Fast-spiking, Parvalbumin^{+} GABAergic Interneurons: From Cellular Design to Microcircuit Function

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Review summary (print version)

Background

Fast-spiking, parvalbumin-expressing interneurons (PV^+ interneurons) play a key role in several functions of the brain. They contribute to feedback and feedforward inhibition, and are critically involved in the generation of network oscillations. A hallmark property of these interneurons is speed. In essence, these cells convert an excitatory input signal into an inhibitory output signal within a millisecond. How these remarkable signaling properties are implemented at the molecular and cellular level has been unclear. Furthermore, how PV^+ interneurons shape complex network functions has remained an open question.

Advances

Recent work sheds light on the subcellular signaling properties of PV^+ interneurons. PV^+ cells show a high degree of polarity. The weakly excitable dendrites allow PV^+ interneurons to sample activity in the surrounding network, whereas the highly excitable axons enable analogue–digital conversion and fast propagation of the digital signal to a large number of target cells. Additionally, tight coupling of Ca^{2+} channels and release sensors at GABAergic output synapses increases the efficacy and speed of the inhibitory output.

Recent results also provide a better understanding of how PV^+ interneurons operate in neuronal networks. Intriguingly, PV^+ interneurons are not only involved in basic microcircuit functions, such as feedforward and feedback inhibition or gamma-frequency oscillations, but also in complex network operations, including expansion of dynamic activity range, pattern separation, modulation of place and grid field shapes, phase precession, and gain modulation of sensory responses. Thus, PV^+ interneurons are critically involved in advanced computations in microcircuits and neuronal networks.

Outlook

PV^+ interneurons may also play a key role in numerous brain diseases. These include epilepsy, but also complex psychiatric diseases, such as schizophrenia. Thus, PV^+ interneurons may become important therapeutic targets in the future. However, much needs to be learned about the basic function of these interneurons before clinical neuroscientists will have a chance to successfully use PV^+ interneurons for therapeutic purposes.

Full article (online)

Abstract

The success story of fast-spiking, parvalbumin-expressing (PV^+) GABAergic interneurons is amazing. In 1995, the properties of these interneurons were completely unknown. 20 years later, thanks to the massive use of subcellular patch-clamp techniques, simultaneous multiple-cell recording, optogenetics, *in vivo* measurements, and computational approaches, our knowledge about PV^+ interneurons became more extensive than for several types of pyramidal neurons (Box 1). These findings have implications beyond the "small world" of basic research on GABAergic cells. For example, the results provide a first proof of principle that neuroscientists might be able to close the gaps between molecular, cellular, network, and behavioral level, which represents one of the main challenges at the present time. Furthermore, the results may form the basis for using PV^+ interneurons as therapeutical targets for brain diseases in the future. However, much needs to be learned about the basic function of these interneurons before clinical neuroscientists will be able to use PV^+ interneurons for therapeutic purposes.

Introduction

In a reductionist's view of the brain, neuronal networks are comprised of two types of neurons: Glutamatergic principal neurons and GABAergic interneurons. Across all cortical circuits, glutamatergic neurons form approximately 80–90% of the neuronal population, whereas GABAergic neurons constitute the remaining 10–20% (*1–3*). Thus, in terms of neuron numbers, GABAergic cells only represent a minority. Nevertheless, these GABAergic neurons serve extremely important functions. Most remarkably, they control the activity level of principal neurons in the entire brain. If GABAergic interneuron function breaks down, excitation takes over, leading to seizures and failure of higher brain functions (*4*).

A hallmark of interneurons is their structural and functional diversity (Fig. 1A). 21 different classes of interneuron have been distinguished in the CA1 region of the hippocampus (*5*), and a probably even larger number of types can be dissected in the neocortex (*6*). These interneurons can be distinguished on the basis of three sets of criteria: (1) morphological properties, particularly the target selectivity of the axon, (2) expression of molecular markers, such as neuropeptides (somatostatin, cholecystokinin, vasoactive intestinal peptide, and neuropeptide-Y) and Ca^{2+}-binding proteins (parvalbumin, calretinin, and calbindin), and (3) functional characteristics, most importantly the action potential phenotype (*7*).

How can we systematically and quantitatively study the function of such an enormously diverse population of cells? One approach is to focus on "models", identifiable on the basis of standardized criteria. That is why around 1990 several laboratories started to work on one particular type of GABAergic interneuron: The fast-spiking, parvalbumin-expressing interneuron (PV^+ interneuron; Box 1). In the hippocampal CA1 region, 11% of neurons are GABAergic, and 24% of those are PV^+; thus, PV^+ interneurons represent only 2.6% of the total neuronal population (*8*). Thus, PV^+ interneurons appear to be somewhat exotic. However, numerous technical advantages outweigh this potential disadvantage (Fig. 1). The selective expression of the Ca^{2+}-binding protein PV allows unequivocal post-hoc labeling by highly specific antibodies (*9,10*; Fig. 1B). Both the short action potential duration and the fast-spiking action potential phenotype make it easy to identify these cells under experimental conditions (Fig. 1D). Finally, the high selectivity of the promoter of the PV gene can be used to genetically target these cells by enhanced green fluorescent protein (EGFP) and optogenetic methods (*11,12*; Fig. 1E and F). Finally, the specific

developmental trajectory of cortical PV^+ interneurons, which are born in the medial ganglionic eminence and depend on specific sets of transcription factors (i.e. Nkx2-1 and Lhx6), may be exploited for labeling (*13–15*).

In the present review, we will summarize our current knowledge about fast-spiking, PV^+ interneurons at the molecular, cellular and network level. We concentrate on basket cells (the classical PV^+ interneurons), but include information about axo-axonic cells or other types of GABAergic interneurons also expressing PV (*5*; Box 2). Furthermore, we focus on the hippocampus and the neocortex. For *in vitro* analysis of PV^+ interneurons, the advantages of the hippocampus are evident, especially the clearly defined layering and the availability of elaborate classification schemes (*5*). For *in vivo* analysis, the advantages of the neocortex become apparent, including the superficial localization of cells in the brain and the opportunity to easily define adequate behavioral stimuli.

Morphological properties and connectomics of PV^+ interneurons

How can we understand the function of PV^+ interneurons at the molecular, cellular and network level? Following Francis Crick's statement "If you want to understand function, study structure" (*16*), let us first take a look at the structure of PV^+ interneurons, particularly their input domains, the dendrites, and their output domains, the axons.

