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Cortical synaptic architecture supports flexible sensory computations

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Abstract

Establishing the fundamental principles that underlie the integration of excitatory and inhibitory presynaptic input populations is critical to understanding how individual cortical neurons transform signals from peripheral receptors. Here we review recent studies using novel tools to examine the functional properties of excitatory synaptic inputs and the tuning of excitation and inhibition onto individual neurons. New evidence challenges existing synaptic connectivity rules and suggests a more complex functional synaptic architecture that supports a broad range of operations, enabling single neurons to encode multiple sensory features and flexibly shape their computations in the face of diverse sensory input.

Introduction

Cortical neurons form complex networks that transform sensory signals into reliable, behaviorally-relevant representations. Neuroscientists have long sought to understand how this process is accomplished at the level of individual neurons, establishing basic principles to describe the integration of excitatory and inhibitory presynaptic populations. Electrophysiological and anatomical studies have identified several rules thought to explain the functional organization of recurrent connections in visual cortex. Excitatory synaptic connectivity has been characterized as “like connects with like”, meaning that pyramidal cells exhibiting similar functional properties (selectivity for orientation, direction of motion, spatial receptive field, etc.) are preferentially connected [1-3]. Inhibitory synaptic activity has been characterized as “balanced” or “co-tuned”, meaning that the functional properties of inhibitory inputs onto pyramidal cells match excitatory inputs [4]. Both of these rules were deduced from measurements of cellular responses that could not resolve the functional properties of the individual synaptic inputs that the neurons receive. Moreover, for practical reasons, most attention has been directed to the identification of rules responsible for a single computation, such as the generation of orientation selectivity [5, 6]. Thus, how synaptic input patterns can be altered under different stimulus conditions and by behavioral state remains an open question.

New technologies and genetic tools to label, target, or manipulate cells and synapses [7, 8] begat a new era in the ability to dissect the presynaptic networks converging onto individual cortical neurons. Recent studies using these tools reveal that the functional properties of synaptic inputs onto cortical neurons appear far more diverse than previously thought, often deviating from the simple rules that have dominated our perspective on cortical connectivity. Here we provide an overview of these studies and how they are reshaping our view of

cortical circuits. These recent observations suggest the functional synaptic organization of cortical circuits reflects a broad range of operations performed by individual neurons, and a computational flexibility enabling the encoding of multiple sensory features and contextual modulation. This perspective is reinforced by theoretical models of cortical circuits consistent with operational flexibility.

Functional diversity of excitatory synaptic inputs in cortical neurons

The operations of individual cortical neurons are primarily shaped by excitatory drive. A prevailing principle of cortical connectivity linking excitatory neurons is functional specificity (e.g. ‘like-connects-to-like’) [1-3]. This specificity is thought to amplify synaptic drive for a given sensory feature [9], enhancing selectivity of cortical neuron responses. However, results from recent studies examining the functional synaptic architecture of individual neurons seem inconsistent with this rule.

Pioneering *in vivo* studies used multiphoton microscopy and fluorescent calcium indicators to record sensory-driven activity in individual dendritic spines [10], making it possible to characterize the functional properties of presynaptic inputs onto a single cortical cell. This approach is effective because: (1) dendritic spines are typically innervated by a single excitatory presynaptic bouton [11], (2) synaptic calcium signals are localized to individual spines [12], and (3) the displacement of the spine away from the dendritic branch enables its activity to be captured with multiphoton imaging techniques. Using more sensitive genetically-encoded indicators, several labs have examined a classic property of visual receptive fields: orientation tuning [5, 13]. Based on the principle of excitatory functional-specificity, one would expect a neuron’s synaptic inputs to match the orientation preference of the somatic output. Instead, individual synaptic inputs onto visual cortical neurons in mouse, ferret, and macaque exhibit a high degree of diversity in orientation preference compared to the somatic output [14-17]. As these studies span a variety of mammalian model systems, they provide compelling comparative evidence that functional synaptic diversity is likely a principle, rather than unique to a single model organism. A lack of strict excitatory synaptic functional-specificity has also been observed for other stimulus features such as direction of stimulus motion [18] and receptive field spatial organization [19, 20]. Spatial receptive field structure, in particular, can vary substantially in visuotopic location, size, sensitivity to light or dark light, and ocular specificity.

