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Interneuron Cell Types: Fit to form and formed to fit

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Abstract

Understanding brain neural circuits begins with understanding their component parts, the cells that form them. GABAergic interneurons, although a minority of cells within the brain, are critical in the control of inhibition. While understanding their diversity has been a central goal of neurobiologists, this amazing cell type has to date defied a generalized classification system. Here we review data that supports that interneuron complexity within the telencephalon can be simplified by viewing them as elaborations of a much more finite group of developmentally specified cardinal classes.

Within the forebrain, interneurons possess the largest diversity in morphology, connectivity, and physiological properties¹. Up until ten years ago their classification, with a few notable exceptions², has remained descriptive. Moreover interneuron diversity was often treated either as a quasi continuum or a diversity space with cell types numbering potentially in the hundreds^{3,4}. The last few years of studies have coalesced into the surprising view that interneuron diversity may be fundamentally far more limited. When one considers their commonalities: at a genetic, circuit or functional level, an argument can be made for condensing large subclasses of interneurons into more finite groups. Here we suggest that based on both developmental and functional criteria interneuron diversity can be simplified and addressed experimentally. The ultimate connectivity, gene expression and physiological properties of interneurons found across the range of brain structures appear enormous (Figure 1). Nevertheless we argue this complexity arises from a small number of non-overlapping cardinal classes, which represent developmental genetic ground states that possess the ability to further specialize through their later interactions with other neurons. The ultimate goal of defining their identity through a set of computational principles remains daunting. However, with the advent of new tools that provide unprecedented specificity, coupled with the means to modulate *in vivo* the activity of specific targeted populations this goal is becoming attainable.

1. Birth and specification of interneurons

How is neuronal diversity created? Developmental studies across various species^{14,5} and systems^{15,6} have suggested that cell diversity arises from specification programs established in progenitors modified to varying extents by their subsequent postmitotic interactions. The balance between these two appears to represent a compromise dictated by the organizational constraints of the particular system. Within the cortex, the pyramidal cells undergo a relatively orderly migration from the proliferative zone to the overlying cortical plate. As such cell identities are largely controlled by programs established within progenitors⁷. By contrast, interneuron progenitors of the telencephalon undergo incredibly complex patterns of dispersion. At the extremes, this could either be due to exquisitely precise preprograms

for migration to particular structures or plasticity mechanisms that allow them to adapt to local environments.

Until the late nineties it was widely assumed that the excitatory and inhibitory neurons within the cortex shared a common lineage. The seminal breakthrough came from the realization that interneurons originated within focal subcortical proliferative zones⁸. This first came to light with landmark papers showing that the GABAergic populations from the ganglionic eminences migrated dorsally to populate the cortex⁸, as well as to all other structures within the telencephalon^{9,10}. Following work in the spinal cord, it was conjectured that an understanding of how specific subtypes are generated would fall out of a detailed analysis of gene expression within progenitors. It was assumed that combinatorial transcriptional codes in subpallial progenitors functioned to establish distinct cortical interneuron subtypes.

The connection between developmental origins and interneuron diversity has steadily expanded over the past twenty years. Virtually all GABAergic interneurons within the telencephalon arise from one of two embryonic subcortical progenitor zones, the medial and caudal ganglionic eminences (MGE and CGE, Figure 2). Moreover, those arising from each structure represent complementary interneuron subtypes^{11–14}. These major areas are augmented by specialized subpopulations from the lateral ganglionic eminence⁹ and the preoptic region¹⁵. It also became clear that there is a strong correspondence between interneuron class and the specific progenitor zones that gives rise to them. Within the cortex, the MGE gives rise to the parvalbumin (PV)-expressing fast spiking interneurons (including both basket and chandelier cells) and the somatostatin (SST)-expressing populations, of which the Martinotti cells form the largest subset^{11,16,17}. The CGE produces the relatively rarer subtypes including the neurogliaform, bipolar and VIP-expressing multipolar interneurons¹².