The morphological properties of the dendrites of PV^+ interneurons are remarkable in several ways (*1*). PV^+ interneurons have multiple dendrites which often cross layers (*17–20*). This will permit PV^+ interneurons to receive input from different afferent pathways, such as feedforward and feedback pathways. The cumulative dendritic length of single PV^+ interneurons ranges from 3.1 to 9 mm (*17–20*). Long dendrites allow PV^+ interneurons to sample input from a large population of principal cells. Finally, somata and dendrites of PV^+ interneurons are densely covered with synapses. PV^+ interneurons in the hippocampal CA3 or CA1 region have ~16000–34000 synapses, 94% of which are excitatory and 6% are inhibitory (*17,20*). A large proportion of inhibitory synapses is PV^+ (*17*), but inhibitory inputs from vasoactive intestinal peptide- and somatostatin-expressing interneurons are also present (*21,22*). Thus, PV^+ interneurons receive convergent excitatory input from principal neurons, and inhibitory input primarily from other PV^+ interneurons. Because the dendrites of PV^+ interneurons are largely aspiny, excitatory synapses are formed on dendritic shafts. This may facilitate the generation of fast excitatory postsynaptic potentials (EPSPs; *23*).

The morphological properties of the axon of PV^+ interneurons are also intriguing (*1*). In the classical anatomical literature, GABAergic interneurons were sometimes referred to as "short axon" cells. However, for many PV^+ interneurons, this seems entirely incorrect. The axon shows extensive arborization, and the cumulative axonal length of single PV^+ interneurons is 30–50 mm (33 mm in the dentate gyrus, *18*; 46 mm in the hippocampal CA1 region, *24*; 20 and 24 mm in the frontal cortex, *25*). A huge number of "en passant" terminals emerge from the extensive axonal arbor (10400 in CA1, *24*; 3200 and 3800 in the frontal cortex, *25*). Thus, PV^+ interneurons generate a massively divergent inhibitory output (*8*). Finally, PV^+ interneurons innervate postsynaptic target cells in the perisomatic domain. In "basket cells", the axon forms basket-like arrangements around principal cell somata and proximal dendrites. In "axo-axonic cells", the axon of the interneuron follows the axon initial segment of the principal cell, resulting in a chandelier-like configuration (*5*). These morphological characteristics suggest that PV^+ interneurons generate a particularly powerful inhibition, because they innervate a large number of target cells

near the site of action potential initiation. However, these properties also raise new questions. For example, one may wonder how reliable action potential propagation is achieved in the highly branching interneuron axon (*26*) and how the functions of signal propagation and transmitter release are integrated into a single structure.

To address these questions, we have to examine the function of PV^+ interneurons directly at the subcellular level with micrometer spatial and microsecond temporal resolution. Subcellular patch-clamp recording now allows researchers to obtain such measurements in both dendrites and axons of PV^+ interneurons.

The subcellular physiology of PV^+ interneurons: Dendrites

Direct dendritic recordings have provided a detailed quantitative picture of the electrical events in PV^+ interneuron dendrites (Fig. 2A and B). First, action potentials backpropagate into the dendrites in a highly decremental manner (*27*), confirming findings of previous Ca^{2+} imaging experiments (*28–31*; Fig. 2C). Similar results were obtained in both basket and axo-axonic cells (*27*). These properties differ from those of pyramidal neurons, where backpropagation is active (*32*). Second, dendritic spikes cannot be initiated, neither by dendritic current injection nor by synaptic stimulation (*27*), although a recent study suggested that dendritic spikes may be evoked by massive glutamate uncaging (*31*). Again, these properties differ from those of pyramidal neurons, where dendritic spikes are abundant (*33*). Third, the dendrites of PV^+ interneurons contain only a low density of voltage-gated Na^+ channels; Na^+ channels are almost absent at distances > 100 µm from the soma (*27*). Fourth, the dendrites of hippocampal PV^+ interneurons contain a high density of voltage-gated K^+ channels, consistent with the results of previous Ca^{2+} imaging experiments using K^+ channel blockers (*28*). The high dendritic K^+- to Na^+-channel ratio distinguishes PV^+ interneurons from pyramidal cells, and also from other interneuron subtypes (*32–35*). Finally, analysis of gating and pharmacological properties revealed that these channels are primarily of the Kv3-type, one of the four main subfamilies of voltage-gated K^+ channels (*7*). These channels show high activation threshold, fast activation, and fast deactivation (*7*).

Why should PV^+ interneurons express high-threshold K^+ channels in the dendrites if the amplitude of backpropagated action potentials is too small to activate them? As it turns out, dendritic Kv3 channels work synergistically with the small diameter of dendrites and the large amplitude and fast time course of the AMPA receptor-mediated postsynaptic conductance at excitatory input synapses (*23,36*,*37*). In the thin dendrites of PV^+ interneurons, AMPA receptor-mediated conductances generate local EPSPs with large peak amplitude (*18*), resulting in efficient activation of dendritic Kv3 channels (*7,27*; Fig. 2D). This has profound functional consequences. First, dendritic K^+ channel activation accelerates the decay time course of the EPSP, shortening the time period of temporal summation and promoting action potential initiation with high speed and temporal precision (*27,38*; Fig. 2E; Table 1). Second, K^+ channel activation conveys sublinear integration (*27*). This may allow PV^+ interneurons to accurately sample principal neuron activity over a wide range. Finally, K^+ channel activation makes PV^+ cells less sensitive to clustered excitatory input, which activates K^+ channels efficiently, but relatively more sensitive to distributed input, which activates these channels only minimally (*27*; Fig. 2E).

Dendrites of PV^+ interneurons in both the hippocampus and the neocortex are highly interconnected by gap junctions (*39–42*). Such a syncytial organization of dendritic trees will also affect synaptic integration. Gap junctions will lead to speeding of the EPSP time course, because excitatory charge can escape into adjacent dendrites. Furthermore, gap junctions may widen the spatial range of detection of

principal neuron activity, including input synapses that are unconnected to a given PV^+ interneuron, but connected to adjacent interneurons (*37*). Finally, gap junctions may boost the efficacy of distal inputs and increase the average action potential frequency following repetitive synaptic stimulation of distal synapses (*35*).

The subcellular physiology of PV^+ interneurons: Axons

Direct recordings also revealed several surprising properties of axons of hippocampal PV^+ interneurons (*43*; Fig. 3A and B). First, they showed that the action potential is initiated very proximally, ~20 µm from the soma (*43*; Fig. 3A). This is different from pyramidal neurons, where the initiation site is more remote, sometimes even beyond the axon initial segment (*44*). Second, APs propagate with high reliability; failures of action potential propagation occur only rarely. Third, the orthodromic action potential propagation velocity is ~1.5 m s^{-1} at near-physiological temperature, quite remarkable for a thin, largely unmyelinated axon (*43*). The propagation velocity is faster than that of principal neuron axons under comparable conditions (*45,46*). Fourth, PV^+ interneurons exhibit a unique Na^+ channel distribution: a stepwise density increase from the soma to the proximal axon, followed by a further gradual increase to the distal axon (*43,47*; Fig. 3B). In the distal axon, the Na^+ conductance density is ~600 pS μm^{-2}, comparable to values in invertebrate axons (*43*). Thus, PV^+ interneurons show a weakly excitable, "analogue" somatodendritic domain (with graded synaptic potentials) and a highly excitable, "digital" axonal domain (with all-or-none action potentials), separated by a steep transition zone. Assuming that the axon represents ~74% of the surface area (*18*), ~99% of the Na^+ channels would be located in the axon. Thus, the excitability mechanism of PV^+ cells is almost entirely axonal. Finally, the axon of PV^+ interneurons contains voltage-gated K^+ channels (*43*,*48;* H. Hu, unpublished observations).

