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Review

Inhibitory Interneurons Regulate Temporal Precision and Correlations in Cortical Circuits

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GABAergic interneurons, which are highly diverse, have long been thought to contribute to the timing of neural activity as well as to the generation and shaping of brain rhythms. GABAergic activity is crucial not only for entrainment of oscillatory activity across a neural population, but also for precise regulation of the timing of action potentials and the suppression of slow-timescale correlations. The diversity of inhibition provides the potential for flexible regulation of patterned activity, but also poses a challenge to identifying the elements of excitatory–inhibitory interactions underlying network engagement. This review highlights the key roles of inhibitory interneurons in spike correlations and brain rhythms, describes several scales on which GABAergic inhibition regulates timing in neural networks, and identifies potential consequences of inhibitory dysfunction.

Highlights

The intrinsic and synaptic properties of GABAergic interneurons shape their impact on temporal patterns in the local circuit.

Synaptic inhibition enhances short-timescale correlations in spiking, such as spike synchrony, but suppresses long-timescale correlations, such as noise correlations.

Different inhibitory interneuron populations, including parvalbumin and somatostatin cells, may engage distinct rhythms in the cortex.

The emergence of circuit timing characteristics is shaped on the developmental timescale by multiple interneuron populations.

Inhibitory Effects on Multiple Timescales

Inhibitory regulation of neural activity occurs on several distinct but interacting timescales. GABAergic influences on local circuits are constrained by the intrinsic properties of interneurons, which vary across diverse populations. The postsynaptic impact of inhibitory transmission is further sculpted by short- and long-term synaptic dynamics. In particular, synaptic depression and facilitation can rapidly modulate both the excitatory synaptic recruitment of interneurons and their postsynaptic efficacy in regulating spiking in their targets on a millisecond timescale. In turn, the actions of synaptic inhibition in a neural network can have opposing impacts on correlations at fast (>30 Hz) and slow (<1 Hz) timescales. Although inhibition promotes fast spike synchrony between excitatory neurons, it suppresses slower noise correlations between the firing rates of those neurons, an effect that scales with network size and firing rates. On much slower timescales, integration of interneurons into local circuits is required for proper progression of circuit development. In developmentally immature circuits, interneurons organize large correlated population events. The subsequent shift from depolarizing to hyperpolarizing GABAergic inhibition is associated with a robust change in the overall timing of population activity, with large population events giving way to more decorrelated activity.

Dysregulation of inhibition can lead to loss of temporal organization, exhibited as either too much or too little correlated activity. Substantial disruption of GABAergic inhibition, whether from loss of interneurons or from decreased synaptic impact, is associated with hypercorrelation and seizure. Dysfunction of inhibition associated with neurodevelopmental disorders can lead to disruption of oscillations and loss of fine spike synchrony. Despite substantial recent advances, key aspects of inhibitory function remain unclear, including the respective roles of the diverse GABAergic populations in temporal control at each timescale.

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The role of synaptic inhibition in regulating network activity has largely been studied in rodents owing to the availability of genetic tools. However, both the diversity of GABAergic interneurons and their participation in temporal patterns of neural activity are also observed in other species, including cats, ferrets, and non-human primates. In this review I focus on general principles of interneuron connectivity and the circuit-level impact of inhibitory interneurons on spike timing at the single-neuron and population levels in the neocortex and hippocampus. I further examine evidence for the roles of interneurons in brain rhythms, including theta and gamma oscillations, and highlight the consequences of developmental and disease-related dysregulation of interneuron function.

Diverse Sources of GABAergic Inhibition

One major challenge to identifying the function of GABAergic inhibition is the diversity of inhibitory interneurons, which can be subdivided into distinct classes with different physiology, synaptic targets, and molecular markers [1,2]. Recent work has focused on three major classes: (i) fast-spiking basket cells that target the cell bodies of excitatory neurons and coexpress the calcium-binding protein parvalbumin (PV), (ii) low-threshold spiking cells that target the distal dendrites of excitatory neurons and coexpress the peptide somatostatin (SST), and (iii) sparse dendrite-targeting cells that synapse onto SST interneurons and the dendrites of pyramidal neurons, and coexpress vasoactive intestinal peptide (VIP). VIP interneurons are a subset of the larger 5HT3aR-expressing interneuron class [3].

