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Neocortical Interneurons: From Diversity, Strength

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Interneurons in the neocortex of the brain are small, locally projecting inhibitory GABAergic cells with a broad array of anatomical and physiological properties. The diversity of interneurons is believed to be crucial for regulating myriad operations in the neocortex. Here, we describe current theories about how interneuron diversity may support distinct neocortical processes that underlie perception.

Perception, action, and cognition in higher vertebrates all depend crucially on the neocortex. Reflecting these many roles, neocortical neurons are selective for many different kinds of stimuli. Sensory neocortical neurons, for example, can respond preferentially to a specific face, to a specific auditory tone, or to taps on a fingertip. This tuning is robust across a variety of stimulus conditions. The same neuron can respond to the same face presented as a line drawing or in a naturalistic form (Tsao et al., 2006). This sustainability of tuning is believed to be one key to perceptual constancy. We can recognize our grandmother on a rainy day in Illinois, on a sunny day in Arizona, and in a faded grainy photograph.

Neocortical neurons also demonstrate modulation of their sensitivity on the timescale of milliseconds to seconds. These dynamics can be driven by external or internal changes in context. A classic example is the adaptation generated by recurring sensory stimulation. The same neuron gives a much smaller response to the repeated presentation of a stimulus, compared with the initial presentation that occurred only milliseconds earlier. Neuronal sensitivity may also shift to reflect internal changes—for example, during tasks that require focused attention, neurons can show an enhanced response to the attended stimulus. This flexibility of neocortical circuits is thought to underlie our ability to adjust and process information optimally under a wide variety of situations.

Both of these key properties of the neocortex—stable tuning and dynamic shifts in processing—may depend critically on a special population of neurons in the brain called interneurons. These small cells that make local projections comprise ~10%–20% of the neurons in the neocortex. Interneurons shape the output of local neural circuits by releasing the inhibitory neurotransmitter GABA and neuropeptides such as somatostatin. These intriguing neurons vary widely in their physiology and anatomy, and there may be up to several thousand types. Such variation can be profound. Evidence suggests that one type of interneuron, termed neurogliaform, can regulate local neural networks by releasing GABA outside of the synapse, the typical site for communication between neurons (e.g., Olah et al., 2009). Another type of interneuron, chandelier cells, can induce depolarization of target neurons (e.g., Woodruff et al., 2009) by release of GABA, in contrast to the typical hyperpolarizing inhibitory effect of this substance. The different types of interneurons can be distinguished according to their neuropeptide content, Ca²⁺-binding proteins, K⁺ channel composition, connectivity, spine density, axonal targets, firing properties, and in vitro functional responses (for review, see Ascoli et al., 2008).

Here, we describe current theories about how interneuron diversity may support these distinct neocortical processes. We focus on interneurons in different regions of the primary sen-

sory cortex, as these regions are the best studied with regard to neocortical interneuron physiology and are key to understanding how tuning and dynamics impact perception.

Interneuron Diversity in the Service of Constancy Balanced Inhibition for Tuning

A key challenge for the neocortex is to balance the ongoing battle between excitation and inhibition. Excessive inhibition prevents the transfer of information, but excessive excitation can lead to the induction of seizures. This excitation-inhibition balance is necessary to keep neurons close enough to the spike (action potential) threshold to allow them to be rapidly activated yet in close enough check to prevent runaway excitation or, in the case of the sensory neocortex, distortion of the receptive field (see review by Haider and McCormick, 2009).

One way to achieve matched inhibitory input across sensory stimuli that vary in intensity is for the neocortex to possess a variety of interneuron types, each responsive to a different level of input (Figure 1). As Markram et al. (2004) stated: “Interneuron diversity might be crucial for providing sufficient sensitivity, complexity and dynamic range for the inhibitory system to match excitation regardless of the intensity and complexity of the stimulus.”

These ideas can be illustrated by two interneuron types that have been studied intensively in vitro. Under conditions of weak drive—that is, a low intensity of