Why should PV^+ interneurons express an excessively high density of Na^+ channels in the axon? The first guess was that the high density guarantees reliability of action potential propagation (*26*). However, experiments and simulations indicate that Na^+ channels are expressed at higher density values than the critical value required for reliability (*43*). The "supercritical" Na^+ channel density has two additional advantages. It increases the speed of action potential propagation, and it also increases the maximal action potential frequency during sustained somatic current injection (*43*). Thus, the high Na^+ channel density in the axon contributes to rapid signaling in PV^+ interneurons (Table 1). In relation to propagation speed, the high channel density compensates for the unfavorable morphological properties of interneuron axons (small segmental diameter, extensive branching, and high bouton density).

What is the molecular identity of Na^+ and K^+ channels in the axon of PV^+ interneurons? For voltage-gated Na^+ channels, $Na_V1.1$ and $Na_V1.6$ immunoreactivity is abundantly present in the axons (*49,50*). However, the contribution of other subunits cannot be excluded, because $Na_V1.2$, 1.4, and 1.7 mRNAs are also detectable in PV^+ interneurons (*51*). For voltage-gated K^+ channels, Kv3 subunits are heavily expressed in PV^+ interneurons, and Kv3 immunoreactivity has been localized to axons (*7,52*). Furthermore, the pharmacological and gating properties of axonal K^+ channels imply that they are primarily of the Kv3 subtype (*48;* H. Hu, unpublished observations). The high activation threshold and the fast deactivation of these channels may ensure fast action potential repolarization in the axon. Finally, Kv1 channels are present in the axon initial segment of hippocampal and neocortical PV^+ interneurons (*50,53,54*). The low activation threshold and the slower gating of these channels may define characteristic input-output conversion properties in PV^+ cells.

Long current pulses will activate these channels, suppressing the initiation of action potentials (*53*). In contrast, fast EPSPs will bypass Kv1 channel activation, leading to action potential initiation with short delay (*53*). Thus, Kv1 channels may implement a fast coincidence detection mechanism in PV^+ interneurons (Table 1). In addition, the profound inactivation of these channels may explain delayed spiking during long-lasting depolarizations (*53*).

From axons to presynaptic terminals: Fast GABA release

Multiple properties of dendrites and axons of PV^+ interneurons are specialized for rapid signaling. But how is the electrical signal in the axon converted into GABA release (*55*)? Several factors are important for this conversion, including the duration of the presynaptic action potential, the gating of the presynaptic Ca^{2+} channels, the coupling between Ca^{2+} channels and release sensors, and the Ca^{2+} binding and unbinding rates of the release sensor. Collectively, these factors will determine the "synaptic delay", the time interval between the action potential in the presynaptic terminal and the event of exocytosis.

Many of these factors in PV^+ interneuron output synapses are optimized for speed (Fig. 3C). First, direct recordings revealed that axonal action potentials are brief, comparable to those at the soma (*43*). Because presynaptic terminals are of the "en passant" type, this will directly translate into fast and synchronous transmitter release. Consistent with this hypothesis, broadening of the presynaptic action potential by K^+ channel blockers enhances both presynaptic Ca^{2+} transients and peak amplitudes of postsynaptic currents (*48*).

Second, whereas several types of synapses use mixtures of P/Q-, N-, and R-type Ca^{2+} channels for transmitter release (*56*), the output synapses of PV^+ cells in both the hippocampus and the neocortex exclusively rely on P/Q-type channels (*57–60*). As P/Q-type Ca^{2+} channels show the fastest gating among all Ca^{2+} channel subtypes (*56*), the specific usage of these channels will contribute to both the shortening of the synaptic delay and the increase in the temporal precision of transmitter release.

Third, another specific property of transmission is the tight ("nanodomain") coupling between Ca^{2+} channels and release sensors of exocytosis (*61,62*; Fig. 3C). Tight coupling increases the efficacy of release, shortens the synaptic delay, and increases the temporal precision of release (*61*). Furthermore, GABA release at presynaptic terminals of PV^+ interneurons is initiated by a small number of Ca^{2+} channels, probably only two or three per release site (*59*). The usage of a small number of Ca^{2+} channels could help avoiding the broadening of presynaptic action potentials or, in extreme cases, the generation of Ca^{2+} spikes in presynaptic terminals. Thus, the small number of Ca^{2+} channels per release site at PV^+ interneuron output synapses contributes to fast and temporally precise transmitter release.

Finally, a subset of PV^+ interneurons in the hippocampus and the neocortex uses synaptotagmin 2 (one out of the 15 members of the synaptotagmin family) as a release sensor for synaptic transmission; in contrast, principal neurons primarily rely on synaptotagmin 1 (*63–65*). Recent studies have even used synaptotagmin 2 immunolabeling to selectively visualize PV^+ boutons in the visual cortex (*66*). As synaptotagmin 2 has the fastest Ca^{2+}-binding kinetics throughout the synaptotagmin family (*67*), the expression of this synaptotagmin isoform may also contribute to rapid signaling. Direct measurement of Ca^{2+}-binding rates of different synaptotagmin isoforms will be needed to quantitatively test this hypothesis.

What are the effects of PV on GABA release at PV^+ interneuron output synapses? The EF-hand domains of PV bind both Ca^{2+} and Mg^{2+} ions (Fig. 3D). Thus, it is generally thought that Mg^{2+} must leave before Ca^{2+} can bind, conferring slow Ca^{2+} binding properties to this protein (*68*). How can such a Ca^{2+} buffer act in nanodomain coupling regimes? The high PV concentration may provide an answer to this question. If the PV concentration is at millimolar levels, as found in cerebellar basket cells (*10*), or if the PV concentration is upregulated during behavior (e.g. contextual fear conditioning or learning completion), as observed in the hippocampal PV^+ interneurons (*69*), the free "apo" form of PV may become functionally relevant (Fig. 3D). Under these conditions, PV may modulate transmitter release, for example, by acting as an anti-facilitation factor (*10*).

Role of PV^+ interneurons in microcircuits: Beyond simple inhibition

GABAergic interneurons are involved in both feedforward and feedback inhibition (*70–73*; Box 3). But what is the specific contribution of PV^+ cells, and what is the functional relevance of their fast signaling mechanisms? Experimental evidence indicates that PV^+ interneurons in the hippocampus are involved in feedforward inhibition (Fig. 4). In the hippocampal CA1 region, feedforward inhibition initiated by stimulation of Schaffer collaterals is primarily mediated by perisomatic inhibitory interneurons, because somatodendritic recordings from CA1 pyramidal neurons reveal a distance-dependent decline of inhibition (*72*). Furthermore, this inhibition is primarily mediated by fast-spiking PV^+ cells, because these interneurons fire early after stimulation, before pyramidal cells and regularly spiking interneurons (*74*; Fig. 4C).