PV cells are the most abundant type of interneuron. They are rapidly activated by afferent inputs [4–9] and are thought to regulate the output of excitatory neurons with millisecond-level precision via strong shunting inhibition at the cell body [10]. By contrast, SST cells require repetitive, facilitating, afferent input to be activated, and may regulate the dendritic integration of synaptic inputs over a longer timescale (Figure 1) [11–15]. Moreover, synaptic inhibition mediated by PV and SST interneurons exhibits distinct short-term plasticity. Inhibitory postsynaptic potentials (IPSPs) from PV synapses depress rapidly at high rates of activity [16,17], suggesting that PV inhibition may only be effective within a short window. This brief window of PV efficacy may serve to tightly constrain the temporal precision of the first spike evoked in cortical neurons by sensory input [8,18,19], which encodes substantial information [20,21]. By contrast, SST IPSPs depress only slightly with repeated activation and regulate voltage-dependent calcium signals [22–24], and may therefore exert a sustained inhibitory influence over dendritic inputs [25,26]. PV and SST cells are thus expected to exhibit distinct temporal patterns of activity and postsynaptic impact. Indeed, computational modeling of interactions in a circuit with multiple inhibitory cell types suggests a key role for cell type-specific synaptic dynamics in PV and SST regulation of excitatory neuron activity [27]. Although synapses onto VIP interneurons and from VIP cells to their targets are less well studied, a recent report found that VIP synapses onto SST cells showed frequency-dependent facilitation [28]. These findings suggest a potential enhancement of disinhibitory interactions in the local circuit following periods of repeated VIP interneuron activation, as is observed in sensory cortex during bouts of locomotion [29–31].

Although considerable research has focused on inhibitory innervation of excitatory neurons, recent work has highlighted inhibitory-to-inhibitory connectivity as a repeated motif in neocortical circuits (Figure 2). SST interneurons robustly inhibit PV interneurons, potentially providing a tradeoff between somatic and dendritic inhibition [32–34]. In turn, PV interneurons provide reciprocal innervation of SST interneurons [28,33]. VIP interneurons strongly inhibit SST interneurons [30,33,34], potentially disinhibiting both excitatory pyramidal neurons and PV interneurons, and receive reciprocal innervation from the SST interneurons. VIP interneurons also innervate PV interneurons and receive reciprocal inhibition from them [34,35]. Together, these connections comprise a network of reciprocal inhibitory connections between all three

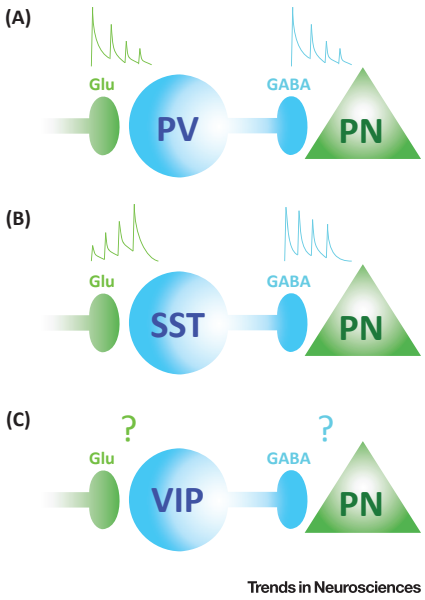

Figure 1. Diversity in the Temporal Synaptic Properties of GABAergic Interneurons. Inhibitory interneurons exhibit distinct temporal dynamics of both their synaptic inputs and outputs. (A) Excitatory synaptic inputs to parvalbumin (PV) interneurons recruit these cells quickly, but rapidly show synaptic depression. In turn, the inhibitory synapses from PV interneurons to excitatory pyramidal neurons (PNs) likewise show synaptic depression. (B) By contrast, excitatory inputs to somatostatin (SST) interneurons require repeated activation and exhibit synaptic facilitation, resulting in delayed recruitment of spiking activity. However, SST synapses onto PNs show little synaptic depression. (C) The short-term plasticity of excitatory synapses onto vasoactive intestinal peptide (VIP) interneurons and from VIP interneurons to PNs remain largely unexplored. Abbreviation: Glu, glutamate.