Genetic lineage analysis within the hippocampus reinforces the idea that specific interneurons arise from specific structures but demonstrates that a simple correspondence across forebrain regions is untenable. For instance, while in the cortex neurogliaform neurons are CGE-derived, a large proportion of the corresponding population in the hippocampus arises from the MGE¹⁹. Furthermore, while some classes such as fast-spiking basket cells show marked similarities across structures, others subclasses do not yet appear to have obvious paralogs. For instance, the CCK basket cells, while a large population within the cortex and hippocampus, do not appear to be present within other brain areas¹⁸. Similarly, there appears to be at least two populations of the so called OLM cells (named in accordance with the position of their cell body and dendrites^{20,21}) that derive from distinct sources, one which expresses the ionotropic serotonin receptor 5HT3aR and one that does not. Adding further complexity, analysis of the basal ganglia suggests that only the MGE is a major source of interneuron populations within these structures²².

These differences across areas raise two possibilities. First, there might be dedicated populations of interneuron progenitors that are committed to populating specific brain structures. Alternatively the notion of referring to an interneurons origin as deriving from a specific embryonic structure may be an imprecise proxy for gene expression. For instance,

even though hippocampal neurogliaform cells arise from both the MGE and CGE, a common constellation of specification genes may be acting within both embryonic regions. Similarly, the differential expression of functional determinants such as serotonin receptors, in otherwise similar interneuron subtypes are unlikely to represent distinct cardinal classes. Rather they likely represent iterations produced by cardinal cousins or differential postmitotic interactions by members of a single cardinal class.

These details emphasize the importance of mapping interneuron diversity onto molecular mechanism. GABAergic lineages can be divided into those with long-range projections such as those in the striatum or globus pallidus and the breadth of interneuron populations that are largely locally projecting. A number of factors appear to be utilized within all GABAergic neurons (Figure 2 bottom), most notably the *Dlx1/2*, *Ascl2* and *Gsh1/2* genes that encode transcription factors that themselves form a regulatory network^{23–25}. In the pallium (the region of the forebrain that will give rise to cortical structures), a similar cohort of transcription factors, including *Emx1*, *Ngn1/2* and *Pax6*, function analogously in the specification of the excitatory populations²⁶.

The *Dlx1/2* genes in particular function at multiple stages of GABAergic maturation: in the acquisition of GABAergic identity²⁷, the initiation and cessation of tangential migration^{4,28,29} and in the morphological and physiological maturation of specific subclasses²⁹. The specific role of *Dlx1/2* in these disparate developmental activities has become clearer as their transcription targets have been identified. These include *Elmo1*, *Dlx5/6*, *Arx* and *Sip1* (*Zfhx1b*), each of which have been shown to be required in the control of migration and regional identity^{30,43,44,45}. Moreover, their mutations, presumably via interneuron dysfunction, contribute to a variety of affective psychiatric disorders³⁰.

In addition, a number of factors appear more restricted to specific subtypes. Although far from complete, a genetic hierarchy for the MGE-derived PV and SST lineages has begun to emerge. Within the MGE, the cascade begins with *Nkx2.1*, which acts as master regulator in promoting MGE-derived interneuron fates over CGE-derived cell types^{31,32}. Moreover, in the cleanest example of a single gene contributing to the generation of a specific interneuron subtype, Chandelier or axo-axonic interneurons have been shown to arise relatively late in embryonic development (E15-E18 in mice) from a population of *Nkx2.1* progenitors^{33,34}. In addition, *Nkx2.1* is a gene with both activator and repressor function. Its repressor function attenuates the expression of CGE-specific genes, while its activator function induces the expression of *Lhx6*¹⁷, which is needed to promote the differentiation of both PV and SST-expressing interneurons. *Lhx6* in turn drives the expression of a series of factors including *Sox6* and *Satb1*^{35,36} whose actions selectively affect the development of both PV- and SST-expressing interneurons. By contrast, only a few genes as yet have proven to be specific to the CGE-derived lineages. While, collectively the specific functions of these transcription factors and their targets are still a work in progress, the tools to crack this problem are at hand.