The diversity of synaptic inputs raises an obvious question: why are the spiking responses of pyramidal cells exquisitely selective to specific visual features? First, for many receptive field properties there is a bias in the distribution of synapses aligned to somatic preferences (e.g. orientation/direction) [15, 16, 18] and the spike threshold ‘iceberg effect’ [21] would conceal the full range of synaptic inputs. Second, there may be differences in input strength or synapse efficacy. Several lines of evidence suggest that excitatory inputs functionally-similar to the soma are strongest [1-3], but these studies use indirect measures of synaptic strength or functional properties. Third, dendritic functional clustering [15, 19] could amplify the excitatory inputs that match somatic output, and inhibitory inputs could offset inputs tuned to non-preferred stimuli [15]. While it is possible to envision mechanisms that would sharpen the somatic response over that supplied by synaptic inputs, why should such

a broad range of synaptic inputs be present in the first place? Pooling over a broad range of inputs might be the basis for generating cells with diverse orientation tuning profiles, some narrow, some broad, allowing for more efficient encoding of natural scenes [22]. Finally, functional diversity may simply reflect the fact that, within the total population of excitatory inputs, distinct subnetworks can drive somatic activity and their recruitment depends on the pattern of sensory information present.

Subcellular imaging of individual excitatory synaptic inputs is not the only approach challenging the ‘like connects with like’ rule. Technological advances have made it possible to monitor and manipulate the activity of large populations of excitatory neurons [23], mapping the ‘influence’ of functionally defined excitatory neurons on their neighbors. In a clear departure from the amplification expected for ‘like-to-like’ excitatory connectivity, Chettih and Harvey (2019) show that activation of excitatory neurons results in the suppression of nearby functionally-similar excitatory neurons [24]. It remains to be seen how this competitive interaction between neurons with similar response properties is achieved at the synaptic level, but at the very least it emphasizes the complex nature of the functional interactions between excitatory neurons and the need to understand how inhibitory neurons are integrated into this process.

Functional imbalance of excitation and inhibition in cortical circuits

Cortical neurons are continually bombarded by co-occurring excitatory and inhibitory inputs. Inhibitory (GABAergic) neurons comprise a smaller fraction of all cells, but are undoubtedly important for normal cortical function. Despite their importance and a decade of research revealing diversity in anatomy, genetic profiling, and functional response properties [25], a single principle prevails: co-tuning of excitatory and inhibitory inputs onto a target neuron [4]. Co-tuning is proposed to stabilize or normalize sensory-driven activity of cortical neurons [9, 26]. However a different picture is emerging whereby excitatory and inhibitory inputs can be functionally balanced (e.g. co-tuned) and imbalanced (e.g. differentially-tuned) depending on sensory input and behavioral state. Although there are a number of studies that have characterized inhibitory cells *in vivo*, in this section we specifically focus on studies measuring inhibitory inputs directly with *in vivo* whole-cell electrophysiology that are best able to address synaptic interactions.

Adesnik (2017) recently showed that the ratio of inhibition to excitation in mouse depends on stimulus strength in visual cortex of awake animals. Weak (low contrast) or small visual stimuli drive primarily excitation, but as stimulus strength (grating size/contrast) increases, inhibition is recruited [27]. Thus, the functional balance between inhibition and excitation would be different for weak/small compared to stronger/larger visual stimuli. In ferret visual cortex, Wilson et al. (2018) examined the role of inhibition in shaping direction selectivity (e.g. preference for visual motion direction) in anesthetized ferrets. Instead of a strict co-tuning regime, they found numerous examples where selectivity resulted from an imbalance between inhibition and excitation, whereby greater inhibition suppressed neural activity driven by the non-preferred direction of motion [18]. In addition, this study demonstrated the presence of long-range inhibitory projections emanating from cortical regions that preferred the direction of motion opposite to the direction preferred by the targeted cell.