Feedforward microcircuits incorporating PV^+ cells may have several functions beyond simple inhibition. For example, feedforward inhibition by PV^+ interneurons narrows the window for temporal summation of EPSPs and action potential initiation in principal neurons (*72*; Fig. 4D). Feedforward inhibition by PV^+ interneurons will expand the dynamic range of activity in large principal neuron ensembles (*74*; Fig. 4E). For both functions, the fast signaling of PV^+ interneurons is critically important. PV^+ interneuron-mediated inhibition has to be fast enough to ensure that a significant inhibitory conductance is generated before action potentials are initiated in principal neurons.

PV^+ interneurons are also involved in feedback (recurrent and lateral) inhibition (Fig. 5). First, reciprocal coupling between principal neurons and fast-spiking interneurons has been demonstrated in several circuits, including the hippocampus and the entorhinal cortex (*23,75*; Fig. 5B and C). Antidromic activation of hippocampal CA1 pyramidal neurons by alveus stimulation generates substantial inhibition after both single stimuli and high frequency trains (*73*; Fig. 5D). Early inhibition is primarily mediated by perisomatic inhibitory interneurons, whereas late inhibition during trains is primarily mediated by dendritic inhibitory interneurons, as shown by the different slope of the EPSP at somatic and dendritic recording sites (*73*; Fig. 5D). Quadruple recording in the entorhinal cortex also suggests a substantial contribution of PV^+ interneurons to both recurrent and lateral inhibition (*75*).

Feedback and lateral microcircuits involving PV^+ cells may have several functions beyond simple inhibition. Feedback inhibition implements a "winner takes all" mechanism (*76,77*; Fig. 5E): Once the principal cells with the strongest input fire, action potential initiation in the remaining cells is inhibited. This computation could be particularly important in the dentate gyrus, where it may contribute to sparsification of activity (*78*), pattern separation (*79*), and grid–to–place code conversion (*77,80*). Network models with recurrent inhibitory connectivity are under certain conditions

also able to generate grid cell response patterns (*75,81*; Fig. 5F). This may suggest that PV^+ interneurons contribute to the grid cell activity of stellate cells in the entorhinal cortex (but see *82*).

In the "winner takes all" feedback inhibitory microcircuit (*76,77*), it has been suggested that the cells that receive excitation within a certain percentage of the maximum excitation fire (independently of the distribution of excitation), and this percentage is determined by the ratio of the delay of disynaptic inhibition over the membrane time constant of the principal cells (*76*; Fig. 5E). Thus, the fast signaling properties of PV^+ interneurons, which define the delay of disynaptic inhibition, are critically important for the "winner takes all" mechanism.

It is often assumed that connectivity in feedforward or feedback inhibitory microcircuits is random and that the properties of inhibitory synaptic transmission are uniform (*83*). However, this may not be the case. PV^+ basket cells in the hippocampal CA1 region receive stronger excitatory input from superficial pyramidal neurons, but provide more powerful output to deep pyramidal neurons (*84*). Furthermore, inhibition at the output synapses of PV^+ interneurons in the dentate gyrus has distance-dependent properties, with stronger and faster inhibition at short distances and weaker and slower inhibition at long distances (*85*). Finally, inhibition at the output synapses on PV^+ interneurons is stronger in target cells with strong synaptic excitation and high activity levels (*86*). In summary, PV^+ interneurons are substantially more than simple "network stabilizers". They contribute to advanced computations in microcircuits and neuronal networks. Furthermore, they are not randomly and uniformly connected, but embedded in microcircuits according to specific rules.

Activity of PV^+ interneurons *in vivo*

A central question in neuroscience is how specific neuron types shape higher brain functions, up to the level of animal behavior. The unique experimental accessibility and the detailed knowledge about the cellular properties of PV^+ interneurons may give us a chance, for the first time, to rigorously address this question.

One way to approach the problem is to examine the activity of PV^+ interneurons *in vivo* in awake, behaving animals during ongoing network activity (Fig. 6A to C). The activity of PV^+ interneurons in the hippocampus substantially changes during network oscillations, such as theta (4–10 Hz), gamma (40–100 Hz), and ripple activity (140–200 Hz). In the absence of oscillatory activity, action potential frequency is low (6.5 Hz; *87*). During theta oscillations, action potential frequency markedly increases (21 Hz). During sharp wave ripples, the firing frequency increases by more than an order of magnitude, to 122 Hz (*87,88*; see *89* for similar *in vitro* data; Fig. 6A). The massive activation of PV^+ interneurons during sharp wave ripples (*87*) may be explained by the ability of these cells to efficiently respond to synchronous distributed input, which will be generated by pyramidal cell activity during sharp wave ripples (*90*). Furthermore, the high action potential frequency in PV^+ interneurons in this network state (*87*) demonstrates that PV^+ interneurons make use of their fast-spiking phenotype (*7*) under *in vivo* conditions.

An alternative way to approach the question is to examine the activity of PV^+ interneurons following adequate stimuli. In the hippocampus, a substantial proportion of neurons are place cells, so the location of the animal appears to be the adequate stimulus. Whereas pyramidal neurons show narrow place fields, PV^+ interneurons have much broader place fields (*91,92*; Fig. 6B). Similarly, whereas a large proportion of stellate cells in the entorhinal cortex are grid cells (*80*), PV^+ interneurons show substantially broader spatial tuning (*82*; but see *81*; Fig. 6B). In

the primary visual cortex, neurons are often sensitive to both orientation and contrast of the stimulus, for example when animals are exposed to drifting gratings. However, PV^+ interneurons exhibit broader orientation tuning and weaker contrast specificity than pyramidal neurons (*93–95*; but see *96*; Fig. 6C). In all these cases, the broad tuning of PV^+ interneurons may be explained by the convergent input from a large number of principal neurons with wide range of spatial or orientation preferences. Interestingly, the action potential frequency of PV^+ interneurons in both hippocampal and neocortical circuits increases with running (*88,97*). Thus, PV^+ interneurons may receive a velocity-modulated input that, for example, could be used for path integration.

Role of PV^+ interneurons in network function and animal behavior *in vivo*

A more direct approach to bridge the gap between cellular and network level is to interfere with the activity of PV^+ interneurons *in vivo*, and to examine the behavioral consequences in awake animals (Fig. 6D to F). In principle, optogenetics (e.g. channelrhodopsin, *11*; halorhodopsin or archaerhodopsin, *12*) or pharmacogenetics (e.g. pharmacologically selective effector molecules = PSEMs in combination with chimeric ligand-gated ion channels; *98*) now allow researchers to interfere with the function of PV^+ interneurons in either positive or negative direction.