Although the emerging picture is exhilarating, rather than coalescing into an explanation for the myriad of distinct subtypes that populate all areas of the forebrain, it appears to only reveal a handful of genetic cascades. If the goal were to simply account for the neuronal

markers that have been classically used to categorize interneurons then a mere six (PV, SST, VIP, NOS, REELIN, Calretinin) could collectively divide most of the range of interneurons within the forebrain. But clearly such a classification would belie the regional complexity of interneurons. Within the hippocampus alone there are easily four or five SST-expressing cell types and at least three PV-expressing populations. Similar distinct subpopulations of SST- and PV-expressing populations are being discovered in the cortex and more will likely be found. Although we believe the cardinal specification of interneurons is only the first, -- albeit critical--, step in the progressive specification of subpallial progenitors, can our cardinal identity hypothesis account for this increasing wealth of interneuron subtypes? It is certainly possible that we have grossly underestimated the cardinal subtypes. Indeed, complex maps showing intricate embryonic patterns of gene expression within the subpallium have been posited to combinatorially specify different cell types³⁷. We however think that the cell types generated by developmental programs are unlikely to explain all the regional diversity observed. First, the loss of specific genes results in phenotypes that are invariably not restricted to specific interneuron subtypes. Second, the loss of specific genes affects the generation of interneurons across a variety of structures arguing against the existence of progenitor populations dedicated to the generation specific interneuron classes. That said, one could imagine a combinatorial gene regulation strategy in which an individual gene could be necessary for a variety of disparate differentiation programs. Hence another way to explore the question of whether regional diversity is established in progenitors is through lineal analysis.

2. Lineages: families of interneurons

Are the interneuron populations that populate particular structures, such as the hippocampus or cortex, derived from dedicated progenitor pools? Two recent studies have directly explored the role of lineage in the development of cortical interneurons^{38,39}. Both have shown that clonally related progenitors appear to be preferentially relegated to specific cortical columns or layers, supporting the idea that progenitor lineages are dedicated to producing lineages destined for particular brain structures. Given the long and convoluted paths taken by these progenitors as they transit to their mature position^{40,41} that clones could collectively target particular parts of cortex was stunning. Interestingly, such clones were equally likely to be comprised of mixed SST- and PV-expressing interneurons rather than one subtype. Perhaps this lack of tendency for clones to “breed true” should not come as a surprise. A wealth of lineage analysis in invertebrates⁴², as well as the vertebrate retina⁴³ and spinal cord⁴⁴ indicates that neuronal lineages while stereotyped do not in general produce cells of a single subtype. Moreover, it will be interesting to explore whether in addition to being clustered, lineally-related cells are also dispersed and if so to what extent^{45,46}. If they do, it will be intriguing to assess the afferent and efferent connectivity of such clones, as this would speak to the question as to how intrinsic versus local cues impact the connectivity of interneurons.

3. How circuits nurture interneuron subtypes

The accumulated evidence supports a strong role for developmentally regulated genetic programs in the allocation of interneurons to broad “cardinal” classes. What it does not

appear to explain is how interneurons from the same cardinal class are able to form connections with such a wide variety of synaptic partners. In favor of a role for local cues contributing to this process, a variety of studies have suggested that both excitatory and inhibitory signals may influence the migration and positioning of developing interneurons^{47,48}. Recent data has shown that attenuating the activity of specific interneuron populations affects both their migration and morphological development⁴⁹. Although acting in a class-specific manner, it has yet to be demonstrated that this activity is instructive rather than simply permissive. That said there appears to be growing support for the notion that local signals may direct the region specific differentiation of interneurons. In support of this, a number of genes are specific to interneurons within the cortex but not the striatum, including *Zfhx1b*, *Dlx1*, *Elmo1* and *Mef2c*, the later three of which are activity-regulated^{30,49–52}. While it may be that activity simply promotes the maturation of interneuron populations that are already pre-specified, it is also possible that activity directs region-specific differentiation. Extensive work has indicated that voltage-gated calcium influx may result in *de novo* gene expression (reviewed in⁵³). Indeed, it is the present failure to identify genes within proliferative populations that are indicative of region specific differentiation that has led us to propose a two-phase model of interneuron specification. We envision that activity-regulated gene expression during “critical periods” may be responsible during the second phase for the allocation into cardinal classes into specific subclasses. Recent work has shown that MGE-derived cells can productively integrate into both normal and abnormal neuronal circuits^{54–56}. This supports the idea that local cues can direct nascent interneurons to form appropriate connectivity with a variety of synaptic partners. Understanding how interneurons can form functional circuits in a variety of structures is a critical question that remains to be answered.