Scholl et al. (2019) used similar techniques in ferret visual cortex to map the orientation tuning of superficial presynaptic inhibitory neurons. Albeit a coarse measure of synaptic connectivity (whole-cell physiology combined with 1-photon photostimulation), inhibitory populations were rarely co-tuned with postsynaptic targets [28]. Rather, presynaptic inhibitory inputs mostly conveyed a diverse array of orientation preferences onto postsynaptic targets. While the exact functional composition of inhibitory presynaptic networks converging onto individual neurons is largely unknown, some insights are being gained. For example, a possible explanation for the observations by Adesnik (2017), is that parvalbumin-expressing interneurons, which project locally in cortex, provide inhibition for small stimuli and larger stimuli recruit greater inhibition from somatostatin-expressing interneurons [29]. We hope that with the advent of novel genetic tools [30], future studies will extend this work to functionally defined presynaptic networks and a variety of model systems.

Additional recent evidence for functional imbalance in the tuning of excitation and inhibition has been shown in the auditory cortex, an area in which previous studies had described a co-tuned organization [31, 32]. In awake animals, Kato et al. (2017) demonstrated the presence of inhibitory inputs driving suppression of excitatory drive outside the classical V-shaped pure-tone frequency tuning curve of individual neurons, uncovering the presence of inhibitory inputs specifically tuned to frequencies outside the range of preferences of postsynaptic targets [33]. Moreover, Kuchibhotla et al. (2017) showed that inhibitory inputs in auditory cortex can be behaviorally modulated. Using *in vivo* whole-cell recordings in awake, behaving mice they found that the same auditory stimuli can elicit either functionally balanced or imbalanced inhibition and excitation [34]. At least in auditory cortex it appears that a functional imbalance in frequency tuning is evident in awake animals, although how these observations might relate to other auditory sensory features (such as sound localization) is unknown. It is worth noting that anesthesia can impact inhibitory-excitatory balance. In visual cortex of awake mice, neurons exhibit an imbalance where inhibition dominates excitation, but under anesthesia, more balance is observed [35].

From these recent studies it would appear that an imbalance can sculpt or enhance the neural selectivity to specific features of sensory inputs or even dramatically reshape selectivity in a behaviorally-relevant manner. The culmination of previous and recent studies suggest that cortical synaptic architecture supports both balanced and imbalanced excitation/inhibition, rather than being strictly 'like-to-like' connectivity. In this way, the networks of excitatory and inhibitory inputs converging onto single cortical neurons can exhibit balance or imbalance, depending on the sensory information present, behavioral context, and likely other variables yet to be discovered.

Theoretical models of cortical circuits supporting flexible computation

Several observations we discuss in this review are seemingly inconsistent with simple rules of cortical connectivity (e.g. 'like-connects-to-like'). A recently developed class of theoretical models of cortical circuits might be able to provide a better description of these observations: stabilized supralinear networks [26]. In these models, recurrently connected

excitatory and inhibitory neurons with supralinear input-output functions (a power law function) [36] are driven by external input. Under sufficiently strong external drive, networks are stabilized dynamically by feedback inhibition, whereby they are termed an inhibitory-stabilized network [26, 37, 38]. This type of model has been successful in describing a number of features of visual cortical neurons, demonstrating how amplification can be achieved and the functional balance between excitation and inhibition depends on the strength of external input [27, 33, 34]. It has also been successful in describing the behavior of cortical circuits under optogenetic perturbation of specific cell types during visual stimulation [39]. Further, in these models, excitatory and inhibitory cells share similar receptive field properties, mainly consistent with experimental measurements in carnivores [40, 41], rather than requiring a specialized forms of synaptic connectivity.

