca^{2+}-permeable AMPA receptors (Lei and McBain, 2002; Matta et al., 2013). While MGE-derived inhibitory cells (PV and SOM neurons) express few NMDA receptors, the CGE-derived neurons (5HT3aR cells) have synaptic conductances with a large NMDA component. Whether these opposite expression patterns mean that PV and SOM cells are more involved in precisely timed inhibitory control compared to 5HT3aR cells, remains to be determined.

In contrast to AMPA and NMDA receptors, the function of kainate receptors in interneurons is less understood. Although exogenous kainate application can depolarize and drive action potential firing in several types of interneurons (Frerking et al., 1998; Mulle et al., 2000; Semyanov and Kullmann, 2001), the contribution of kainate receptors to synaptic activation of GABAergic neurons under physiological conditions is currently debated (Cossart et al., 2002; Oren et al., 2009).

Interneuron dendrites are also targeted by GABAergic synapses (Gulyás et al., 1999; Pettit and Augustine, 2000; Hioki et al., 2013; Sohn et al., 2016). Such inhibitory synapses on interneuron dendrites are important for disinhibition (Chamberland and Topolnik, 2012; Letzkus et al., 2015). Studies of the biophysical properties of interneuron–interneuron synaptic connections in both the hippocampus and neocortex (Bartos et al., 2001; Pfeffer et al., 2013; Xu et al., 2013) show that fast inhibitory synaptic inhibition between interneurons are mainly mediated by GABAa receptors. Interestingly, hippocampal fast-spiking interneurons have reciprocal inhibitory synapses of which the conductance decays twice as fast as the conductance of inhibitory synapses onto principal neurons (Bartos et al., 2001). This remarkably fast interneuron–interneuron synaptic communication, together with electrical coupling via gap junctions, is thought to be crucial for generating high-frequency network oscillations (Wang and Buzsáki, 1996). For many types of neurons, the activation of GABAergic synapses causes a hyperpolarization because the reversal potential of GABAa-mediated conductances is below the resting membrane potential. However, the reversal potential of GABAa receptor-mediated conductance in hippocampal fast-spiking neurons is slightly more depolarized than the resting membrane potential (Vida et al., 2006). Thus, activation of GABAa receptors at these synapses produces a 'shunting' effect. Shunting inhibition reduces the gain of the input–output relationship of nerve cells (Mitchell and Silver, 2003). In the presence of shunting inhibition, the interneuron responds to a broad range of excitatory input intensities with nearly identical action potential frequencies. Computer simulations indicate that this mechanism makes network synchrony among fast-spiking interneurons more robust to heterogeneities in the network, such as differences in the excitatory drive of the interneurons (Vida et al., 2006).

Electrical synapses

Electrical synapses mediated by gap junctions are specialized connections between the membranes of adjacent cells. These structures provide a direct electrical contact between the cytoplasm of two cells. While electrical synapses between pyramidal cells are extremely rare and debated, they are ubiquitously found between inhibitory neurons in the cortex (Galarreta and Hestrin, 2001). Nearly all cortical inhibitory neurons investigated so far have electrical synapses (Hestrin and Galarreta, 2005). Interestingly, only inhibitory neurons of the same class are connected by electrical synapses. For example, cortical PV cells only connect to other PV cells (Galarreta and Hestrin, 2002), and the same rule applies to SOM cells and most types of 5HT3aR neurons (Galarreta and Hestrin, 1999; Leão et al., 2012; Karnani et al., 2016). The sole exceptions are neurogliaform neurons, an inhibitory cell type that, at least in the neocortex, belongs to the 5HT3aR class. In both neocortex and hippocampus, neurogliaform cells not only form electrical synapses with each other, but also promiscuously couple to most other inhibitory neurons, including PV-positive basket cells, axo-axonic cells, and 'regular-firing non-pyramidal neurons' that are most likely SOM or 5HT3aR neurons (Simon et al., 2005). Thus while inhibitory neurons of the same type couple to each other forming cell type-specific sub-networks, neurogliaform cells wire these sub-networks together.

Because electrical synapses provide a direct electrical connection between inhibitory neurons, their main function is thought to facilitate spike synchrony and to promote network oscillations (Galarreta and Hestrin, 1999; Gibson et al., 1999; van Welie et al., 2016). The identification of connexin-36 (Cx36) as the main protein subunit of gap junctions in cortical neurons has allowed to verify the role of electrical synapses in network oscillations (Deans et al., 2001; Hormuzdi et al., 2001). In brain slices of Cx36 knock-out ($Cx36^{-/-}$) mice, pharmacologically induced network oscillations were reduced (Deans et al., 2001; Hormuzdi et al., 2001), and *in vivo* recordings from hippocampus showed a reduction in the power of gamma oscillations (30–80 Hz) (Buhl et al., 2003).

However, enhancing network synchrony may not be the only function of electrical synapses. Since electrical synapses act as low-pass filters (Galarreta and Hestrin, 1999), fast action potentials propagating from one neuron to another are strongly attenuated and rarely exceed 1 mV in the post-synaptic cell. In contrast, the slower AHP following action potentials, which is particularly large in inhibitory neurons (up to 20 mV following a single spike), propagates much better and is typically an order of magnitude larger than the propagated spike (Vervaeke et al., 2010; Connors, 2017; but see van Welie et al., 2016). This mechanism allows inhibitory neurons to inhibit each other by means of their AHP, and this electrical synaptic inhibition can be as powerful as chemical synaptic inhibition (Vervaeke et al., 2010). Moreover,

the propagation of AHPs in gap junction coupled networks with heterogenous coupling strength can also cause network desynchronization (Vervaeke et al., 2010). Although the role of electrical synapses in promoting either spike synchrony or desynchronization may depend on the specific biophysical properties of the network (Ostojic et al., 2009; van Welie et al., 2016), it is generally agreed upon that electrical synapses allow neurons to share synaptic charge. Thus, an inhibitory neuron that receives synaptic inputs will share some of that synaptic charge with electrically coupled neurons, thereby losing some response specificity to synaptic stimuli (Amsalem et al., 2016). This redistribution of synaptic charge via gap junctions could in part contribute to the broadly tuned receptive fields of inhibitory neurons in rodent sensory cortex (Sohya et al., 2007; Kerlin et al., 2010). Indeed, recent computer simulations predict that electrical synapses contribute to the weak orientation selectivity of PV neurons in mouse visual cortex (Amsalem et al., 2016). While the influence of gap junctions on the tuning and receptive fields of inhibitory neurons remains to be confirmed by experiments, this is an interesting prediction that can be tested in $Cx36^{-/-}$ mice.