Until now we have taken a bottom-up developmental view, aimed at examining events by which interneuron subtypes are integrated into functional circuits. In the next section, we will take a top-down view and examine circuit specific functions of interneuron types. A prediction of our model is that the developmental genetic programs functioning in interneuron progenitors lead to the production of a relatively small number of cardinal subclasses. We believe that the much larger diversity of interneurons observed in mature brain circuits reflects later refinements imposed locally on specific subclasses. If this were true, it would predict that interneurons from the same cardinal class would within the same circuit be exposed to similar cues and hence develop similar functional properties. While the data to date is in its nascent stages, the availability of genetic driver lines^{57,58} to reliably target particular interneuron cohorts, has provided the means to test this hypothesis.

4. The function of cortical inhibitory interneurons

What is a meaningful measure of the function of an interneuron subtype? Because interneurons generally project locally, their firing needs to be understood in the context of the circuits they contribute to. There are two complementary ways of approaching the question of what an interneuron does (Figure 3). First, we can ask about *recruitment*: what drives an interneuron to fire? Under what circuit and brain state configurations or behavioral contingencies is a given neuron active? This is strongly constrained by the neuron’s afferent connectivity, which in turn is likely dictated by their developmental genetic program.

However, interneurons are not hardwired. A set of afferents that drive interneurons to fire in one context may fail to do so in another. Clearly understanding their recruitment must take into account a large number of factors. We will consider two large classes of recruitment hypotheses (Figure 4). The classic idea is that interneurons serve to ‘Coordinate’ networks, such that their recruitment is best understood in reference to the local population activity. Alternatively we consider an alternative view we term the “Flow control” hypothesis, where interneurons serve to gate information flow within a given circuit and are excited at precise moments in reference to specific behavioral events. These two ideas are by no means mutually exclusive, as successful flow control must depend on the signals being suitably coordinated. Second, we can ask about *circuit impact*: how does the firing of an interneuron influence the activity of neurons in its local circuit? This aspect of function is strongly constrained by the efferent connectivity of a neuron, which is thought to be dependent on their developmental genetic program. In addition, the impact of an interneuron type will also greatly depend on whether their recruitment is coordinated with other neurons of the same cohort.

Historically, models of cortical function have focused on “circuit motifs”, repeated patterns of connectivity, to infer computational function for specific cell types⁵⁹. Perhaps because inhibitory interneurons are largely local they have been generally considered to simply guard excitatory networks against runaway excitation⁶⁰. In recent years our understanding of their function has become significantly more sophisticated. Among the lessons learned were that interneurons could normalize the activity of local excitatory networks as well as provide feed-forward inhibition. The later strongly influences the timing of signals and enables excitatory signals to remain subthreshold while carrying information. Of course, these are just two motifs out of a vast range of possibilities, including cross-coupling that can lead to synchronization, lateral inhibition that can segregate principal neuron populations and disinhibition generating elevated activity. Indeed, it has become clear that there are at least as many inhibitory circuit motifs as there are cell types.

Interneurons in cortical computations

How then does the diversity of interneurons contribute to neural computations? First, it’s worth noting that it would be difficult to imagine networks with only excitation. In fact from an engineering standpoint, such networks would either have to have extremely time-limited dynamics or they would become intrinsically unstable. Moreover, inhibition not only provides balance. It ensures richness in the possible dynamics within networks of principal neurons. These considerations lead to the idea that interneuron diversity allows for a vast increase in the computational power of cortical circuits⁶¹. What then are these computations? Broadly speaking, the computational functions of interneurons can be grouped into either arithmetic or timing.

A long-held idea is that different interneurons perform essentially arithmetic operations, such as subtraction or division^{62,63}. Inhibition can provide gain control by changing the input-output relationship between the excitatory drive and the resulting firing rate in principal cells: either by decreasing the slope divisively or by a subtractive shift. In turn these elementary operations are the building blocks for cortical computations such as

normalization, an operation that provides divisive gain in proportion to the summed activity in a circuit^{64,65}. Such gain modulation might result from shunting⁶⁶, synchronous⁶⁷ or balanced⁶⁸ inhibition. Originally proposed to explain early visual cortical responses⁶⁴, it has become one of the most studied cortical computations^{73,74}.