Such experiments are beginning to provide insight into the function of PV^+ interneurons at both network and behavioral level. Optogenetic manipulation of PV^+ interneuron activity showed that they are necessary and sufficient for the generation of network oscillations in both hippocampus and neocortex. Stimulation of PV^+ cells at theta frequency induces theta spike resonance in CA1 pyramidal cells (*99*), and stimulation of PV^+ cells at gamma frequency leads to gamma oscillations in the local field potential in somatosensory cortex (*11–12*). Conversely, suppression of PV^+ cells reduces gamma oscillations (*12*). This confirms a major role of PV^+ interneurons in network oscillations, as previously inferred from *in vitro* data (*100*).

Experimental manipulation of PV^+ interneuron activity in the hippocampus demonstrated that PV^+ interneurons regulate both the precise shape of place fields and the phenomenon of phase precession in CA1 pyramidal neurons (*92*; Fig. 6D). As an animal moves from the periphery towards the center of a place field, the action potentials in pyramidal neurons shift to earlier phases of the theta cycle (*101*). When PV^+ interneurons are inhibited, the steepness of the phase–position relation becomes reduced (*92*; Fig. 6D). Thus, PV^+ interneurons regulate the precise timing of action potential initiation in a pyramidal neuron ensemble, probably making use of their unique fast signaling properties.

Manipulation of PV^+ interneuron activity revealed that PV^+ interneurons regulate the gain of sensory responses (*94,95,102*; Fig. 6E). In the primary visual cortex, activation of PV^+ interneurons increases the gain of orientation tuning curves in pyramidal neurons, whereas the width of these curves remains largely unchanged (*94,95*; but see *102*). Such a gain modulation would be consistent with an underlying feedback inhibition mechanism (*76*). Similarly, in the barrel cortex, activation of PV^+ interneurons changes the amplitude of sensory responses evoked by whisker stimulation (*11*). However, the changes are more complex in this system, since number of spikes, latency, and spike precision are affected (*11*).

Finally, PV^+ interneurons are involved in the regulation of plasticity and learning (*69,103–106;* Fig. 6F). PV^+ interneurons in the visual cortex are transiently inhibited after monocular deprivation, and this downregulation appears to be necessary to enable ocular dominance plasticity in the critical period (*103,106*). Furthermore, PV^+ interneurons in the auditory cortex are inhibited by aversive foot

shocks in an auditory fear conditioning paradigm, and this inhibition plays a critical role for associative fear learning (*104,105*; Fig. 6F). Additionally, stimulation of PV^+ interneurons in the prefrontal cortex accelerates extinction of reward seeking behavior (*107*). In summary, suppression of PV^+ interneurons (i.e. disinhibition of pyramidal neurons) is necessary for certain forms of learning, whereas activation of PV^+ cells may promote extinction. Recent results further suggest that not only PV^+ interneurons regulate learning, but also learning induces plastic changes in PV^+ interneurons (*69*). Thus, the involvement of PV^+ interneurons in learning is bidirectional.

Role of PV^+ interneurons in neurological and psychiatric diseases

Another major challenge in neuroscience is to understand how specific neuron types are involved in neurological or psychiatric diseases. In this case: What are the links between PV^+ interneurons and brain diseases? The problem is not to find links – the problem is that there are too many! In several neurological and psychiatric diseases, the function of PV^+ interneurons appears to be altered. These include epilepsy, schizophrenia, depression, autism, and Alzheimer's disease (*108*). The detailed knowledge about PV^+ interneurons at the molecular, cellular and network level now may help us to focus on the most significant relations, where the disease gene is selectively expressed in PV^+ cells and the phenotype can be replicated by restricted disease gene expression in PV^+ interneurons.

One recently identified link leads from the axonal $Na_V1.1$ channel in PV^+ interneurons to Dravet's syndrome (severe myoclonic epilepsy of the infancy; SMEI) and GEFS+ (generalized epilepsy with febrile seizures plus) (*109*). Truncation mutations in the $Na_V1.1$ / SCN1A gene have been identified in SMEI patients, and mouse models with general or PV^+ interneuron-selective deletion of the SCN1A gene replicate the disease phenotype (*110–113*). Thus, haploinsufficiency of the SCN1A gene in PV^+ interneurons appears to be the cause of the disease. As $Na_V1.1$ mRNA is highly expressed in PV^+ interneurons (*51*), and $Na_V1.1$ immunoreactivity is primarily present in the axons of these cells (*49*), both fast-spiking action potential phenotype and fast signal propagation in the axon will be affected. Furthermore, missense mutations in the $Na_V1.1$ / SCN1A gene have been identified in GEFS+ patients. In one of the most common mutations, the Na^+ channel inactivation curve is left-shifted, which will reduce the number of available Na^+ channels (*114*). Thus, we increasingly understand the relations between the fast signaling properties of PV^+ interneurons and a neurological disease phenotype.

Another link leads from the receptor tyrosine kinase ErbB4 (epidermal growth factor receptor 4), a protein selectively expressed in PV^+ interneurons (basket cells and axo-axonic cells) of several brain regions (*115*), to schizophrenia (*116*). Mutations in both the ErbB4 gene and the gene of neuregulin 1, the putative ErbB4 ligand, are frequently found in schizophrenic patients. Furthermore, mouse models with general or PV^+ interneuron-specific genetic elimination of ErbB4 replicate aspects of the disease phenotype (*117*). However, even in such a clearly defined case, the underlying mechanisms are highly complex. Genetic elimination ErbB4 impairs both the excitatory synaptic input (*115, 119*; see *118*) and the inhibitory synaptic output of PV^+ interneurons (*115,119*). Consistent with the hypothesis of deficient PV^+ interneuron excitation, ErbB4 immunoreactivity is located in postsynaptic densities of glutamatergic input synapses on dendrites of PV^+ interneurons (e.g. *87,115*). Finally, neuregulin 1 application impairs the fast-spiking action potential phenotype by regulating Na^+ and Kv1 K^+ channels (*120,121*). Thus,

we are beginning to understand the relations between the fast signaling properties of PV^+ interneurons and the extremely complex phenotype of a psychiatric disease.

Figure legends

Fig. 1. The PV^+ interneuron: An interneuron subtype with salient properties and unique experimental identifiability.

(**A**) The placement of PV^+ interneurons in interneuron diversity schemes (*122*). Left, scheme showing a subset of the 21 types of GABAergic interneurons currently known in the hippocampal CA1 region. PV^+ axo-axonic cells and basket cells are located on the left side. Right, PV^+ basket cell (the probably most abundant type of PV^+ interneuron). Soma and dendrites are shown in orange, axons are depicted in yellow.

(**B**) PV^+ basket cell in the CA1 region of the hippocampus recorded in a freely moving rat. Upper left inset, movement trajectory of the animal. Upper right inset, PV immunoreactivity; lower right inset, electron micrograph of output synapses. Data from Lapray et al., 2012 (*87*).