How do electrical synapses affect dendritic integration in inhibitory neurons? It is well established that gap junctions are located on the dendrites of inhibitory neurons. Beautiful but painstaking work using dual whole-cell patch-clamp recordings of electrically coupled cells, followed by electron microscopy to verify the location of the gap junctions, unequivocally showed that gap junctions are located in the dendrites (Tamás et al., 2000; Szabadics et al., 2001; Oláh et al., 2009). Furthermore, patch-clamp recordings from electrically coupled inhibitory neurons have shown that the connection probability and connection strength are strongly correlated with the spatial overlap of their dendritic trees, providing further evidence that inhibitory neurons are coupled by their dendrites (Vervaeke et al., 2010). In two of the most extensive anatomical studies so far, reconstruction of connected PV neurons in layer 2/3 and layer 4 of cat visual cortex showed that single-PV neurons formed ~60 and ~30 gap junctions respectively with other cells (Fukuda et al., 2006; Fukuda, 2017). In mice and rats, the probability of finding two electrically coupled PV or SOM cells is also very high (50–70%) (Galarreta and Hestrin, 2001). The large number of electrical synapses implies that each inhibitory neuron participates in a large, continuous syncytium (Fukuda, 2017). The conductance of a single gap junction composed of Cx36 channels between PV neurons is approximately 0.05–0.25 nS (Amsalem et al., 2016). Assuming that each neuron typically establishes 30 gap junctions with other neurons, the total conductance contributed by electrical synapses is 1.5–7.5 nS. This is in the same order of magnitude as the membrane conductance of inhibitory neurons at the resting membrane potential (~2.5–12.5 nS) (Doischer et al., 2008; Prönneke et al., 2015). Thus, gap junctions can contribute 50% or more to the total membrane conductance of inhibitory neurons. In close agreement, in $Cx36^{-/-}$ mice, the membrane conductance of fast-spiking cells (most likely PV cells) decreased by 32%, and in low-threshold spiking cells (most likely SOM and 5HT3a neurons) the membrane conductance decreased by 42% (Deans et al., 2001; Hormuzdi et al., 2001). This is, however, most likely an underestimate due to a developmental compensation of membrane conductance, since pharmacological blockade of Cx36 gap junctions with mefloquine at concentrations that only partly block these channels, decreased the membrane conductance by 70–80% in neocortical fast-spiking neurons (Cruikshank et al., 2004). In summary, gap junctions in inhibitory neuron dendrites contribute a significant fraction of the membrane conductance.

How will the membrane conductance in the dendrites mediated by gap junctions affect the excitability of inhibitory neurons? Electrical synapses between inhibitory neurons reduce the input resistance and thus the excitability of all coupled cells in the network. Simulations however predict that the effect of gap junctions on excitability is dependent on how inhibitory networks are stimulated by synaptic input (Ostojic et al., 2009; Vervaeke et al., 2010, 2012). In networks where a sparse number of inhibitory cells receive strong synaptic excitation and others little synaptic input, there will be a redistribution of synaptic charge through the syncytium. Thus a sparse number of inhibitory neurons will lose synaptic charge while the majority of inhibitory cells will receive extra synaptic charge via gap junctions (Vervaeke et al., 2012). In this case, a sparse number of inhibitory neurons will be less excited, while the majority of inhibitory neurons will be more excited. In addition, cable theory predicts that the presence of gap junctions changes the synaptic integration properties of electrically coupled cells. Because gap junctions increase the leak conductance, dendritic electrical synapses reduce the dendritic membrane time constant and accelerate the decay of EPSPs. With a narrower temporal window of synaptic integration, dendritic gap junctions decrease the efficacy of EPSP–AP coupling (Amsalem et al., 2016). On the other hand, the fast time course of synaptic potentials enhances the coincidence detection in interneurons (Nörenberg et al., 2010; Amsalem et al., 2016). PV neurons are hypothesized to be important for providing precisely timed inhibitory input (see below) (Jonas et al., 2004; Hu et al., 2014) and thus gap junctions may also contribute to the enhanced spike time precision in these cells. In summary, while this list of gap junction effects on dendritic integration is not exhaustive, it illustrates that the effects of gap junctions on cellular excitability can be complex and requires a lot more investigation.

The surprisingly complex effects of electrical synapses on network dynamics call for further analysis with computer models. While simplified models have provided substantial insights into the behavior of electrically coupled networks, biophysically detailed models are also required in order to capture the influence of dendrites, voltage-gated ion channels, and network heterogeneity on network dynamics (Vervaeke et al., 2010, 2012; Amsalem et al., 2016). Gap junctions however, pose a significant problem when measuring the passive properties that are needed to determine the

cable equation parameters such as R_m, C_m and R_i. These parameters are determined in pyramidal cell dendrites using dual somato-dendritic patch-clamp recordings (Stuart and Spruston, 1998). While challenging, this technique is nevertheless the gold standard for measuring these parameters. Single-electrode recordings from the soma are generally not accurate enough, in particular when the passive membrane parameters are non-uniform along dendrites (Stuart and Spruston, 1998). Since gap junctions can be distributed non-uniformly along dendrites, there is a need for dual somato-dendritic patch-clamp recordings of inhibitory neurons, but this is technically challenging. Two recent studies estimated the density and conductance of gap junctions and the passive properties of inhibitory neurons dendrites, using a combination of patch-clamp electrophysiology, morphology reconstruction and advanced anatomical techniques (Amsalem et al., 2016; Szoboszlay et al., 2016). The combination of laborious and difficult methods that was used illustrates the need for new technological approaches to study the effect of gap junctions on neural inhibition (see outlook section).

BIOPHYSICAL PROPERTIES OF CORTICAL INHIBITORY NEURON DENDRITES

Parvalbumin-expressing inhibitory neurons

Inhibitory neurons expressing parvalbumin (PV cells) represent ~40% of the total GABAergic interneuron population in the cortex (Fishell and Rudy, 2011). PV cells can roughly be separated into two groups: PV-expressing basket cells (PV-BCs) and axo-axonic neurons. PV-BCs establish inhibitory synapses at the soma and proximal dendrites of their postsynaptic targets, whereas axo-axonic neurons specifically target the axon initial segment of principal cells (Freund and Buzsáki, 1996). A PV-BC has 4–6 main dendrites that originate from the soma and fan out in all directions (Fig. 1A). When compared to principal neurons, PV-BCs have relatively short and less branched dendrites (Hu et al., 2014). Another distinct morphological feature of PV-BC dendrites is their smooth appearance due to the lack of spines. The functional implication of this remains elusive. Some have suggested that spines modify the dendritic cable properties and increase the low-pass filtering of synaptic potentials in dendrites (Rose and Call, 1992; Tsay and Yuste, 2004). The lack of spines may therefore allow faster inhibitory neuron signaling. Spines in pyramidal neurons are important for input specificity, because they electrically and chemically compartmentalize individual synapses (Tsay and Yuste, 2004). One may question the existence of a similar synaptic compartmentalization mechanism in smooth interneuron dendrites. With 2-photon dendritic Ca^{2+} imaging, Goldberg found that activation of single synapses created highly localized Ca^{2+} microdomains in aspiny interneuron dendrites (Goldberg et al., 2003a). This compartmentalization depends on the fast gating of specialized Ca^{2+}-permeable AMPA receptors, a rapid local Ca^{2+} extrusion mechanism, and the Ca^{2+} buffering properties of parvalbumin (Goldberg et al., 2003a).

Detailed computer simulations of PV-BCs with reconstructed morphologies showed that PV-BC dendrites also have distinct passive properties. The R_m of PV-BCs is substantially lower than in pyramidal neurons (Nörenberg et al., 2010). Moreover, the R_m of the distal dendrites of PV-BCs is about nine times higher than that of the proximal dendrites, creating an R_m gradient that is the opposite of what has been found in pyramidal neurons. (Stuart and Spruston, 1998; Golding et al., 2005). This unique R_m gradient of PV-BCs promotes the efficacy of synaptic inputs in distal dendrites and enhances coincidence detection in the perisomatic regions (Nörenberg et al., 2010).