populations. However, interactions between interneuron populations are not always equally weighted in each direction (Figure 2), and the influence of these interactions on circuit activity remains poorly understood. Furthermore, it remains unclear how the extensive regulation of GABAergic interneuron activity by neuromodulators including acetylcholine, norepinephrine, and serotonin affects the efficacy of these interactions and their contributions to ongoing rhythmic activity.

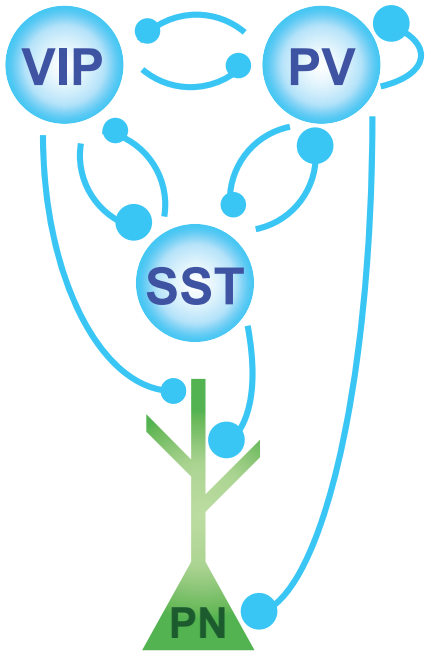

Figure 2. Reciprocal Connectivity between Interneuron Populations. Three major subtypes of neocortical inhibitory interneurons are interconnected in a repeated motif of reciprocal inhibition. The relative interaction strength is shown by the sizes of the circles denoting synaptic connectivity, largely based on current knowledge from *in vitro* electrophysiology in superficial layers of primary sensory cortex. These reciprocal interactions likely play a key role in the regulation of neural timing by inhibition. Parvalbumin (PV) interneurons are unique in having both strong reciprocal synaptic connectivity with other interneurons and also robustly inhibiting other PV interneurons via chemical and electrical synapses. Strong PV–PV and PV–pyramidal neuron (PN) interactions promote fast oscillations and precise spike timing.

Excitation–Inhibition Interactions and Spike Timing

Locally recurrent networks in the hippocampus and neocortex show a typical pattern of synaptic recruitment, with feed-forward excitatory input (E) preceding locally recruited inhibition (I). This temporal pattern of E–I interactions allows a 'window of opportunity' in which spikes may be evoked by excitation before further responses are quenched by the following inhibition [8]. The influence of synaptic inhibition recruited by feed-forward inputs into a network temporally restricts sensory-evoked spiking [19], and both the delay between E and I and the relative strength of excitation may shape tuning for sensory inputs [36–38]. The short delay between E and I also promotes the temporal fidelity of spiking, increasing spike-timing precision and reliability [19,36] and enhancing the temporal sensitivity of neurons to convergent inputs [5,18,39–42]. Previous work *in vitro* and in anesthetized animals focused on the role of soma-targeted inhibition, arising largely from PV interneurons, in regulating spike timing. However, more recent work in awake behaving animals suggests that soma- and dendrite-targeting interneurons are recruited by sensory inputs at different latencies. Initial spike timing evoked by sensory inputs to excitatory neurons may thus be regulated by PV inhibition, but spiking later in the response period may be more strongly influenced by SST inhibition [43,44] or delayed VIP inhibition [45].