The advent of tools to probe interneuron function *in vivo* is presently allowing the contributions of different interneuron types to be explored. Several recent studies have focused on the computational functions of PV- and SST-expressing interneurons in the visual cortex. Optogenetic control of PVs can bidirectionally modulate the gain of visual responses^{69,70}. Under some conditions optogenetic activation of PV neurons can even sharpen the tuning of cortical responses⁷¹. In contrast, SST interneurons have broader spatial tuning in visual cortex and they mediate surround suppression of visual responses^{72,73}.

Another line of theoretical investigation has focused on the role of interneurons in controlling the timing of neural activity. More complex network functions require that neurons do not fire together. This can be achieved by dynamically balancing excitation with inhibition so that the resulting network activity becomes temporally irregular and asynchronous. These balanced networks thus provide rich dynamics and rapid responses⁷⁴. Indeed, recordings from cortex often reveal finely balanced excitation and inhibition^{75–78}, consistent with these models. When inhibition precisely tracks excitation, it can alternatively serve to increase temporal precision^{75,79} or decorrelate networks⁸⁰.

5. Circuit impact of identified interneuron types

Understanding how computations are implemented in neural networks requires understanding how interneuron subtypes impact local networks. While traditionally studied *in vitro*, we will focus mostly on recent *in vivo* work using transgenic mice for targeting interneurons based on markers, such as parvalbumin (PV), somatostatin (SST) and vasointestinal peptide (VIP)^{57,58}. However, these cre-driver mouse lines neither demarcate entirely homogeneous interneuron populations nor map precisely onto cardinal interneuron types. Nevertheless they provide a convenient and powerful tool for parsing interneuron heterogeneity because these three major markers target distinct non-overlapping populations and in aggregate can label ~85% of all cortical interneurons^{13,81,82}. When combined with optogenetic modulators^{83,84} these have enabled researchers for the first time to test many long held theories about the roles of inhibition.

PV-expressing interneurons (either soma-targeting basket cells or chandelier cells targeting the axon initial segment) are strategically positioned to control spiking and are also strongly interconnected, which promotes their synchronous activity^{85–89}. Recent studies showed that PVs control the timing of spikes with respect to theta oscillations in hippocampus^{90–92}.

SST-expressing cortical Martinotti neurons are dendritic-targeting interneurons that project to layer 1 and provide inhibition to the tufts of deep layer pyramidal cells. Inhibition by Martinotti cells strongly suppresses dendritic calcium spikes and bursting⁹³ and can mediate di-synaptic inhibition between neighboring pyramidal cells^{94,95}. Similarly, in the hippocampus, dendritic inhibition by SST neurons controls burst firing^{90,91,96}. However,

SST-expressing neurons are anatomically diverse, with some subtypes specializing in disinhibition of local principal cells⁹⁷.

VIP demarcates the third major class of interneurons, comprising ~15% of all interneurons^{81,82} and are mostly located in the superficial layers of cortex. VIP-expressing interneurons have been long proposed to mediate disinhibition^{98,99}. Recent studies have shown that in four different cortical regions VIP interneurons tend to inhibit most SST and a sub-fraction of PV interneurons^{88,100,101} and thus disinhibits principal cells, providing a form of gain control¹⁰¹. These results demonstrate that VIP-expressing neurons form a disinhibitory microcircuit that is conserved across cortical regions with shared computational functions.

A final example is provided by neurons within layer 1, which are all almost all inhibitory interneurons¹⁰². Recent results found that two major interneuron types have opposing functions: neurogliaform cells inhibited layer 2/3 pyramids, while single bouquet cells inhibited other interneurons within layer 2/3, and may provide disinhibition in vivo^{103,104}.

These studies have begun to allow for causal testing of hypotheses using optogenetics. In addition, these provide support for the hypothesis that cardinal classes of interneurons have defined circuit functions. However, these carry the caveat that optogenetically targeted neural population correspond to functional classes that “act together” that needs to be tested on a case-by-case basis by recording them during behavior.