Using optical imaging and electrophysiological techniques, several studies have determined the active properties of PV-BC dendrites. Functional imaging using Ca^{2+} and voltage indicators suggest that action potentials backpropagate poorly into PV-BC dendrites (Goldberg et al., 2003 b; Camiré and Topolnik, 2014; Casale et al., 2015). In close agreement, dendritic patch-clamp recordings show a strong attenuation of backpropagating action potentials (Fig. 1B) and sublinear dendritic integration in PV-BCs (Hu et al., 2010). These dendritic properties differ from those of excitatory pyramidal neurons, which support active action potential backpropagation, dendritic spike initiation and supralinear synaptic integration (Spruston, 2008; Larkum et al., 2009). At ~250 μm from the soma, backpropagating spikes in PV-BCs attenuate to ~15% of the amplitude measured at the soma, while in pyramidal neurons, spikes only attenuate to about ~70% at a similar distance (Spruston, 2008; Hu et al., 2010). Mapping of voltage-gated ion channels has provided a detailed description of the underlying biophysical mechanisms (Fig. 1C) (Hu et al., 2010). PV-BC dendrites contain a high density of voltage-gated Kv3-type K^+ channels. By contrast, the density of voltage-gated Na^+ channels decreases steeply as a function of distance from the soma. More than 100 μm away from the soma, Na^+ currents are almost undetectable. This high K^+/Na^+ conductance ratio reduces dendritic excitability and functionally distinguishes PV-BC dendrites from those of glutamatergic pyramidal neurons. Less is known about voltage-gated Ca^{2+} channels in PV-BC dendrites. Two-photon uncaging of glutamate onto PV-BC dendrites to simulate synaptic inputs revealed that voltage-gated Ca^{2+} channels also contributed to synaptically evoked Ca^{2+} entry in interneuron dendrites (Chiovini et al., 2014), but a comprehensive study of dendritic Ca^{2+} channel functions in PV-BCs is still missing. Finally, PV-BCs also express HCN channels that generate the membrane hyperpolarization-activated h-current (Aponte et al., 2006). In hippocampal CA1 and neocortical pyramidal neurons, a high density of HCN channels in the distal dendrites plays a key role in synaptic integration (Magee, 1998; Williams and Stuart, 2000). Whether HCN channels have a similar distribution and function in PV-BCs, remains to be determined.

PV-BCs perform a number of temporally precise operations that are important for cortical processing (Cobb et al., 1995; Pouille and Scanziani, 2001;

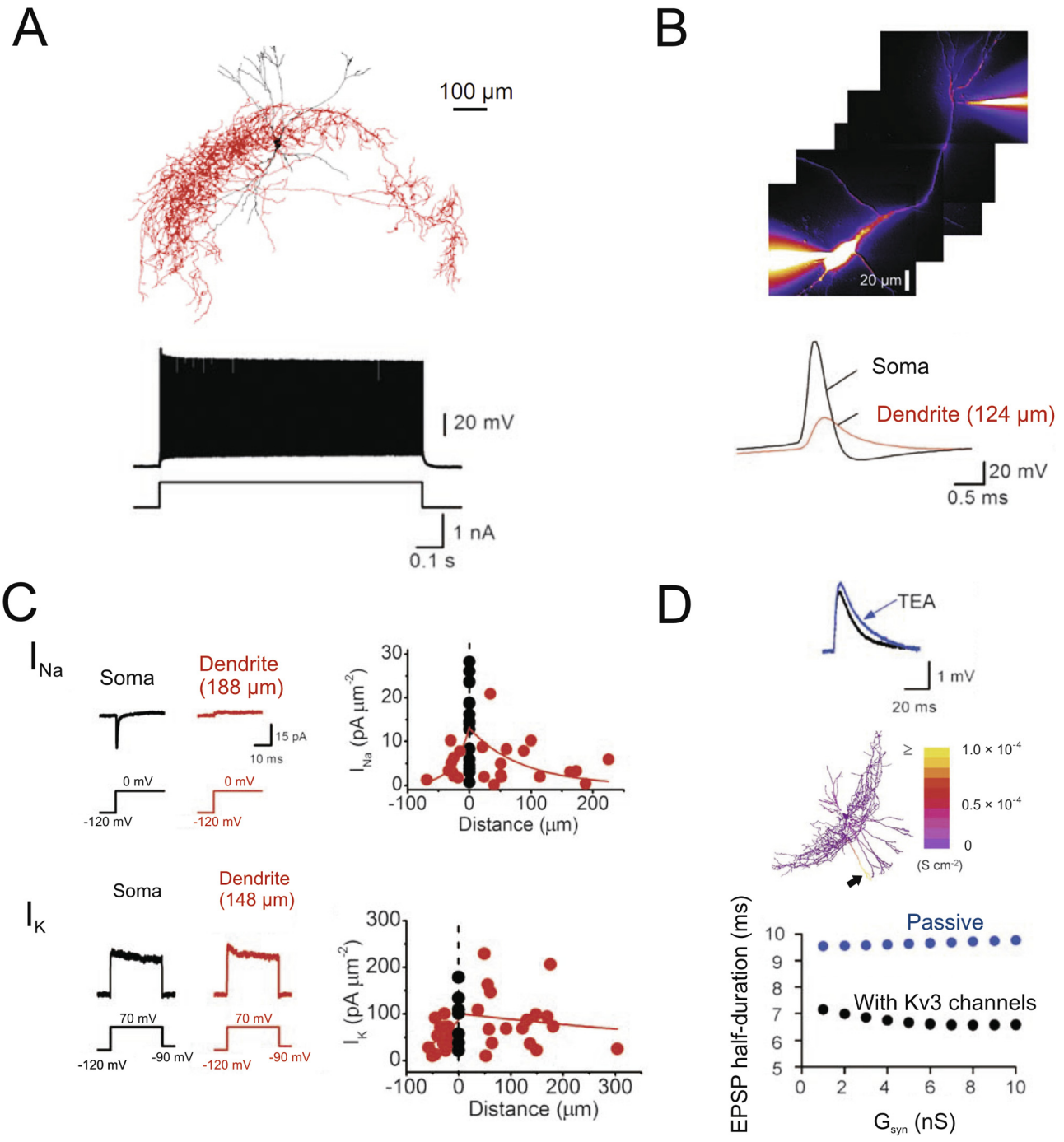

Fig. 1. Biophysical properties of PV neuron dendrites. (A) Top, reconstruction of a PV-expressing basket cell in the hippocampal dentate gyrus (soma and dendrites in black; axon in red). Bottom, fast-spiking phenotype of a hippocampal PV-expressing basket cell *in vitro*, in response to a 1-s-long current pulse at the soma. (B) Top, confocal image of simultaneous patch-clamp recording from the soma and dendrite of a PV neuron *in vitro*. Bottom, strong attenuation of backpagating action potential amplitude in PV neuron dendrites. (C) Left panels, current responses to voltage steps using outside-out patches from the soma (black) or the dendrites (red). Right panels, Na^+ and K^+ current densities in PV neuron somata (black) and dendrites (red). (D) Top, blocking Kv3 channels with tetraethylammonium (TEA, blue trace) reduced the decay speed of synaptic potentials in PV neurons. Middle: Cable modeling demonstrating local synaptic activation of Kv3-type K^+ channels in PV-expressing interneuron dendrites (a synapse was activated in the apical dendrite, arrow). Pseudocolor code indicates the activated K^+ conductance. Bottom: dendritic Kv3-type channels reduce the half-duration of EPSPs in a PV Neuron cable model. Data in (A) is adapted from Nörenberg et al. (2010), and data in (B–D) is adapted from Hu et al. (2010).