presynaptic input such as a single action potential—fast-spiking interneurons with a basket-cell morphology are strongly activated (Beierlein et al., 2003; Kapfer et al., 2007). In vivo, these interneurons can be driven to spike and to generate inhibitory currents in neighboring excitatory cells, even with weak sensory input such as a light tactile deflection (Swadlow, 2003). In vitro studies show that, as the intensity of presynaptic input increases, these interneurons become saturated or adapt their responses. In contrast, other classes of interneurons require sustained presynaptic spiking or a greater number of synchronous presynaptic inputs for activation (Beierlein et al., 2003; Kapfer et al., 2007; Silberberg and Markram, 2007). One example is provided by neocortical interneurons containing the neuropeptide somatostatin that often have Martinotti-type anatomy and axons that target the apical dendrites of layer V cells in the supragranular layer. Their in vitro properties predict that these interneurons will be activated during strong sensory stimulation, creating a new source of suppressive input under those perceptual conditions. Both of these interneuron types (fast-spiking and somatostatin-positive) are connected to each other by gap junctions (e.g., Beierlein et al., 2003), potentially enhancing the synergy of their impact on the local neuronal network. The generality of these observations, typically made in somatosensory and visual primary sensory cortices, are supported by recent data showing that these different interneurons have similar dynamics in the olfactory neocortex (e.g., Suzuki and Bekkers, 2010), which is distinct from other primary sensory cortices in its pattern of input and laminar organization.

In support of the prediction of “balanced” inhibition, in vivo intracellular recordings from primary somatosensory and auditory cortices show that a rise in excitatory drive with increased sensory input is often matched by a rise in inhibitory drive (Moore and Nelson, 1998; Wehr and Zador, 2003; Zhu and Connors, 1999). In the auditory cortex, for example, the excitation-inhibition balance between conductances is maintained across a range of preferred and nonpreferred auditory tones and across

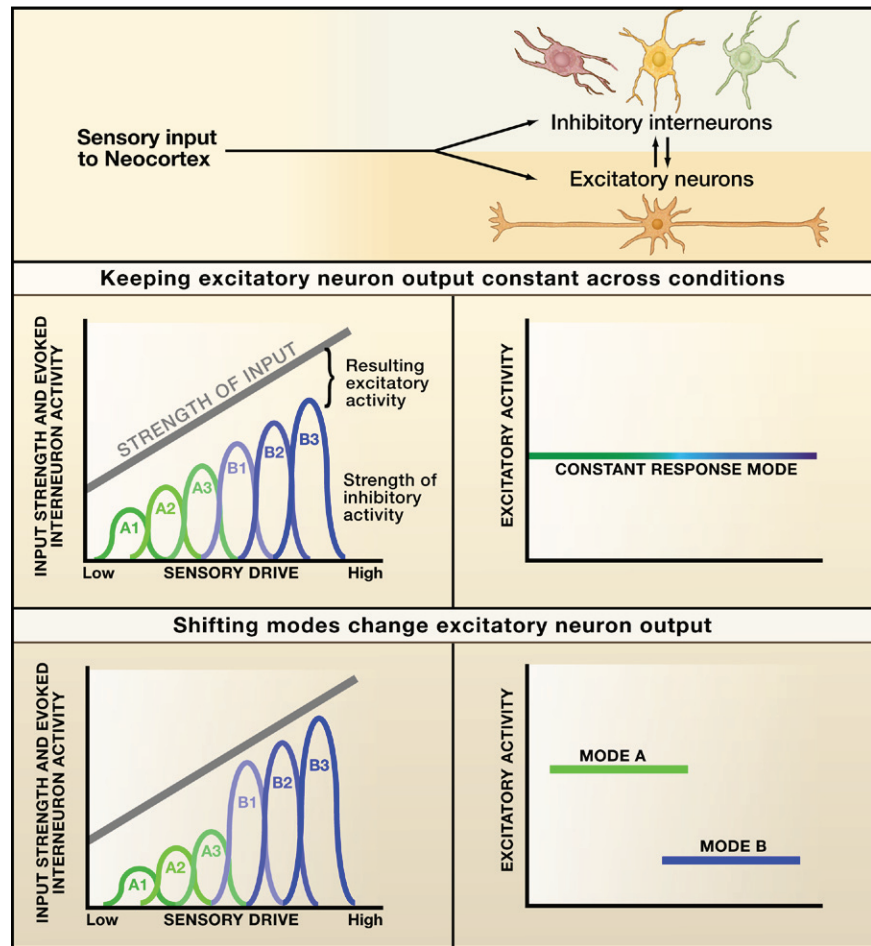


Figure 1. Interneuron Sensitivity and Sensory Input

(Top) Sensory input to the neocortex, relayed through the thalamus, activates interneurons directly and by relay through adjacent excitatory cells. These interneurons, which produce the inhibitory neurotransmitter GABA, in turn suppress excitatory neurons.

(Bottom) Response curves are shown for six hypothetical interneuron types (A1–B3) that require different levels of excitatory input to be activated (that is, to fire an action potential) and that subsequently generate a different amount of inhibition in their excitatory neuron targets.