(**C**) Basket cell in layer 5 of motor cortex. Data from Thomson et al., 1996 (*123*). Color code in B and C: Soma and dendrites are shown in black; axon is depicted in red.

(**D**) Fast-spiking action potential phenotype of a putative PV^+ interneuron in the neocortex *in vitro*. Long somatic current pulses evoked a high-frequency train of action potentials in the intracellularly recorded neuron. Data from McCormick et al., 1985 (*124*).

(**E**) Genetic fluorescent protein labeling of PV^+ interneurons, using mice expressing Cre recombinase under the control of the PV promoter. Left, mCherry labeling after adenoassociated virus infection; center, PV immunoreactivity; right, overlay. Inset on top shows targeted PV gene. Data from Hippenmeyer et al., 2005 (*125*) and J.G., unpublished.

(**F**) Functional labeling of PV^+ interneurons, using mice expressing Cre recombinase and channelrhodopsin or halorhodopsin under the control of the PV promoter *in vivo*. Left, identification of unit activity in PV^+ interneurons expressing channelrhodopsin in an awake, freely moving mouse recorded with “optrodes”. Data from Kvitsiani et al., 2013 (*126*). Right, activity of a PV^+ interneuron expressing halorhodopsin in an awake mouse moving on a linear track. Note that the light pulse completely abolishes action potential initiation in the PV^+ interneuron (top), but increases the action potential frequency in a simultaneously recorded pyramidal neuron (bottom). Data from Royer et al., 2012 (*92*). CA1, cornu ammonis region 1; MC, motor cortex; CA3, cornu ammonis region 3; PFC, prefrontal cortex.

Fig. 2. The “in” and “out” of PV^+ interneurons: dendrites.

(**A**) Direct patch-clamp recording from subcellular processes of PV^+ interneurons in the dentate gyrus, using confocally targeted patch-clamp recording in a brain slice *in vitro*. The cell was first loaded with fluorescent dye (Alexa Fluor 488) via a somatic recording pipette. A dendritic recording was subsequently obtained on the distal dendrite.

(**B**) Decremental action potential backpropagation into dendrites. Peak amplitude of the action potential at the dendrite was plotted against distance, with recording sites at basal dendrites (negative distance) and apical dendrites (positive distance). Inset on top shows action potentials at the soma (black) and dendrite (red), with the current pulse applied to the soma.

(**C**) Dendritic Ca^{2+} transients in PV^+ interneurons in the hippocampal CA1 region *in vitro*. Top panels, dendritic Ca^{2+} transients at 10 and 50 µm distance from the soma. Bottom graph, decline of amplitude of dendritic Ca^{2+} transients as a function of distance from the soma. Data from Camiré and Topolnik, 2014 (*30*).

(**D**) Dendritic Kv3-type K^+ channels in a PV^+ interneuron model are locally activated by synaptic input (apical dendrite, arrow). Pseudocolor code indicates the activated K^+ conductance.
(**E**) Dendritic Kv3-type K^+ channels in PV^+ interneurons accelerate EPSP time course (top) and enhance the ability of the neuron to detect temporally coincident, but spatially distributed inputs (bottom). Blue, passive dendrites; black, K^+ channels in synapse-containing dendrites. Data in A,B and D, E from Hu et al., 2010 (*27*).
(**F**) Schematic illustration of the different rules of dendritic integration in PV^+ interneurons (left) and pyramidal neurons (right). In PV^+ interneurons, the high K^+- to Na^+-channel ratio in dendrites confers linear or sublinear integration (Σ = linear summation mechanism). In pyramidal neurons, the high Na^+- to K^+-channel ratio in dendrites enriches the repertoire of single-neuron computations ($\int$= sigmoidal threshold mechanism; see *127*). DG, dentate gyrus; CA1, cornu ammonis region 1.

Fig. 3. The "in" and "out" of PV^+ interneurons: axons and presynaptic terminals.
(**A**) Proximal initiation of action potentials. Latency between action potentials in axon and soma was plotted against distance, with negative values indicating "axon first" and positive values representing "soma first" behavior. Note the sharp initiation site in the axon ~20 µm from the soma. Top, action potentials at the soma (black) and axon (blue) in two different soma–axon recordings with different axonal distance.
(**B**) Voltage-gated Na^+ channel spatial distribution profile. Channel density measured in the outside-out patch configuration plotted against distance, with negative values indicating dendritic and positive values indicating axonal location. Note the stepwise increase of Na^+ channel density from the soma to the proximal axon, followed by a gradual increase to the distal axon. Data in A, B from Hu and Jonas, 2014 (*43*).
(**C**) Tight coupling between Ca^{2+} channels and release sensors at the output synapses of PV^+ interneurons. Top left, chemical structure of the fast Ca^{2+} chelator BAPTA and the slow Ca^{2+} chelator EGTA used to probe the coupling configuration. Top right, concentration dependence of the effects of the two chelators on GABA release. Curves represent linearized models fit to the experimental data, revealing a coupling distance of 12 nm. Bottom left, dependence of simulated time course of release on coupling distance in a source–sensor model. Bottom right, simulated synaptic delay and half-duration of the time course of release as a function of coupling distance. Data from Bucurenciu et al., 2008 (*61*).
(**D**) Action of the endogenous Ca^{2+} binding protein PV on transmitter release. Top left, secondary structure of PV, with the spheres indicating bound Ca^{2+} ions. Data from Bottoms et al., 2004 (128). Top right, activity-dependent regulation of PV concentration in interneurons of the hippocampal CA3 region. EE, enriched environment; cFC, contextual fear conditioning. Data from Donato et al., 2013 (*69*). Bottom, estimation of absolute PV concentration in the soma of different types of inhibitory interneurons by calibrated immunocytochemistry. Data from Eggermann and Jonas, 2012 (*10*). DG, dentate gyrus.

Fig. 4. The role of PV^+ interneurons in feedforward inhibitory microcircuits.
(**A**) Schematic illustration of the feedforward inhibitory microcircuit.
(**B**) Time course of disynaptic feedforward inhibition in the hippocampal CA1 region. Traces indicate control signal (monosynaptic EPSC and disynaptic IPSC), pharmacologically isolated EPSC, and analogue subtraction. Note the short latency of the disynaptic IPSCs (inset). Data from Pouille and Scanziani, 2001 (*72*).