Cruikshank et al., 2007; Lamsa et al., 2007; Kruglikov and Rudy, 2008; Cardin et al., 2009). During synaptic activation, hippocampal PV-BCs are capable of translating excitatory synaptic inputs into the release of GABA from the axon terminals within less than 2 ms (Pouille and Scanziani, 2001). Such fast feed-forward inhibition enhances the temporal precision of action potentials in principal neurons. This remarkably rapid interneuron sig-

naling critically depends on several specialized synaptic and dendritic properties. First, fast Ca^{2+} permeable AMPA receptors generate rapid excitatory synaptic conductance changes at excitatory synapses in the interneuron dendrites (Geiger et al., 1995; Hull et al., 2009). Second, the low R_m reduces the membrane time constant (see Table 1 to compare with other cell types) and limits the duration of the temporal integration window, allowing synaptic conductances to generate postsynaptic potentials with fast kinetics (Nörenberg et al., 2010). Third, dendritic voltage-gated K^+ channels further enforce the rapid time course of excitatory postsynaptic potentials (Fig. 1D) (Hu et al., 2010). Moreover, the absence of voltage-gated Na^+ channels in the dendrites functionally isolates dendritic synapses from the axonal spike generation site, preventing synaptic potentials from being reset by the shunting effect of backpropagating action potentials (Häusser et al., 2001). This may be important because PV neurons generally have high firing rates (Gentet et al., 2012). Fourth, in layer 4 of the neocortex, a single excitatory thalamo-cortical fiber makes several clusters of synaptic contacts onto the proximal dendrites of PV neurons causing fast and large-amplitude depolarizing potentials (Bagnall et al., 2011). Altogether, these dendritic properties, as well as axonal specializations (Goldberg et al., 2008; Hu and Jonas, 2014; Li et al., 2014), enhance the capability of PV-BCs to detect coincident synaptic inputs and convert them into action potential outputs with high speed and temporal precision.

A systematic analysis of the biophysical properties of axo-axonic cell dendrites has not been performed yet due to the difficulty to identify these interneurons. Patch-clamp recordings from putative hippocampal axo-axonic cell dendrites, however, indicate that backpropagating action potentials also strongly attenuate in the dendrites, similar to PV-BCs (Hu et al., 2010). The strong attenuation of backpropagating spikes in axo-axonic neurons may stem from a high dendritic K^+ to Na^+ conductance ratio like in PV-BCs. Whether axo-axonic cell and PV-BCs also have similar dendritic integration properties remains, however, to be determined.

Somatostatin-expressing inhibitory neurons

Inhibitory neurons that express somatostatin (SOM cells) represent ~30% of the total cortical inhibitory neuron population (Fishell and Rudy, 2011). A hallmark of these neurons is that they form inhibitory synapses on pyramidal neuron dendrites. SOM cells represent a diverse population of GABAergic neurons. Neocortical SOM cells are roughly separated into Martinotti and non-Martinotti cells, and Martinotti cells can be defined by their axon that targets cortical layer 1. In the hippocampus, SOM cells include oriens-lacunosum moleculare (O-LM) cells, bistratified cells and long-range projecting inhibitory neurons that target the septum (Somogyi and Klausberger, 2005). Because these subgroups display a high degree of diversity in their molecular, morphological and functional properties, it is tempting to speculate whether their dendritic properties are also heterogeneous. Here, we focus on two subtypes of SOM cells that inhibit pyramidal neuron

Table 1. Summary table of the basic biophysical properties important for synaptic integration. Questions marks indicate a lack of data. The table is restricted to direct electrophysiological evidence and does not include indirect evidence from for example Ca^{2+} imaging

	Parvalbumin neurons		Somatostatin neurons		5HT3aR neurons	
	Basket cells	Axo-axonic cells	Oriens-lacunosum moleculare cells	Martinotti cells	VIP cells	Non-VIP cells
Input resistance (soma)	86 ± 6 MΩ[(a)]	73.9 ± 2.8 MΩ[(c)]	315.1 ± 41.6 MΩ[(d)]	198.2 ± 79.9 MΩ[(f)]	387– 763 MΩ[(h)]	273– 587 MΩ[(h)]
Time constant (soma)	7.3 ± 0.5 ms[(a)]	7.7 ± 3.8 ms[(c)]	33.3 ± 1.4 ms[(d)]	24.0 ± 8.4 ms[(f)]	18.9 – 32.5 ms[(h)]	16.1 – 18.6 ms[(h)]
Backpropagating AP	Strong attenuation[(b)]	Strong attenuation[(b)]	Weak attenuation[(e)]	Weak attenuation[(g)]	?	?
Dendritic g_{Na} density	Dend < 100 µm: 22 ± 5 pS µm^{-2}; Dend > 100 µm: 18 ± 6 pS µm^{-2}[(b)]	?	Dend < 100 µm: 113 ± 9 pS µm^{-2}; Dend > 100 µm:?[(e)]	?	?	?
Dendritic g_K density	Dend < 100 µm: 81 ± 13 pS µm^{-2}; Dend > 100 µm: 93 ± 22 pS µm^{-2}[(b)]	?	Dend < 100 µm: 860 pS µm^{-2}; Dend > 100 µm: ?[(e)]	?	?	?

(a). Doischer et al. (2008), (b). Hu et al. (2010), (c). Buhl et al. (1994), (d). Gloveli et al. (2005), (e). Martina et al., 2000, (f). Wang et al. (2004), (g). Kaiser et al. (2001), (h). Miyoshi et al. (2010).

distal dendrites: Martinotti cells in the neocortex and O-LM cells in the hippocampus (Fig. 2A, D).