Interestingly, stabilized supralinear networks do not require an exact co-tuning between synaptic inputs from inhibitory and excitatory neurons. Given sufficiently strong feedback inhibition, network dynamics may ensure that the *average* inhibition and excitation onto neurons remains balanced across different patterns of activity [37]. This suggests that the functional balance between excitation and inhibition may not be the same for two different visual stimuli eliciting different activity patterns. But the inhibition and excitation received over all possible visual stimulus conditions would remain roughly balanced. Notably, not all aspects of these network models are necessarily consistent with measurements of synaptic diversity. Functional diversity in excitatory input populations and superficial inhibitory inputs may be greater than current models predict. However, future studies bridging the gap between physiology and theory will work to develop targeted experiments and converge to a more comprehensive understanding.

Conclusions

Here we reviewed recent studies revealing that the functional properties of synaptic inputs onto cortical neurons appear far more diverse than previously thought, often deviating from the simple rules that have dominated our perspective on cortical connectivity. Excitatory input populations exhibit greater functional diversity than predicted by simple rules describing functional connectivity between pyramidal neurons (e.g. “like connects to like”). Additionally, observations of functional imbalances between excitatory and inhibitory inputs onto single neurons is a departure from a simple rule of “co-tuning.” However, these observations suggest that the functional synaptic organization of cortical circuits supports a broad range of operations. This architecture would support flexibility in the encoding features from dynamic sensory information, multiplexed computations, and the encoding of multiple sensory features by single neurons.

In this review we suggest that a new picture of functional cortical synaptic connectivity is emerging: diversity of excitatory synaptic inputs and both balanced and imbalanced excitation/inhibition that can form the basis for flexible network operations. Although we acknowledge there are relatively few examples of cortical network flexibility directly attributed to these features, we are inspired by previous and recent work in the retina suggesting that a flexible circuit design supports dynamic sensory computations (for a detailed review see [42]). In particular recent studies of retinal ganglion cell (RGC) motion

sensitivity, a receptive field property akin to that found in visual cortex, suggest that this property arises from a multitude of synaptic mechanisms, many of which are selectively recruited or modulated by specific features of visual motion (see [43]). For example, in a recent study, Huang et al. (2019) demonstrate that motion signals in the receptive field center and surround differentially modulate direction selectivity of posterior ON-OFF RGCs [44]. In another recent study, Deny et al. (2018) observed that fast OFF RGCs multiplex the encoding of object spatial position and visual motion [45]. These are just two examples among many recent studies illuminating how retinal circuitry, previously described as neural ‘hardware’, supports flexible operations and multiplexing of sensory computations. As we continue to unravel the flexibility of cortical synaptic architecture, these corollary lines of inquiry in the retina may provide key insights.

Due to brevity, a number of important issues could not be addressed in this review. Dendrites compartmentalize synaptic inputs and recent theoretical papers now demonstrate how dendrites could be used to multiplex sensory information [46, 47]. Synaptic diversity and, in particular, modulations in the balance of excitation/inhibition might be shaped by attentional state or behaviorally-relevant sensory inputs (for a recent review see [48]). Input source could be a critical factor in explaining the observed departures from previous conclusions about the rules of excitatory cortical connectivity. Much of the previous work has focused on characterizing inputs from nearby pyramidal neurons, while spine measurements likely draw from a broad range of inputs, including feedforward, feedback, and long range as well as local recurrent inputs. As computational and experimental approaches improve, a standard set of naturalistic stimuli could be used to probe synaptic functional properties, providing a better appreciation of the operational flexibility of cortical circuits and illuminating the underlying functional connectivity patterns that are responsible.

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Highlights

1. Functional properties of excitatory inputs onto cortical neurons are more diverse
2. Cortical neurons can receive imbalanced synaptic excitation and inhibition
3. Current theoretical models are consistent with these findings
4. New evidence suggests cortical circuits support operational flexibility