Intriguingly, individual cell types may have distinct temporal windows of postsynaptic impact on different targets. In one example, recent work found that a population of 5HT3aR-expressing interneurons caused fast $GABA_AR$ inhibitory postsynaptic potentials (IPSPs) on target PV interneurons but slower $GABA_AR/GABA_BR$ IPSPs on excitatory neurons, suggesting differential temporal regulation of spiking in downstream excitatory and inhibitory populations [46]. However, it remains unknown how prevalent such differential targeting is across the different GABAergic populations. Although fast PV inhibition has been well characterized, much less is generally known about the role of non-PV interneurons in regulating spike timing. Furthermore, although the patterns and strengths of connections between interneuron populations are well established for some brain areas [33,34], very little is known about how inhibition regulates spike timing in interneurons *in vivo*. In addition, because single synapses are difficult to assay *in vivo*, the impact of short-term synaptic dynamics at inhibitory synapses in active circuits remains largely unknown.

Inhibitory Control of Brain Rhythms

Inhibition plays key roles in the generation of oscillations in the neocortex and hippocampus, as well as in other brain areas. Gamma-band activity (30–80 Hz) relies on fast inhibitory synaptic transmission by GABAergic interneurons [47]. Optogenetic activation of fast-spiking basket interneurons [39,48] or pyramidal neurons [40] in sensory cortex evokes robust gamma oscillations that depend on both GABAergic and glutamatergic synaptic transmission. Spontaneous gamma oscillations *in vivo* are eliminated by optogenetic suppression of interneurons [39], and both spontaneous and optogenetically evoked cortical oscillations are abolished by application of AMPAR and NMDAR blockers [48]. Together, these data strongly suggest that temporally coordinated activity of excitatory and inhibitory neurons (E–I) is necessary for the expression of neocortical gamma rhythms. In the hippocampus, both E–I and I–I mechanisms may underlie gamma activity [41,42].

GABAergic interneurons in the neocortex and hippocampus are highly diverse, but converging evidence points to fast-spiking, PV-expressing basket cells as an important source of synaptic inhibition for generating gamma oscillations. PV interneurons are heavily connected to each other via chemical and electrical synapses [17,49–54], and exhibit extensive reciprocal synaptic connectivity with nearby excitatory neurons, allowing them to synchronize and respond to

excitatory spiking [16,55]. Basket cells fire at high rates, have intrinsic resonance in the gamma range, and are robustly entrained to endogenous gamma oscillations [56,57]. Furthermore, the timecourse of $GABA_A$ receptor-mediated IPSPs is optimal for generating a 40 Hz oscillation cycle [58,59], thereby enhancing the entrainment of excitatory neurons. Theoretical and computational work suggests that these specialized synaptic and firing properties promote gamma oscillations [49,50,58,60–62].

The interaction between synaptic inhibition and temporal patterns of neural activity can be spatiotemporally complex. In the dentate gyrus, inhibitory interactions among distant interneurons show distance-dependent variation in synaptic strength and the duration of inhibitory events. These interactions promote the emergence of complex temporal patterns, generating focal bursts of gamma-range activity correlated with exploratory behavior and action selection [63,64]. In addition to dynamic regulation of gamma rhythms, inhibition plays a key role in the hippocampal theta rhythm [65]. In the hippocampus, optogenetic activation of PV interneurons specifically amplifies theta-frequency resonance in pyramidal neurons, whereas activation of pyramidal neurons increases power in a broad frequency range [66]. Suppression of PV cell activity alters the phase relationship between pyramidal neuron spiking and the theta rhythm [67].

Although soma-targeting inhibition from PV interneurons has been relatively well characterized, less is known about the roles of non-basket interneuron populations in directly generating oscillations. In the neocortex, PV cells receive innervation from other interneuron populations, including SST and VIP interneurons, and their firing is strongly regulated by these inputs [32–34]. Gamma activity could thus also be strongly modulated by synaptic inhibition of PV cells from multiple sources. Computational modeling of the emergence of gamma oscillations from neural networks suggests that synaptic inhibition of PV basket cells may promote the flexible expression of gamma oscillations with varying frequencies [61].