Martinotti cells often have a bitufted dendritic morphology (Wang et al., 2004) and their dendritic tree can span multiple layers. This morphological feature suggests that Martinotti cells may monitor the activity in different neocortical layers. By contrast, hippocampal O-LM cells have horizontal dendrites that are confined to the stratum oriens of the hippocampus (Fig. 2A) (Sik et al., 1995). Unlike smooth PV cell dendrites, Martinotti cell and O-LM cell dendrites are covered by spines (Wang et al., 2004; Gloveli et al., 2005), but with a much lower density than in pyramidal neurons. A detailed study to determine the passive properties using dendritic patch-clamp recordings and computer simulations is still lacking. The slow membrane constant of Martinotti cells and O-LM cells suggests a high membrane resistance (see Table 1 to compare with PV cells) (Gloveli et al., 2005). Indeed, the R_m value of O-LM cells was tentatively estimated to be 20 KΩ cm^{-2} (Saraga et al., 2003), almost 2 times larger than the average somatodendritic R_m of PV-BCs. The active properties of Martinotti and O-LM cell dendrites are also remarkably different from those of PV-BCs. Mapping of voltage-gated channels with dendritic patch-clamp recordings indicated that the density of Na^+ channels in O-LM cell dendrites was more than double the density of Na^+ channels found in hippocampal and neocortical excitatory pyramidal dendrites (Martina et al., 2000). This high concentration of dendritic Na^+ channels is matched by a high and distance-independent density of voltage-gated K^+ channels (Fig. 2B). The high density of dendritic Na^+ channels in OL-M cells support active action potential backpropagation (Fig. 2C) and initiation of dendritic spikes. Using Ca^{2+} imaging, active invasion of the entire dendritic tree by backpropagating spikes has also been shown in Martinotti cells (Fig. 2E) (Goldberg et al., 2004). These backpropagating spikes elicited dendritic Ca^{2+} signals that were reduced by the selective Na^+ channel blocker tetrodotoxin, indicating that spike backpropagation is dependent on dendritic Na^+ channels. These dendritic Ca^{2+} signals are also sensitive to low doses of nickel, suggesting the presence of T-type Ca^{2+} channels in Martinotti cell dendrites. Dual somatodendritic recordings up to ~60 μm from the soma of SOM neurons in the neocortex also indicate that backpropagating spikes do not attenuate over this distance (Fig. 2F) (Kaiser et al., 2001). Recordings further on the dendrite are, however, necessary to compare Martinotti cells to PV cells and pyramidal neurons, because at such short dendritic recording distances, very little attenuation is expected regardless of whether the dendrites support active backpropagation. Finally, HCN channels are functionally expressed in both Martinotti cells and O-LM cells (Maccaferri and McBain, 1996; Wang et al., 2004), but the subcellular distribution of HCN channels in these interneurons remains unknown.

Although it has been shown that neocortical SOM cells can be activated by ascending thalamo-cortical fibers (Tan et al., 2008), these cells are typically recruited by local principal neurons. In the primary sensory cortex, Martinotti cells can be recruited by a high-frequency action potential burst from a very small number of pyramidal cells (Kapfer et al., 2007; Silberberg and Markram, 2007). Several mechanisms may contribute to this highly efficient recruitment. First, Martinotti cells receive strongly facilitating synaptic inputs from pyramidal neurons (Silberberg and Markram, 2007). Second, Martinotti cells have a large membrane time constant (Table 1) (Wang et al., 2004), that enable these cells to sum excitatory synaptic inputs over large time windows. Because of the broad synaptic integration time window and the facilitating nature of input synapses, each successive synaptic input progressively brings the membrane potential of Martinotti cells closer to the action potential threshold. Third, dendritic Na^+ and T-type Ca^{2+} channels most likely increase EPSP–action potential coupling by amplification of excitatory synaptic potentials (Martina et al., 2000; Goldberg et al., 2004).

The efficient synaptic activation of Martinotti cells by pyramidal neurons has several important functional implications. At the single-cell level, Martinotti cells determine the gain of the input–output relationship of single cortical–pyramidal neurons (Murayama et al., 2009; Lee et al., 2012). Martinotti cells target the distal tuft dendrites of pyramidal neurons and control the initiation of dendritic Ca^{2+} spikes that are thought to be instrumental for burst firing in pyramidal cells. The high sensitivity of Martinotti cells to detect such bursts allows them to track and suppress regenerative Ca^{2+} signals in pyramidal neuron dendrites with feedback inhibition. Gain decreases when Martinotti cells inhibit dendritic Ca^{2+} spikes that often underlie action potential bursts (Larkum et al., 2004). At the circuit level, Martinotti cells play a key role in organizing the spatial structure of network activity. Each single Martinotti cell generates a massively divergent inhibitory synaptic output that inhibits nearly 80% of neighboring pyramidal neurons (Silberberg and Markram, 2007; Fino and Yuste, 2011). Thus, a burst of action potentials from a small number of pyramidal neurons is capable of suppressing many other pyramidal neurons in the surrounding network via the intermediate Martinotti cell activation (Silberberg and Markram, 2007). This lateral inhibition mediated by SOM cells was shown to be a key circuit mechanism for surround suppression in the visual cortex and neural ensemble competition during memory formation (Adesnik et al., 2012; Stefanelli et al., 2016).

5HT3aR-expressing inhibitory neurons

5HT3aR cells comprise ~30% of all inhibitory neurons in the cortex (Fishell and Rudy, 2011). Since the 5HT3aR nomenclature is relatively new, many neurons that belong to this class are still best-known by their historical name. 5HT3aR cells are broken into two major subclasses: Those that are positive for vasoactive intestinal peptide (VIP) and those who are not (Tremblay et al., 2016). One of the most numerous VIP-negative cells are neurogliaform cells, a cell type already known in the times of Cajal (note that in the hippocampus most neurogliaform cells are 5HT3aR-negative). The diversity of 5HT3aR