(Middle panels) According to one theory, interneuron diversity keeps excitatory neuron responses constant across a broad range of sensory stimulus conditions. In this example, the six interneuron types provide balancing inhibition to the excitatory cell as excitation increases. The right-hand panel shows that because of the balancing inhibition generated by different interneuron types, there is a constant output from a given excitatory cell, despite a wide range of different inputs. Although the more abstract example of excitatory response amplitude is shown, this kind of balance could maintain constancy in other features. Such features could include keeping the sensitivity of an excitatory neuron to a specific sensory input intact across conditions, for example, when looking at the same face during a real interaction or when viewing it in a photograph.

(Bottom panels) In contrast, interneuron diversity in response to sensory excitation may shift the operating mode of the neocortex. In this example, under conditions of lower sensory input, interneurons A1–A3 (green) would be recruited and would place excitatory neurons in a distinct processing mode (mode A). In this example, under conditions of low activation, excitatory neurons show a relatively strong response because the inhibition generated by the interneurons that are recruited is weak. This more permissive environment may enable excitatory neurons to be responsive to a broader range of sensory inputs thus facilitating the detection of stimuli in a perceptual environment. Under conditions of high sensory input, interneurons B1–B3 (blue) would be recruited, and the stronger inhibition they generate would cause excitatory neurons to show a relatively weaker response to input (mode B). The greater suppression generated by B1–B3 interneurons could create greater selectivity for different sensory inputs, facilitating discrimination of these inputs. These two conceptions (middle, bottom) of the role of interneuron diversity in shaping sensory responses are not inherently opposed. Within a class (A or B), interneuron diversity may provide for constancy in excitatory response properties. When a critical level of drive is reached, the neocortex then switches to a different processing mode (from A to B) by recruiting a different class of interneuron.

changes in loudness (Wehr and Zador, 2003). Further, this balance is re-established following plastic changes (on the time course of minutes) that initially enhance excitatory drive, suggesting that matched inhibition is a feature the circuit seeks to maintain (Froemke et al., 2007).

Different Forms of Inhibitory Balance

Although multiple types of interneurons may provide balance in response to a variety of sensory inputs, there are likely to be differences in the kind of suppression generated by these types in vivo, allowing them to regulate different aspects of sensory-evoked responses. These potential differences are illustrated by the divergent physiology and anatomy of the fast-spiking and somatostatin-positive interneurons. The fast-spiking, basket-type interneurons exhibit high sensitivity and rapid responses and form synapses close to the soma of their target neurons (Somogyi et al., 1983). They are therefore ideally positioned to impose a “window of opportunity” on their targets (Pinto et al., 2000), an initial period of milliseconds during which excitatory drive from a discrete sensory input can evoke an action potential before inhibition dominates. The balanced rise in inhibitory conductances described above is not entirely simultaneous with sensory-driven depolarization, as exact coincidence could prevent any activity from leaving a given neuron. In most contexts, there are brief imbalances in the two opposing factors on the timescale of milliseconds, allowing periods of excitatory dominance in which spiking and signal transmission can occur. Without such signal transmission, sensory inputs could not be relayed beyond the thalamus, preventing neocortical processing.

Intracellular recordings in vivo following punctate sensory stimuli show the timecourse of excitation and inhibition that create this window of opportunity (Figure S1 available online) and how this mechanism plays a functional role across multiple sensory modalities. In the barrel cortex of rodents (which receives sensory input from the whiskers), the timing of fast inhibition determines which whisker evokes action potentials (Moore and Nelson, 1998) and, for a given whisker, which direction of deflection recruits

action potentials (Wilent and Contreras, 2005). Similar temporal windows shape auditory (Wehr and Zador, 2003) and visual (J.A.C., D. Contreras, and Palmer, unpublished data) cortical receptive fields. An important caveat is that these studies are typically conducted using spatiotemporally discrete stimuli presented to anesthetized animals, whereas natural sensory inputs are more rapid, ongoing, and complex. In a more realistic context, cyclical windows of opportunity reflected in brain states such as gamma oscillations—rapid cycles of excitation and inhibition occurring at a frequency of 30–80 Hz—may be more relevant for gating the intensity of the response to natural sensory stimuli.

The somatostatin-positive interneurons, in contrast, exhibit facilitating responses, suggesting a potentially slower onset of their inhibitory impact, and they form synapses on distal dendrites, suggesting more graded control over the activity of target excitatory cells (Goldberg and Yuste, 2005; Kapfer et al., 2007; Silberberg and Markram, 2007). The slower intrinsic biophysical properties and calcium ion dynamics of these cells, compared with most fast-spiking interneurons, also suggest a more temporally dispersed regulation (Goldberg and Yuste, 2005; Pouille and Scanziani, 2004). The bias toward forming contacts with dendrites rather than with the soma of neurons further indicates that these interneurons regulate the input to a given target neuron, by impacting signal relay from specific regions of the dendritic tree. This regulation of “inputs” is in contrast to the impact of inhibition targeted to the soma, which controls the decision to fire a spike and thus regulates the “output” of the target neuron.