Recent work identified SST interneurons as regulators of beta/low-gamma (20–30 Hz) oscillations in the neocortex. Suppression of SST cells in primary visual cortex reduced beta/low-gamma activity evoked by large stimuli, and optogenetic stimulation of these cells augmented activity in this frequency range, whereas PV cell manipulation had little to no impact [68]. Further work suggests that SST activity may preferentially promote cortical low-frequency oscillations (5–30 Hz), whereas PV activity selectively promotes fast frequencies (>30 Hz) in behaving animals, with cooperative activation of both populations giving rise to beta (20–30 Hz) oscillations [69–71]. Together, these findings suggest multiple streams of temporal control by inhibition in cortical networks (Figure 3). The activation of SST interneurons may further entrain local and distant ensembles of neurons, enhancing long-range coherence in the beta/low-gamma range [72]. Because SST cells robustly inhibit PV cells [32,33], interactions between these channels of inhibitory influence are likely to be dynamic according to their recruitment by bottom-up and top-down inputs or in a stimulus-dependent manner.

Interactions among inhibitory interneurons may be enhanced by extensive electrical synaptic connectivity. Both PV and SST interneurons are connected, mainly to other interneurons of the same class, by networks of gap-junction coupling [17,52,70,73,74]. Electrical connectivity via gap junctions may enhance synchrony between interneurons of the same type and facilitate phase coupling to ongoing oscillations [70,75]. Loss of electrical synapses through deletion of the gene for the gap junction protein connexin 36 selectively impairs gamma oscillations in the hippocampus, as well as theta–gamma phase coupling [76,77]. However, recent work *in vitro* found that loss of connexin 36 does not affect the synchrony of gamma-frequency inhibition in

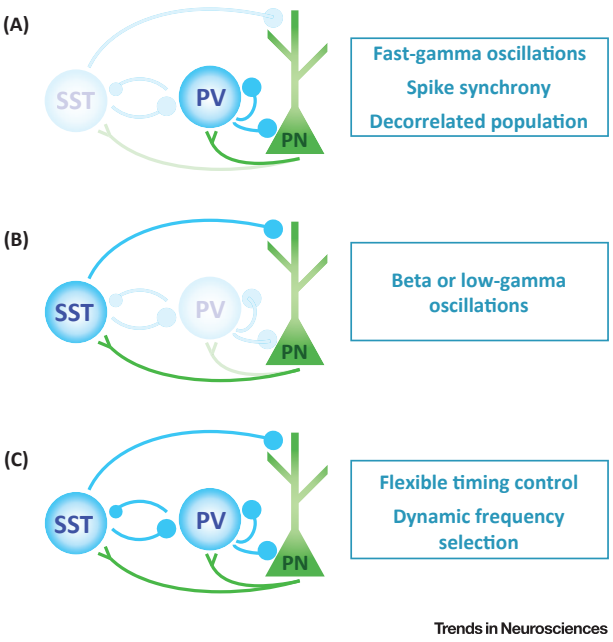

Figure 3. Distinct Interneuron Populations Promote Different Cortical Rhythms. Recent work has highlighted the respective roles of parvalbumin (PV) and somatostatin (SST) interneurons in shaping oscillations in cortical networks. (A) Reciprocal interactions between PV interneurons and pyramidal neurons (PNs) generate ~40 Hz gamma oscillations as a result of fast firing by PV cells and strong reciprocal connections. (B) SST interneurons likewise exhibit reciprocal connectivity with PNs, and their activity may underlie the generation of rhythmic activity at slower frequencies. They may generate activity at 5–30 Hz and are necessary for sensory-evoked cortical beta/low-gamma oscillations in the visual cortex. (C) One intriguing possibility is that the simultaneous interactions of these two circuit motifs allows flexible selection of neural timing in low- or high-frequency bands as demand changes. Such interactions may be mediated by the relative occurrence of bottom-up or top-down inputs that recruit PV and SST interneuron spiking in the active circuit *in vivo*.

the neocortex [78,79], suggesting potentially differential contributions to circuit activity in hippocampus and neocortex. The precise role of interneuron electrical connectivity in patterned network activity is thus not fully understood.