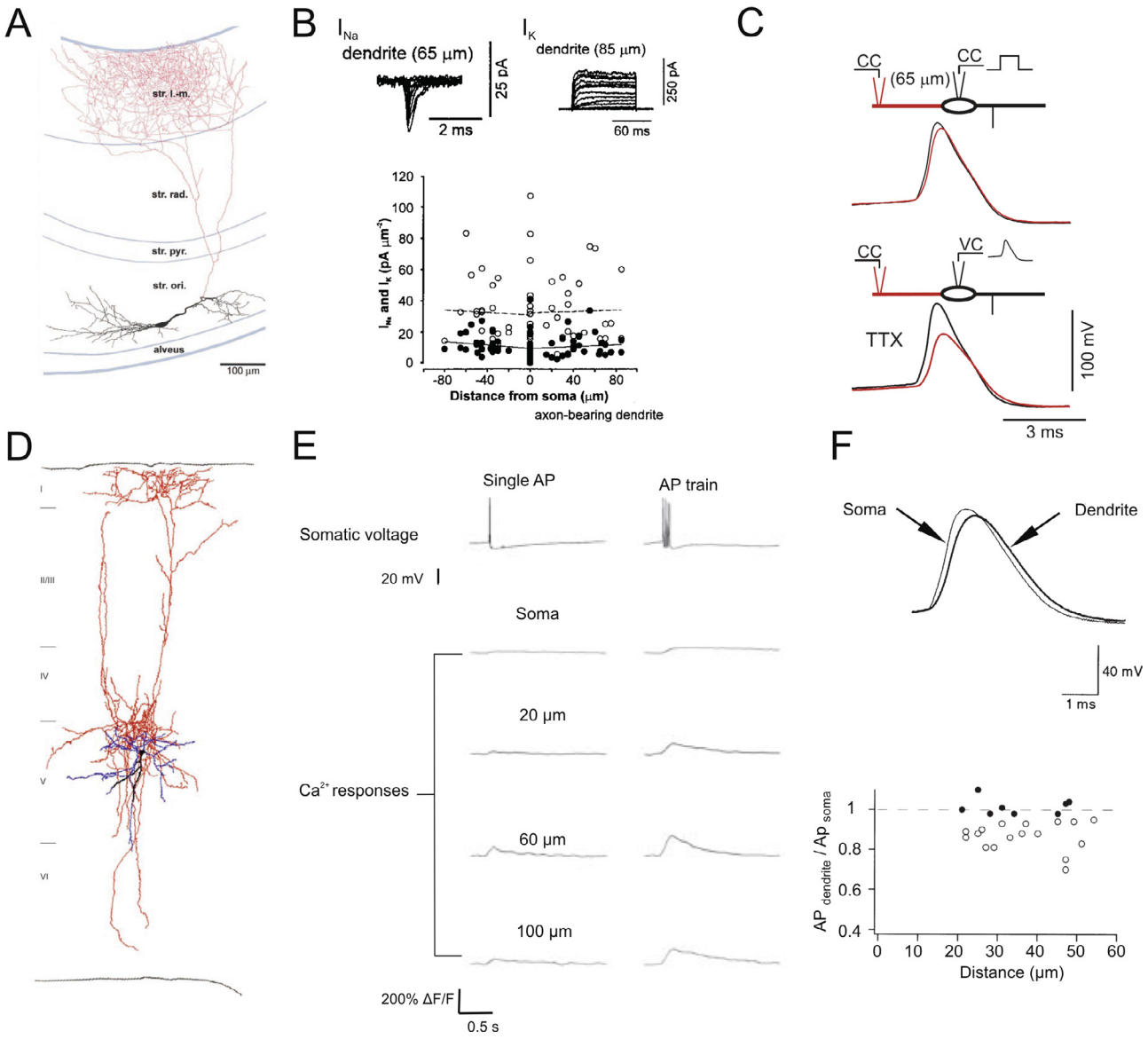

Fig. 2. Biophysical properties of SOM neuron dendrites. (A) Reconstruction of an O-LM cell in the hippocampal CA1 region (soma and dendrites in black; axon in red). CA1, cornu ammonis region 1; str. ori., stratum oriens; str. pyr., stratum pyramidale; str. rad., stratum radiatum; str.l.-m., stratum *lacunosum moleculare*. (B) Top; Patch-clamp recordings of Na^+ and K^+ currents in O-LM cell dendrites. Bottom, distribution of Na^+ (closed symbols and solid lines) and K^+ current (open symbols and dashed lines) densities in O-LM interneuron dendrites. (C) Top; Dual somato-dendritic current-clamp recording of an action potential evoked by a somatic current pulse in an O-LM neuron. Bottom; In the presence of TTX that blocks voltage-gated Na^+ channels, an action potential voltage waveform was imposed at the soma in voltage-clamp. Note the stronger attenuation of the backpropagating spike in the absence of functional Na^+ channels. (D) Reconstruction of a Martinotti cell in the neocortex. (E) Top; A single spike or a train of action potentials were evoked by a current pulse in current-clamp from the soma of a Martinotti cell. Bottom, corresponding Ca^{2+} responses in the soma and different dendritic locations. (F) Top; Simultaneous patch-clamp recordings of somatic- and backpropagting dendritic action potentials in a SOM neuron (putative Martinotti cell). Bottom, ratio of dendritic and somatic action potential amplitude plotted against the distance from the soma. Open symbols: the axon was closest to the somatic pipette. Closed symbols: the axon was the closest to the dendritic pipette. Data in (A–C) are adapted from Martina et al., 2000. Data in (D–E) are adapted from Goldberg et al., 2004. Data (F) are adapted from Kaiser et al., 2001.

cells is also reflected by their functional diversity. A recurring theme is that several types of 5HT3aR neurons selectively inhibit other inhibitory neurons thus providing disinhibition (Lee et al., 2013; Pi et al., 2013; Letzkus et al., 2015). The high density of 5HT3aR cells in the superficial layers of the cortex, and their high levels of nicotinic and serotonergic receptors, make these cells prime targets by which top-down modulation regulates networks (Lee et al., 2013; Fu et al., 2014). However, not all VIP cells target inhibitory neurons. There is a class of VIP-positive basket cells that provides peri-somatic inhibition to principal neurons (Acsády et al., 1996). The VIP-negative neurogliaform cells are then again unique in that they provide GABAergic volume transmission, a form of non-synaptic release, inhibiting the distal dendrites of principal neurons (Oláh et al., 2009). This type of inhibition is slow and presumably provides non-specific inhibition.

Compared to PV and SOM neurons we know even less about the dendritic properties of 5HT3aR cells. While the dendritic properties of at least one type of PV cell (Hu et al., 2010) and two types of SOM cells (Martina et al., 2000; Kaiser et al., 2001) have been examined with dendritic whole-cell recordings, there has not yet been a similar study of 5HT3aR neurons. One report, however, using two-photon Ca^{2+} imaging of putative 5HT3aR neurons can provide some insight (Goldberg et al., 2003 b). In response to somatically evoked action potentials, the authors recorded Ca^{2+} transients in the dendrites of neurons with the following characteristics reminiscent of VIP-positive cells: (1) A bipolar dendritic morphology with a narrow columnar axonal arbor that could reach layer 6, (2) An irregular firing frequency, (3) An elliptical soma, and finally, (4) Immunopositive for calretinin but not for PV or SOM (Goldberg et al., 2003 b). Since many of the used methods are indirect, the results must be interpreted with caution. Nevertheless, the upshot of these experiments (Goldberg et al., 2003 b) is that the authors find evidence for dendritic Na^+ channels, A-type K^+ channels and voltage-gated Ca^{2+} channels. Back-propagating action potentials attenuated rapidly, in part due to A-type K^+ channels that are rapidly activated and are therefore fast enough to reduce the amplitude of backpropagating spikes. The dendrites were endowed with Ca^{2+} channels to support backpropagating spike-evoked Ca^{2+} changes, and, at least proximal to the soma, dendritic Na^+ channels. In summary, the dendrites of 5HT3aR neurons are clearly the least understood, but we hope with the advent of the new classification scheme (Rudy et al., 2011), and with the aid of new mouse lines to selectively target these neurons (Taniguchi et al., 2011), we will soon know more about the function of their dendrites.

Synaptic integration in inhibitory neuron dendrites *in vivo*

In order to reveal the role of dendrites and dendritic conductances, we must know the electrical behavior of dendrites *in vivo*, ideally in behaving animals. Compared to pyramidal neuron dendrites, very little is known about inhibitory neuron dendrites due to their small diameter that prevents direct interrogation with electrodes, and due to the lack of sensitive Ca^{2+} indicators. Ca^{2+} imaging in inhibitory neurons requires more sensitive indicators because Ca^{2+} signals in inhibitory neurons are generally smaller compared to pyramidal cells due to their higher buffering capacity and narrow spike width (Lee et al., 2000; Goldberg et al., 2003 b). Recently, such sensitive genetically encoded Ca^{2+} indicators (GCaMP6) have become available and now allow studying inhibitory neuron dendrites *in vivo* using two-photon scanning fluorescence microscopy (Chen et al., 2013).