Several avenues remain to be explored regarding the idea that different types of interneurons regulate excitation in the neocortex. As discussed above, there are almost no in vivo data describing the specific impact of distinct interneuron types on postsynaptic targets, although data do show that both inhibition of dendritic targets by Martinotti interneurons (Murayama et al., 2009) and selectively driven fast-spiking interneuron activity (Cardin et al., 2009) can impact excitatory responses in vivo. Further, differences in synaptic targeting may not determine the

impact of postsynaptic inhibition. Specific compartments of dendrites may act to equalize the impact of different inputs, minimizing the differences in the amplitude of impact of the two distinct locations (Spruston, 2008).

Interneuron Diversity in the Service of Computational Diversity Sensory-Driven Dynamics

Although sustained tuning across stimulus conditions is a feature of the sensory neocortex, the neocortex is also dynamic, shifting responsiveness on a millisecond to second timescale. One way that the sensitivity and tuning of cortical neurons can shift is through changes in the ongoing pattern of sensory input. In the barrel cortex, for example, increasing the frequency of whisker stimulation decreases the sensitivity of cortical neurons to subsequent stimuli and sharpens the lateral extent of cortical activation (Moore et al., 1999). This transformation in the mode of cortical responsiveness is likely to be important in behavior. During active sensory exploration with the whiskers, self-generated whisking motions (Ferezou et al., 2007) and the high frequency of contact-induced inputs are likely to drive suppression of neuronal activation. These dynamics may serve to mediate a shift from an unadapted perceptual mode favoring detection (larger responses, broader spread of activity, better for alerting the animal) to a mode favoring discrimination (diminished responses, greater separation between neighboring representations) (Moore et al., 1999).

The recruitment of distinct types of interneurons that are differentially sensitive to a strong sensory input may play a role in this shift in the mode of cortical responsiveness. An increase in the frequency of sensory input (e.g., of whisker motions) may recruit interneurons with facilitating dynamics, such as the somatostatin-positive interneurons, whereas weaker inputs would not activate these cells. As such, the in vivo consequence of the different sensitivity and dynamics of different types of interneurons may be to generate sensory-driven shifts in the functionality of the neocortex, placing these networks in alternative processing modes reflecting the present demands of the sensory world.

This hypothesis, that the different sensitivity of different interneuron types creates different response modes in the neocortex, is distinct from the “balanced inhibition” hypothesis described above (Figure 1). Although a hybrid of these two possibilities likely exists in the living animal, the hypothesis that interneurons mediate a transformation in sensory processing based on sensory context has distinct implications. For example, conditions where individuals are overwhelmed by sensory input if an environment is too stimulating, as in some manifestations of autism, could be explained by the inability to shift the sensory-driven state of the neocortex due to dysfunction of a particular class of interneurons. This prediction is supported by changes in interneuron density in the hippocampus of individuals with autism and the predominance of epilepsy in these individuals (Spence and Schneider, 2009).

Distinct Rhythmic Brain States

Much as distinct interneuron types may be crucial for sensory-driven shifts in the mode of neocortical processing, their activity may be key to generating internally driven brain states that are classically associated with patterns of rhythmic activity. The function of these brain rhythms or oscillations has not been resolved. These oscillations may be only a signature of an underlying process, unrelated to ongoing computation, or the frequencies themselves may be intrinsic to neocortical function. Although the computational value of these rhythms is still under debate, there is little argument that they serve as a clear indicator of a shift between modes of signal processing in the brain.

A cardinal example of such oscillations is the gamma rhythm, which is typically centered around 40 Hz and is associated with several cognitive functions, including shifts in attention. When attention is allocated to a region of sensory space, the gamma rhythm increases in local populations of neurons that encode that region—for example, the neurons in the visual neocortex that represent an attended region of visual space (Fries et al., 2001).

Convergent evidence indicates that synchronous activity in fast-spiking interneurons is key to the emergence of the gamma rhythm (Bartos et al., 2007).

These interneurons generate inhibitory potentials that typically have a decay time constant of ~ 25 ms (Figure S1). This inhibition creates a window following the decay of inhibition in which excitatory neurons are more likely to be active. When they are, they not only relay signals to downstream brain areas but also drive local fast spiking interneurons, helping to create a second period of inhibition. These repeated, rhythmic inhibitory cycles are crucial for generating gamma oscillations in the neocortex (Figure S2).