Computational models of networks based on multiple cell types highlight the potential impact of interactions between interneurons in regulating the temporal pattern of neural activity. Inclusion of both SST and PV interneurons may widen the oscillatory behavior of the cortical network, and replicates the impact of SST inhibition on PV cells, supporting the possibility of multiple rhythmic influences within the local cortical circuit [68]. Models of the hippocampal network likewise identify varying interneuron–interneuron interactions as a key element of theta-oscillation generation in different activity regimes [80]. In a recently developed full-scale hippocampal network model, theta rhythms were observed only under conditions of interneuron diversity [81]. Computational modeling of cortical networks further suggests that behavioral or neuromodulatory context may dynamically adjust the functional connectivity among interneurons [82], providing more flexible control of temporal interactions within the local circuit.

Inhibitory influences that regulate oscillatory patterns are not limited to local circuit interactions. Long-range inhibitory projections, such as the population of PV-expressing GABAergic neurons in the basal forebrain that project to the frontal cortex, can also entrain cortical activity and robustly promote gamma oscillations [83]. In the hippocampus, both a subset of SST cells that project to the medial septum and retrohippocampal areas and a population of non-SST GABAergic neurons in the stratum radiatum that project to subiculum and cortex show strong rhythmic activity in the theta band that is reflected at target sites [65,84,85]. Locally recorded oscillations may thus represent a mixture of local and long-range inhibitory influences on circuit-based rhythms.

Inhibitory Regulation of Correlated Spiking

In addition to regulating spike timing, synaptic inhibition promotes synchrony of spiking among interneurons and between groups of excitatory neurons. Synchrony among PV interneurons is enhanced by extensive synaptic interconnectivity [86] and gap junctions [52]. Spike synchrony among interneurons can be observed in extracellular recordings of neocortical fast-spiking putative PV interneurons *in vivo* [29], and appears to promote millisecond-timescale synchrony in the hippocampus both between local pairs of interneurons [87] and between more distant interneurons in CA1 and CA3 [88]. Individual GABAergic interneurons may further synchronize the activity of multiple local pyramidal neurons [89]. During oscillations, the entrainment of excitatory spiking by rhythmic inhibition promotes synchrony among pyramidal neurons. Although individual neurons do not participate in every cycle, pairwise synchrony is enhanced by restricting spiking to a narrow range of phases within the oscillation cycle [90]. Rhythmic activation of inhibitory interneurons increases spike-timing precision and narrows the window for spiking to promote synchronous sensory-evoked spikes [48]. Increased excitatory drive to inhibitory interneurons thus enhances excitatory synchrony [91].

Although synaptic inhibition can increase pairwise synchrony between neurons on a short timescale, previous work has also highlighted a role for inhibition in reducing slow-timescale relationships among large populations of neurons, sometimes called 'noise correlations'. By being temporally coupled to excitation, inhibitory feedback may suppress pairwise correlations that promote shared population fluctuations in firing rate [92–94]. Synaptic activity with both excitatory and inhibitory components modulates the relative amount of fast- and slow-timescale correlations in a rate-dependent manner [95], with low input rates promoting slow-timescale correlations and high rates promoting fast spike synchrony. The impact of inhibition on fast and slow correlations may vary dynamically with overall synaptic input rates and with changes in the relative balance of excitation and inhibition [96]. However, modulation of noise correlation strength is not always coupled to changes in fast correlations in the neocortex [97,98].