To the best of our knowledge, only one report so far has investigated the synaptic response properties of inhibitory neuron dendrites *in vivo* (Fig. 3) (Chen et al., 2013). Chen and colleagues used two-photon fluorescence microscope and sparse expression of GCaMP6s in inhibitory neurons of layer-2/3 in mouse visual cortex V1. They measured Ca^{2+} signals in PV and SOM dendrites in response to drifting gratings in anesthetized mice, to investigate how the dendrites contribute to orientation selectivity. Orientation and direction selectivity of neurons in response to moving visual stimuli of different orientations has been studied for decades but the underlying circuit mechanisms remain unclear. Pyramidal neurons in V1 are typically sharply tuned, and respond only to a narrow range of orientations. Why pyramidal neurons are sharply tuned is a matter of ongoing debate but the answer most likely lies in the tuning of their synaptic inputs (Priebe and Ferster, 2008).

An important role of inhibition is to sharpen the tuning of excitatory neurons in response to sensory stimuli. This is not only the case for vision but also for most other sensory modalities (Isaacson and Scanziani, 2011). While species-dependent, inhibitory neurons in V1 generally show broader orientation tuning compared to pyramidal cells. With the exception of a small subset of SOM interneurons, inhibitory neurons in mice are generally weakly tuned (Sohya et al., 2007; Kerlin et al., 2010; Ma et al., 2010; Hofer et al., 2011). Why is orientation tuning of inhibitory neurons broader than pyramidal neurons? The answer again may lie in how the dendrites of these cells sample synaptic input. While the output of inhibitory neurons is poorly tuned (Fig. 3B), Chen and colleagues showed elegantly using Ca^{2+} imaging that PV cell dendrites have pronounced orientation-tuned domains representing all possible orientations (Fig. 3C, D) (Chen et al., 2013). Nearby dendritic segments could even have very distinct orientation tuning (Fig. 3D). Such well-tuned domains could be seen in both PV and SOM neuronal dendrites. So apparently, PV neurons seem to be integrating synaptic inputs tuned to different orientations without a particular bias toward a specific orientation. Computer simulations also predict that efficient synaptic activation of PV neurons requires tens of coincident synaptic inputs that need to be distributed in the dendritic tree (Geiger et al., 1997). The need for such distributed and coincident input may prevent that input of a particular orientation is dominating. In further support, connectivity studies show that PV cells receive strong synaptic input from nearby pyramidal cells with diverse orientation tuning (Bock et al., 2011; Hofer et al., 2011). Interestingly, a small subset of PV neurons displays sharper orientation tuning (Runyan et al., 2010). These narrowly tuned PV neurons have shorter dendrites that branched closer to the soma (Runyan and Sur, 2013). Thus it appears that shorter PV dendrites enhance the bias toward a few sharply tuned inputs. While the dense, unbiased, sampling of pyramidal cell input appears to be sufficient to explain the poor tuning of PV cells, it is attractive to speculate whether the absence of regenerative dendritic mechanisms in PV dendrites (low density of Na^+ channels and NMDA channels) is also necessary for broad orientation tuning (Hu et al., 2010). Indeed, SOM neurons that have dendrites bestowed with Na^+ channels can have sharper orientation tuning (Ma et al., 2010), and dendritic spikes in pyramidal cells are thought to enhance orientation selectivity (Smith et al., 2013). In summary, the question is probably not whether, but how, the dendritic properties

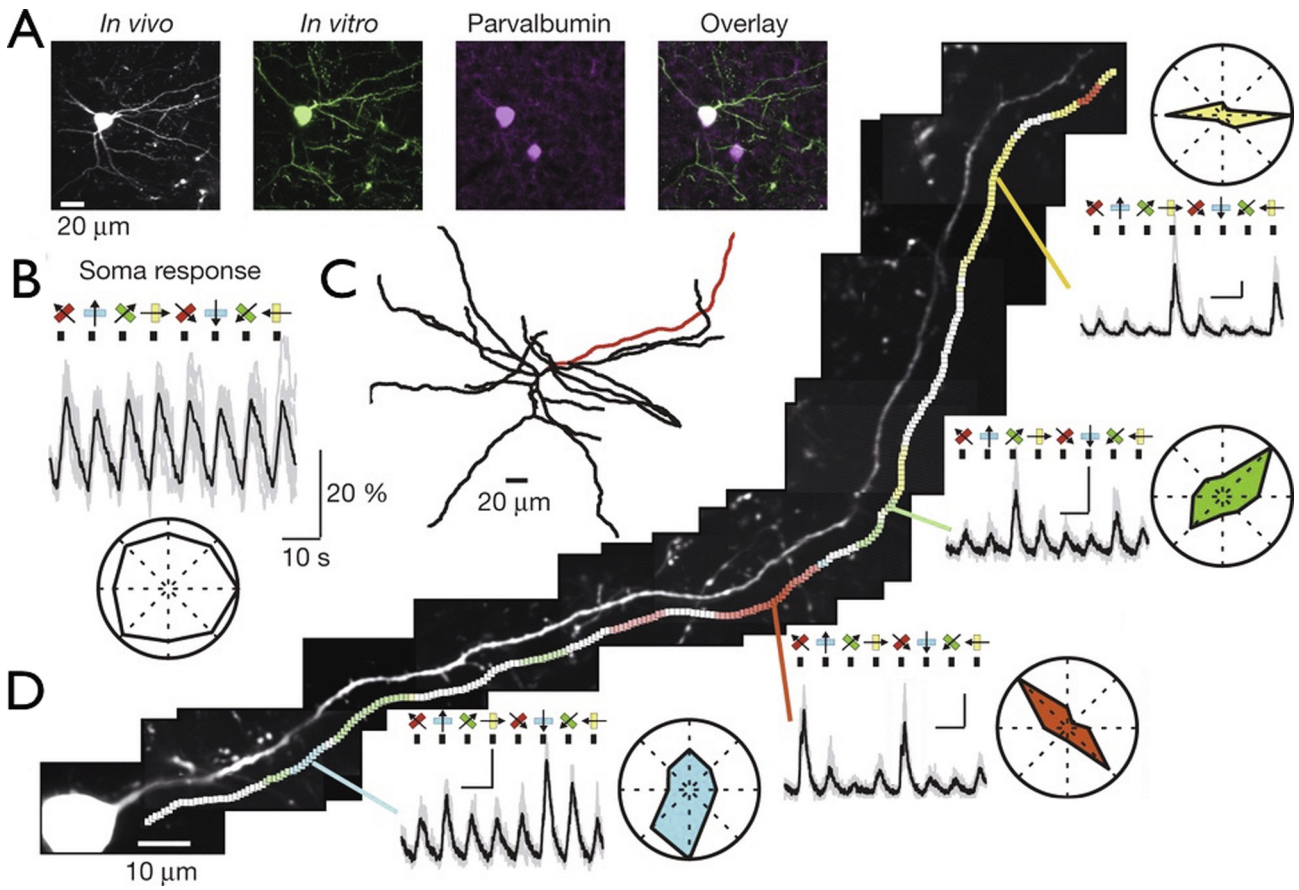

Fig. 3. Dendrites of layer 2/3 parvalbumin neurons in mouse visual cortex have orientation-tuned domains. (A) A neuron expressing GCaMP6s that was first imaged *in vivo* with two-photon microscopy, was subsequently immunolabeled ('*in vitro*') and identified as a PV neuron. (B) Somatic fluorescence responses to drifting gratings of eight different orientations indicates that somatic Ca^{2+} signals are not tuned to a specific orientation. A polar plot is shown at the bottom. (C) Morphological reconstruction of the cell. (D) A dendrite of the cell shown in C (red process) was imaged along its entire length. Several dendritic domains, indicated by colored segments, are tuned to different orientations. Polar plots, shown on the right, indicate clear orientation tuning. Modified from Chen et al. Nature (2014).

of inhibitory neurons contribute to their functional role in the network and in animal behavior, but this question remains entirely open.