(**C**) Activation of pyramidal neurons (top), fast-spiking interneurons (center), and regularly spiking interneurons (bottom) during feedforward inhibition. Upper traces show local field potentials, lower traces illustrate loose-patch recordings. Right panels show corresponding morphological properties of the recorded cells. Inset on top schematically illustrates stimulation procedure. Data from Pouille et al., 2009 (*74*).
(**D**) Feedforward inhibition shortens the coincidence detection window in CA1 pyramidal neurons. Left traces indicate action potentials recorded in the cell-attached configuration following stimulation of two Schaffer collateral inputs at different time intervals under control conditions (top) and after block of inhibition (bottom). Right, spike probability after stimulation of two excitatory inputs with time interval Δt in the presence of inhibition (gray bars) and after block of inhibition (white bars). Arrows indicate time points of first and second stimulus. Data from Pouille and Scanziani, 2001 (*72*).
(**E**) Feedforward inhibition expands the dynamic range of principal neuron population activity. Left, plot of proportion of recruited CA1 pyramidal cells against synaptic input strength. Filled data points and black curves show the results for the entire population of CA1 pyramidal neurons, gray curves show the results for individual cells. Right, comparison of population input–output curves in the presence of inhibition (solid circles) and after block of inhibition (open circles). Although PV^+ interneurons are likely to play an important role, other interneuron types may also be involved. Data from Pouille et al., 2009 (*74*). CA1, cornu ammonis region 1.

Fig. 5. The role of PV^+ interneurons in feedback inhibitory microcircuits.
(**A**) Schematic illustration of the feedback inhibitory microcircuit. Top, recurrent inhibition; bottom, lateral inhibition.
(**B**) Feedback inhibition in the dentate gyrus. Reciprocal coupling between a fast-spiking (putative PV^+) interneuron and a granule cell. Neurons were filled with biocytin during recording and subsequently reconstructed. Black, soma and dendrites of PV^+ interneuron; blue, axon of PV^+ interneuron; green, soma and dendrites of granule cell; red, granule cell axon. Red dots, putative excitatory synapses on interneurons; green dots, inhibitory synapses on granule cells. Data from Geiger et al., 1997 (*23*).
(**C**) Feedback inhibition in the entorhinal cortex. Simultaneous recording from one fast-spiking (putative PV^+) interneuron and three layer 2 stellate cells. Left column, action potential phenotype of the four neurons. Center column, action potentials in a stellate cell evoked EPSPs in the putative PV^+ interneuron. Right column, action potentials in the interneuron evoked IPSPs in all three stellate cells. Top, schematic illustration of connectivity (circle, putative PV^+ interneuron; hexagons, stellate cells). Data from Couey et al., 2013 (*75*).
(**D**) Recurrent inhibition in the hippocampal CA1 region. Top, schematic illustration of the stimulation procedure. Bottom, traces illustrating IPSPs simultaneously recorded in the soma and the dendrite of a CA1 pyramidal neuron. The slope of rise is higher at the somatic than at the dendritic recording site (inset), indicating that inhibition is generated perisomatically. Data from Pouille and Scanziani, 2004 (*73*).
(**E**) Feedback inhibition implements a “winner takes all” mechanism. Top, scheme of the neuronal network with external input and feedback inhibition. Bottom, plot of the proportion of firing cells (k%) and the proportion of cells that receive excitation within E% of the maximal excitation (E%max). Line styles indicate different distributions of inputs. Note that E%max is relatively independent of the stimulus current. Also note that E%max is d / τ_m, where d is the delay of disynaptic inhibition and τ_m is the membrane time constant of the pyramidal cell. Thus, fast signaling in inhibitory

interneurons is critically important for the computational properties of the “winner takes all” mechanism. Data from de Almeida et al., 2009a (*76*).
(**F**) A continuous attractor network model based on feedback inhibition may produce grid cell activity patterns in excitatory neurons. Top, distribution of E–I and I–E synaptic conductances in the model. Bottom, pseudocolor representation of simulated activity of E cells in two-dimensional space. Cells receive background activation, theta-modulated input, velocity-modulated input, and place-cell input from the hippocampus. Furthermore, synaptic output is shifted according to the direction of preferred movement. Data from Pastoll et al., 2013 (*81*). DG, dentate gyrus; EC, entorhinal cortex; CA1, cornu ammonis region 1.

Fig. 6. The role of PV^+ interneurons in complex animal behavior.
(**A**) Activity of PV^+ interneurons in the hippocampal CA1 region of freely moving rats. Top, firing of a PV^+ interneuron during sharp wave ripples (SWR). Upper trace, local field potential (filtered 130–230 Hz); lower trace, unit activity from a PV^+ interneuron. Bottom, summary bar graph indicating the mean action potential frequency (bottom). Note that the action potential frequency of PV^+ interneurons is > 100 Hz during SWRs. Data from Lapray et al., 2012 (*87*).
(**B**) Spatial firing of PV^+ interneurons and principal neurons. Top, place cell firing of hippocampal neurons; bottom, grid cell firing of entorhinal cortex neurons. Warm colors indicate high action potential frequency. Note that putative PV^+ interneurons (PV^+ INs) have broader spatial fields than principal neurons (PNs). Data from Wilson and McNaughton, 1993 and Buetfering et al., 2014 (*82,91*).
(**C**) Orientation selectivity (left) and contrast sensitivity (right) of layer 2 / 3 pyramidal neurons in the primary visual cortex. Top, PV^+ interneuron; bottom, principal neuron. Note the broad orientation specificity and shallow contrast sensitivity of PV^+ interneurons in comparison to pyramidal neurons. Data from Atallah et al., 2012 (*95*).
(**D**) PV^+ interneuron activity regulates place field shape and phase precession in headfixed mice running on a treadmill belt. Top, spike frequency of CA1 pyramidal neurons versus location. Bottom, theta phase of action potentials versus location. Blue, control data; red, data after light pulses, leading to halorhodopsin-mediated inhibition of PV^+ interneurons. Data from Royer et al., 2012 (*92*).
(**E**) PV^+ interneuron activity regulates the gain of orientation-selective visual responses. Tuning curves of pyramidal neuron activity in the primary visual cortex during a visual stimulus (drifting grating). Black curve and points, control conditions; red curve and points, after activation of PV^+ interneurons with channelrhodopsin; green curves and points, after suppression of PV^+ interneurons with archaerhodopsin. Data from Atallah et al., 2012 (*95*).
(**F**) Role of PV^+ interneurons in associative auditory fear conditioning. Left, top: activity of PV^+ interneuron in the auditory cortex during unconditional stimuli (foot shocks; cell-attached recording). Left, bottom: Summary of activity changes of PV^+ interneurons during foot shocks (z score). Right, behavioral freezing of the animal in baseline conditions and in the presence of the conditioned stimulus (CS^+; tone). Black, sham control; blue, with optogenetic stimulation of PV^+ interneurons; red, after reconditioning without optogenetic stimulation. Data from Letzkus et al., 2011 (*104*). CA1, cornu ammonis region 1; EC, entorhinal cortex; V1, primary visual cortex; AC, auditory cortex.

Table 1. Fast signaling properties of PV^+ interneurons.