Inclusion of recurrent inhibition in network models reduces noise correlations [99], thereby enhancing the fidelity of stimulus encoding [100–102]. Physiologically, blockade of inhibitory synaptic transmission enhances noise correlations [103]. Recent work further suggests that top-down modulation of inhibition reduces endogenous slow-timescale correlated activity in cortical networks [104]. However, the actions of inhibition at fast and slow timescales are not mutually exclusive. In the olfactory bulb, inhibition simultaneously enhances fast-timescale correlations, such as synchronous spikes, while decreasing slow-timescale pairwise firing-rate correlations [105]. Both increased synchrony and decreased noise correlations are thought to enhance encoding of information, suggesting that inhibition may promote network function in multiple ways. Of note, the contributions of non-PV interneurons to regulating correlations at either fast or slow scales remain unclear.

Developmental Role of Inhibition in the Timing of Circuit Activity

The overall temporal profile of neural activity is shaped by early developmental events. In rodents, GABA is depolarizing during the first postnatal week of life, and synaptic connectivity has not yet matured, giving rise to large bouts of activity coordinated by inhibitory interneurons [106]. After the developmental shift to hyperpolarizing GABA, mediated by a change in expression of the Cl^- extruder KCC2, synaptic inhibition begins to shape network activity in a more temporally constrained manner [107]. Although the last interneurons migrate into the neocortex and hippocampus by the end of the first postnatal week in mice [108], very little is

known about the role of different interneuron populations in regulating the timing of neural activity in the early postnatal period.

The intrinsic properties of GABAergic interneurons mature during the juvenile and adolescent periods. In the neocortex, both PV cells and principal neurons are innervated by thalamocortical terminals by mouse postnatal days 6–7, and PV interneurons begin to exhibit fast-spiking properties by postnatal day 18, setting up the core components of the recurrent local circuit and allowing somatic inhibition to begin to regulate spike timing [109–111]. During the adolescent period, PV inhibition is required for normal refinement of synaptic connectivity and critical period plasticity [112]. By contrast, much less is known about the development of synaptic dynamics of other interneuron populations in the immature brain. However, the activity of non-PV interneurons appears to be crucial for the proper development of circuit architecture. Loss of VIP interneuron activity early in postnatal life results in loss of temporal organization of excitatory spiking [29]. Early activity of SST interneurons is crucial for the development of thalamocortical connections to PV interneurons, and loss of SST inhibition disrupts normal feedback inhibitory circuit formation [113]. These findings highlight the importance of inhibitory–inhibitory interactions in the development and function of temporal structure of local circuit activity.

Disruption of Inhibition and Abnormal Timing

Dysregulation of inhibition is linked to altered timing of neural activity on several timescales. Profound disruption of GABAergic synaptic transmission or loss of major interneuron populations have long been thought to contribute to the emergence of hypercorrelated activity and seizures [114–116]. However, the specific contributions of different interneuron populations to seizure initiation and resulting pathophysiology remain unclear. Developmental loss of interneuron activity reduces seizure thresholds [117,118], whereas overall reductions in interneuron numbers results in epilepsy [119]. Optogenetic suppression of PV interneuron activity causes cortical networks to produce highly correlated population spikes [68], and developmental impairment of synaptic transmission from PV interneurons results in spike-wave seizures [120]. Loss of SST interneurons in early postnatal life is likewise associated with development of epileptiform activity [121].

Developmental impairment of inhibitory interneuron activity or synaptic inhibition has been identified as a potential mechanism underlying cognitive and psychiatric disorders, including autism and schizophrenia. Patients with schizophrenia exhibit reduced numbers of PV-expressing cells in cortical tissue and impaired gamma-band synchronization [122–124]. Mouse genetic models of neurodevelopmental disorders have likewise highlighted disruption of inhibition as a key element of the underlying pathophysiology. Mutation of the interneuron-specific gene *Erbb4* in PV cells leads to altered PV firing patterns, changes in gamma oscillations, and disrupted temporal coherence between hippocampal and frontal brain regions [125]. Similarly, mice with a mutation in *Disc1*, a gene associated with several human psychiatric diseases, exhibit deficits in PV interneuron activity as well as reduced hippocampal theta and gamma oscillations [126]. Mutations in the autism-associated genes *Cntnap2* and *Fmr1* lead to reduced synaptic inhibition and altered synchrony [127,128]. In particular, *Fmr1* knockout mice exhibit hypersynchrony in the theta and gamma ranges [129], as well as abnormal patterns of hippocampal theta–gamma phase coupling [130] and elevated pairwise spike synchrony in the neocortex [128].