CONCLUSIONS AND OUTLOOK

We have reviewed our current knowledge about cortical inhibitory neuron dendrites. While many gaps remain, accumulating evidence indicates that the biophysical properties of interneuron dendrites are different from those of pyramidal cells in several ways. Pyramidal neuron dendrites are capable of supralinear dendritic integration, initiating dendritic spikes, and supporting active backpropagation of action potentials (Spruston, 2008). While some types of inhibitory neurons show similar dendritic properties, for example O-LM neurons (Martina et al., 2000), it is clear that for example PV and possibly some types of 5HT3aR cells, rather show sublinear synaptic integration and strong attenuation of backpropagating spikes (Hu et al., 2010). We and others speculate that this spectrum of dendritic biophysical properties support specific functions in the network (Hu et al., 2014).

Are the dendritic biophysical properties of neurons belonging to the same class (PV, SOM, 5HT3aR) more similar than those of neurons belonging to different classes? In other words, can we use the dendritic biophysical properties as a functional signature to discriminate inhibitory neuron classes? There are some indications that this may be the case to some extend. It appears that PV-positive neurons in both hippocampus and neocortex, including basket cells (Hu et al., 2010) (Goldberg et al., 2003 b), axo-axonic cells (Hu et al., 2010), and possibly also bi-stratified cells (Camiré and Topolnik, 2014), all show strong attenuation of backpropagating action potentials, and lack dendritic regenerative potentials (Hu et al., 2010), due to the high K^+/Na^+ ratio of dendritic conductances (Table 1) (Hu et al., 2010). On the other hand, it appears that SOM-positive neurons such as O-LM cells in the hippocampus (Martina et al., 2000) and Martinotti cells (Goldberg et al., 2004) and bi-tufted cells (Kaiser et al., 2001) in the neocortex have in common that they support active backpropagation of action potentials (see also (Casale et al., 2015)), possibly due to the high density of dendritic Na^+ channels (Table 1) (Martina et al., 2000). There is anecdotal evidence that some 5HT3aR subtypes may also have poorly

backpropagating spikes (Goldberg et al., 2003 b), thus predicting either a low density of dendritic Na^+ channels, or a high ratio of K^+/Na^+ dendritic conductances. Interestingly, the repertoire of AMPA receptors, and the ratio of AMPA and NMDA receptors also appears to follow the borders of this simple classification scheme (Goldberg et al., 2003c; Matta et al., 2013). Thus the developmental origin of inhibitory neurons, which of course defines whether neurons express PV, SOM or 5HT3aR (Fishell and Rudy, 2011), may to some extend also define the dendritic biophysical properties.

There should however be caution for oversimplification. Clearly, each molecular class can be further subdivided into subtypes on the basis of morphological, additional molecular markers and biophysical properties (Tremblay et al., 2016). There is also increasing evidence that cells within a class are also functionally diverse. For example, *in vivo* recordings demonstrated that subtypes of hippocampal PV-expressing interneurons were differentially recruited during network oscillations, showing that different PV subtypes make distinct contributions to hippocampal network dynamics (Varga et al., 2014). A recent report also elegantly showed that SOM neurons in different layers of the neocortex are differently modulated during active whisking (Muñoz et al., 2017). Whether this functional diversity is due to differences in network connectivity, a consequence of different morphologies, different biophysical properties, or a combination of these factors, is a currently a key question in neuroscience. These questions are very timely because they can be answered due to the explosion of novel tools in cellular and systems neuroscience.

The emergence of Cre mouse lines and Cre-dependent viral strategies that allowed targeting of Ca^{2+} indicator proteins and opsins to PV, SOM, VIP, and 5HT3a neurons has already lead to a rapid expansion of insight into the function of inhibitory neurons (Taniguchi et al., 2011; Gerfen et al., 2013). The development of novel methods will accelerate this progress even more. Recent large-scale single-cell transcriptomics of cortical neurons are further refining the taxonomy of inhibitory neurons on the basis of the proteins they express (Zeisel et al., 2015; Tasic et al., 2016). This in turn will aid the development of intersectional strategies that allow precise targeting of ever more well-defined classes of inhibitory neurons (Fenno et al., 2014; He et al., 2016). But what are the tools that would advance insight into the dendritic properties of inhibitory neurons specifically? Currently, whole-cell patch-clamp recordings of dendrites are the gold standard for determining their electrical properties and for mapping the densities of ion channels. While two-photon-guided patch-clamp recordings greatly facilitate measurements from fine dendrites (Nevian et al., 2007), it is not suited for high-throughput characterization. For the same reason, this technique is most likely unsuited for the characterization of fine dendrites *in vivo*. We foresee that two-photon-targeted whole-cell recordings of inhibitory neurons *in vivo*, in conjunction with sensitive Ca^{2+} indicators, will reveal a substantial amount of new information. This technique is feasible and has revealed important insights into excitatory (Jia et al., 2010) and inhibitory (Chen et al., 2013) neuron dendrites. The interpretation of dendritic Ca^{2+} signals as a proxy for determining dendritic excitation is however not straightforward. In pyramidal neurons, dendritic calcium integration typically follows the same synaptic input–output relationship as dendritic voltage (Losonczy and Magee, 2006). In inhibitory neurons, however, things can be more complicated. A recent study using glutamate uncaging to mimic synaptic input demonstrated that inhibitory neurons can show both supralinear dendritic Ca^{2+} signals and sublinear integration of voltage (Tran-Van-Minh et al., 2016). Similarly, but by a different biophysical mechanism, hippocampal PV neurons can show supra-linear Ca^{2+} signals and linear voltage responses, apparently by facilitated release of Ca^{2+} from internal stores (Camiré and Topolnik, 2014). Moreover, nicotonic- and 5HT3aR receptors, a hallmark of 5HT3aR neurons (Porter et al., 1999; Férézou et al., 2002), are highly permeable to Ca^{2+}, possibly further complicating the interpretation of dendritic Ca^{2+} signals in these cells. Thus overall, it is clear that additional tools need to be developed for studying dendrites *in vivo*. Therefore, much focus is aimed at developing genetically encoded voltage sensors (Hochbaum et al., 2014). While current voltage indicators lack sufficient signal to be useful *in vivo*, we estimate that in the coming years a useful indicator will become available.

In summary, the cell type-dependent diversity of dendritic biophysical properties is yet another factor that makes progress in understanding the role of inhibition in the cortex difficult. We are confident, however, that the rapid development of new tools will accelerate novel insights into why the inhibitory neuron population is so diverse, and what computational functions these cells and their dendrites need to fulfill in the network.

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