Property	Functional consequence	Molecular mechanism	Reference
Fast EPSCs	Fast EPSP time course; coincidence detection	GluA1 and GluA4 AMPA receptor subunits	Geiger et al., 1997; Galaretta and Hestrin, 2001 (*23,37*)
Fast IPSCs	High-frequency network oscillations	GABRA1 $GABA_A$ receptor subunits	Bartos et al., 2001; 2002; Galaretta and Hestrin, 2002 (*129,130)*
Dendritic K^+ channels (high activation threshold, fast deactivation)	Sublinear summation; sensitivity to distributed inputs	Kv3	Goldberg et al., 2003; Hu et al., 2010 (*27,28*)
Perisomatic K^+ channels (high activation threshold, fast deactivation)	Short action potentials; fast-spiking AP phenotype	Kv3	Martina et al., 1998; Rudy and McBain, 2001 (*7,131*)
D-type K^+ channels in axon initial segment	coincidence detection; delayed spiking during long current pulses	Kv1	Goldberg et al., 2008; Lorincz and Nusser, 2008; Campanac et al., 2013 (*50,53,54*)
Supercritical Na^+ channel density in axon	Fast axonal action potential propagation; fast-spiking AP phenotype	$Na_V1.1$ $Na_V1.6$	Hu and Jonas, 2014; Ogiwara et al., 2007; Lorincz and Nusser, 2008 (*43,49,50*)
Fast presynaptic Ca^{2+} channels	Speed and temporal precision of GABA release	Cav2.1, P/Q-type Ca^{2+} channel	Hefft and Jonas, 2005; Zaitsev et al., 2007; Bucurenciu et al., 2010; Rossignol et al., 2013 (*57–60)*
Tight coupling between presynaptic Ca^{2+} channels and release sensors	Speed and temporal precision of synaptic transmission	Unknown	Hefft and Jonas, 2005; Bucurenciu et al., 2008 (*57,59*)
Fast release sensors	Speed and temporal precision of synaptic transmission	Synaptotagmin 2	Pang et al., 2006; Kerr et al., 2008; Sommeijer and Levelt, 2012; Xu et al., 2007 (*63,64,66,67*)

Box 1: The steep scientific career of PV^+ interneurons.
1986: Celio (*9*) suggests that PV is expressed in the majority of GABAergic neurons in the cortex.

1987: Kawaguchi et al. (*132*) suggest that PV is selectively expressed in fast-spiking interneurons.

1995: Geiger et al. (*36*) demonstrate that fast-spiking, PV^+ interneurons express AMPA-type glutamate receptors with high Ca^{2+} permeability and fast gating, caused by a low relative abundance of GluA2 subunit mRNA.

1996: Du et al. (*133*) demonstrate that Kv3 K^+ channel subunits are selectively expressed in PV^+ cells, providing the first suggestion of a molecular mechanism underlying the fast-spiking action potential phenotype.

1997: Geiger et al. (*23*) show that fast-spiking PV^+ interneurons in the dentate gyrus receive fast excitatory synaptic inputs.

2001: Pouille and Scanziani (*72*) demonstrate that feedforward inhibition, presumably provided by PV^+ interneurons, shortens the coincidence detection window in pyramidal neurons.

2005: Hippenmeyer et al. (*125*) generate a PV-Cre mouse line that specifically expresses Cre recombinase in PV^+ interneurons. This opened the door for both selective labeling and manipulation.

2009: Cardin et al. and Sohal et al. (*11,12*) show that rhythmic optogenetic stimulation of PV^+ interneurons results in the generation of gamma oscillations, whereas inhibition of PV^+ interneurons reduces gamma power.

2010: H. Hu et al. (*27*) provide the first recordings from subcellular processes of PV^+ interneurons (dendrites, and later axons). This now results in a complete mapping of the functional properties of these cells along the dendrite-soma-axon axis.

2012 Lee et al., Wilson et al., and Atallah et al. (*84,94,95*) show that PV^+ interneurons control gain of sensory responses. This is probably the first demonstration that a specific aspect of signal processing in neuronal networks can be attributed to a distinct cell type.

June 2014: A Pubmed search for “parvalbumin interneuron” returns 1644 hits, with many recent papers published in Science and Nature.

Box 2: The several caveats of PV^+ interneuron identification.
How can we identify the fast-spiking, PV-expressing “basket cell”? Ideally, for rigorous interneuron identification, one would like to see complete morphological visualization, expression analysis for the most important interneuron markers, and functional characterization. In practice, identification often relies on a subset of

parameters. In the past, identification was often based on the action potential phenotype (*124*; “fast spiking”; action potential frequency > 50 Hz at 22° and > 150 Hz at 34°) and the morphology of the axon (“basket cells”; ~90% of collaterals in the cell body layer; *5*). However, one has to keep in mind that cholecystokinin- and vasoactive intestinal peptide-expressing basket cells have maximal action potential frequencies that are less than a factor of two lower than those of PV^+ neurons (*57*). More recently, identification increasingly exploited PV expression, e.g. in optogenetic experiments (*11,12*). However, one has to be aware that PV is expressed not only in basket cells, but also in a subset of axo-axonic cells, bistratified cells, and even in oriens-alveus–lacunosum-moleculare (OLM) interneurons (*5*). Furthermore, one needs to consider regional differences. In the prefrontal cortex, only a subset of axo-axonic cells may express PV (*14*), and in the dentate gyrus, analogues of bistratified cells may not be present. Finally, PV expression levels will matter, since OLM interneurons express PV at lower concentrations than basket or axo-axonic cells (*10*). More work is needed to elucidate the functional differences between PV^+ cell types, particularly basket versus axo-axonic cells. This distinction is particularly important, since basket cells have inhibitory effects on their postsynaptic target cells, whereas axo-axonic cells may be excitatory (*135*).

Box 3: Feedforward and feedback microcircuits.

In feedforward inhibition, afferent glutamatergic axons activate principal cells and interneurons in parallel (Fig. 4A). In feedback (recurrent and lateral) inhibition, afferent glutamatergic axons activate principal cells, which in turn activate interneurons in series (Fig. 5A).

Feedback inhibition must be further subdivided into recurrent and lateral inhibition. However, the distinction between these two forms often remains fuzzy. Multiple cell recording provides an elegant way to quantitatively distinguish the two forms. Recurrent inhibition in a network can be defined as the proportion of principal cells that provide excitation to and receive inhibition from a given PV^+ interneuron, whereas lateral inhibition is the proportion of principal cells that do not provide excitation to, but receive inhibition from a given PV^+ interneuron (*75*; Fig. 5C).

The speed of both feedforward and feedback inhibition is impressive; the latency of disynaptic inhibition under physiological conditions is only 2 ms or less (*71,72*). This high speed may be unexpected, since inhibition is comprised of several steps (IN excitation via PN-IN synapses → propagation of EPSPs to the soma → action potential initiation in the axon initial segment → action potential propagation into the IN axon → GABA release → PN inhibition via GABAergic output synapses). The fast signaling properties of PV^+ interneurons (Table 1) play a key role in minimizing the delay.

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