Although PV interneuron deficits have received particular attention for their potential role in altered neural activity patterns in disease, dysregulation of other interneuron populations may

also impair the timing of neural activity. Early postnatal disruption of VIP interneuron activity in sensory cortex leads to a near-complete loss of pairwise spike synchrony between excitatory neurons and loss of phase coupling of spiking to both low- and high-frequency rhythms [29], suggesting that these sparse interneurons may represent a point of developmental vulnerability for neocortical circuits.

Concluding Remarks and Future Perspectives

Inhibition plays varied roles in regulating neural timing on several scales. Inhibitory cell types vary in their intrinsic and synaptic properties, and inhibitory interneuron properties, even within the same cell type, can differ depending on developmental stage, neuromodulation, and brain region. Excitatory synaptic recruitment of GABAergic interneuron activity is modulated by cell type-specific short-term synaptic plasticity, as is the impact of synaptic inhibition onto excitatory neurons. In turn, rhythmic synaptic inhibition robustly entrains the firing of excitatory neurons, and promotes the generation of oscillations and pairwise spiking synchrony between excitatory neurons. Inhibition also suppresses pairwise correlations on slower timescales, potentially mediating a two-pronged enhancement of neural encoding. Inhibitory interneurons and synaptic inhibition also modulate network activity on a much slower timescale during development, with interneurons serving as organizers of correlated population activity. Loss or dysregulation of interneurons during development gives rise to long-term dysfunction of oscillations and spike timing in local and long-range circuits, reducing synchrony and enhancing slow correlations.

Much of our current knowledge about the inhibitory regulation of timing in the brain comes from work examining fast-spiking, parvalbumin-expressing interneurons or from studies on somatic inhibition. Findings from recent work suggest that, in addition to somatic inhibition, dendrite-targeting inhibition has the potential to make a rich and dynamic contribution to both generating patterned activity [68,69] and regulating the development of proper circuit architecture [29]. In addition, the available data on synaptic dynamics at synapses onto inhibitory interneurons, and from interneurons to their targets, point to a complex temporal series of local circuit interactions. These intriguing findings point to many unanswered questions about the developmental and mature roles for the diversity of GABAergic interneurons in regulating neural timing (see Outstanding Questions). In particular, the roles of non-PV GABAergic cell types in temporal control at the timescales of synaptic dynamics, synchrony, slow correlations, and developmental coordination remain to be explored.

Outstanding Questions

PV-expressing, fast-spiking interneurons play a well-characterized role in restricting the timing of excitatory spiking. What are the roles of non-PV interneurons, such as SST and VIP cells, in regulating spike timing of excitatory neurons?

How does synaptic inhibition onto interneurons regulate their spike timing?

PV interneurons promote gamma oscillations, whereas SST interneurons promote beta/low-gamma oscillations. Notably, SST interneurons powerfully inhibit PV cells. How do interactions among these different interneuron types regulate the expression of beta/gamma rhythms in the brain? How are those interactions regulated by neuromodulatory influences?

Do 5HT3aR-expressing and/or VIP interneurons promote specific rhythmic activity in local brain circuits?

What are the characteristics of short-term plasticity at synapses between interneuron populations (VIP–SST, SST–PV, etc.)?

Inhibition regulates both fast-spike synchrony and slow-timescale noise correlations, typically enhancing the former and suppressing the later. The GABAergic interneurons that provide this synaptic inhibition are highly diverse. Do all sources of synaptic inhibition promote fast-timescale synchrony and suppress noise correlations?

What is the developmental profile of short-term plasticity at inhibitory synapses onto dendrites?

What are the roles of dendrite-targeting interneurons in the postnatal development of appropriate E–I temporal interactions?

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