Gamma oscillations may facilitate perception during enhanced attention by temporally organizing the output of signals from a sensory cortical area (Borgers et al., 2008; Fries et al., 2007; Uhlhaas et al., 2008). The high level of inhibition during gamma oscillations prevents excitatory activity in neurons that receive weak presynaptic input and provides a specific window for the activity of neurons that can overcome the inhibition. This cyclic inhibition creates windows of opportunity similar to those created by punctate sensory inputs. In this way, only preferred (e.g., attended) representations pass their signals on to other brain areas, filtering out potentially distracting inputs. Further, the preferred signals that are transmitted occur only in the permissive window, increasing the synchrony across output neurons and their efficacy in driving downstream targets. A closely related idea is that gamma-oscillation synchrony imposed across disparate neuronal populations, such as different parts of a sensory cortical map, is key to “binding” the features of a complex object into a coherent whole, in part by unifying the timing of sensory-driven activity and thereby increasing the impact of synchronized excitatory neurons on downstream targets.

The evidence in support of the “fast-spiking gamma” hypothesis is diverse. In vitro studies of rodent brain slices show that blocking GABA suppresses gamma oscillations, and that driving fast-spiking interneurons by activating metabotropic glutamate receptors generates gamma oscillations (Bartos et al., 2007; Whittington et al., 1995). Correlative in vivo studies similarly show that fast-spiking cells fire action potentials in phase with the gamma oscillations in

the neocortex (Hasenstaub et al., 2005; Sirota et al., 2008). Computational models have provided a crucial framework for understanding these data, including emphasis on the need for ongoing excitatory activation of the network for sustainment of gamma oscillations (Vierling-Claassen et al., 2008). Causal evidence for the fast-spiking gamma hypothesis in vivo has been obtained in the neocortex using optogenetics—the activation of selective cell populations that have been made sensitive to light by genetic manipulation. Specific activation of parvalbumin-positive fast-spiking interneurons enhances gamma oscillations, and this rhythm selectively gates the sensory-driven output of somatosensory neurons (Cardin et al., 2009).

In contrast, interneurons with slower recruitment dynamics and a longer window of impact on their postsynaptic targets are predicted to contribute to the emergence of slower brain rhythms. For example, in the hippocampus, oriens-lacunosum moleculare (OLM) interneurons fire in phase with the 4–12 Hz theta rhythm (Klausberger et al., 2003), and computational modeling studies implicate this type of interneuron in the genesis of this rhythm (Tort et al., 2007). Like Martinotti interneurons of the neocortex, OLM cells target dendrites and show facilitation of presynaptic excitatory drive (Ali and Thomson, 1998; Pouille and Scanziani, 2004). Similarly, in neocortical slices in vitro, selective activation of somatostatin interneurons generates an ~ 10 Hz rhythm that matches the frequency band of the alpha oscillation that is common to this brain area (Fanselow et al., 2008).

Internally generated brain states may depend in part on neuromodulators that target distinct types of interneurons. As one example, inputs from the median raphe nucleus target interneurons in the hippocampus and isocortex that contain the neuropeptide cholecystokinin (Somogyi et al., 2004). Similarly, cholinergic inputs and their specific receptor subtypes, which are believed to be key for the production of oscillations, are also localized to distinct types of interneurons (Bacci et al., 2005). Other factors, such as local hemodynamic changes, may also impact interneuron

types selectively and shift the dynamics of local neocortical circuits (Moore and Cao, 2008).

Consolidating Our Gains

As we have discussed here, interneuron diversity provides an attractive mechanism for several theories of neocortical function. This diversity could, in concept, serve all of these roles. Distinct classes of interneurons may, for example, be used to maintain an excitatory-inhibitory balance within a regime of function, whereas other interneurons could be responsible for shifting brain states. Although we have cited well-characterized examples to motivate discussion of these hypotheses, understanding interneuron function will require continued study of the many forms of interneuron diversity. A key next step is to understand the meaningful differences between interneuron types, to distinguish the features that matter for their role in implementing computation in the neocortex from those that are incidental. This task will require not only further studies at the *in vitro* and molecular levels but also *in vivo* studies performed in increasingly realistic contexts, testing the role of different interneurons as the neocortical circuit is performing natural computations in different brain states. This final goal will require continued innovation of new techniques, particularly using imaging and the causal control of specific neuron types in the more complicated *in vivo* context and especially in the freely behaving animal.

Supplemental Information

Supplemental Information includes two figures and can be found with this article online at doi:10.1016/j.cell.2010.07.005.

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