6. Recruitment: coordination and flow control

What are the brain-state and behavior-dependent contingencies that determine when a specific interneuron type is activated? At the broadest scale, different behavioral modes are associated with large changes in global brain activity, therefore it is not surprising that different classes of inhibitory interneurons are activated in a highly state-dependent manner^{105–108}. At a more refined scale, what is the simplest description of the conditions under which a given interneuron is activated? Is recruitment of an interneuron subtype best understood with reference to a network state or a behavioral contingency?

Network recruitment of interneurons: the coordination hypothesis

One idea is that interneurons coordinate the precise timing of principal cell activation such as the network oscillations. There is a long history of experimental and theoretical investigations proposing that the diversity of interneuronal subtypes underlies a division of labor for organizing cortical population activity at different time scales^{61,109–111}.

The best-studied examples of the contribution of different interneurons come from the hippocampus where recordings from targeted cells have been able to correlate their firing to network oscillations^{106,112–115}. These studies, mostly from anaesthetized animals, revealed that distinct interneuron subtypes fire during different rhythms (e.g. theta, gamma, ripple) and with distinct phase-relationships, suggesting they differentially contribute to network dynamics. These results suggest that the spike timing of different interneuron types can be referenced to specific network events^{61,106,116} (Figure 4, left). More generally, this work

supports the “coordination hypothesis” where each interneuron subtype performs as a temporal specialist within a ‘distributed clock system’ that coordinates pyramidal cells ensembles¹¹¹ (Figure 4, left).

These observations set the stage for testing the causal role of different interneuron subtypes in generating oscillations^{105,106}. Recently two important studies probed the role of PV interneurons using either optogenetic activation¹¹⁷ or suppression¹¹⁸ and found increased and decreased gamma oscillations, respectively, suggesting that interneurons are indeed actively involved in their generation.

Behavioral correlates of interneurons: the flow control hypothesis

Alternatively, it is possible that the function of some interneuron types is better described with reference to behavioral events. Although, interneuronal identity has long been inferred in behaving animals on the basis of spike waveform and firing pattern^{109,119,120}, it is only recently that this could be directly ascertained for a handful of genetically defined interneurons during well-controlled behaviors. Using the optogenetics-assisted identification technique in the anterior cingulate cortex (ACC) of mice performing a simple foraging task, the surprising observation was made that deep layer PV and narrow-spiking SST interneurons responded in a functionally homogeneous manner at specific-behavioral epochs⁸⁷ (Figure 4, Right). Similar observations were made in rat motor cortex using juxtacellular labeling in head-fixed rats¹²¹. While pyramidal cells responded in heterogeneous ways, all PVs responded similarly at the moment of movement initiation. This shows that PV interneurons, at least in mouse frontal regions, can be thought as a functional unit. How could such functional homogeneity be achieved? One possibility is that inhibitory interneurons strongly sample local principal cell activity and their activation reflects a “summary” of local activity⁸⁵. Therefore PVs might fire in a behavior and region-dependent manner, which may be the ‘leaving decision’ in ACC owing to its role in foraging¹²²; but movement initiation in motor cortex.

Other examples of behaviorally-activated responses come from the auditory cortex, where a large fraction of interneurons in layer 1 are activated by negative reinforcers during auditory fear-conditioning¹⁰⁴. Similarly, VIP interneurons are strongly and uniformly recruited by negative- (air puff or mild shock) or positive (water reward) reinforcement during an auditory discrimination task¹⁰¹ (Figure 4, Right). Although such reinforcement feedback-related signals may at first pass seem surprising in a primary sensory area, as VIP interneurons mediate disinhibition (see above) they are ideally fit to serve to gate information⁹⁸ (Figure 3).

As we stated above, because interneurons are embedded in a highly interconnected network, their functions need to be understood in the context of local networks¹²³. In this light, the observations that some interneuron types are recruited at specific behavioral events may seem puzzling. Indeed, consistent with the “coordination” hypothesis^{111,116}, one would expect that the majority of the responses would be constrained by the state of the local network, on a time scale of milliseconds, and not by behavioral contingencies. Indeed mechanistically, the observed behaviorally specific activation may reflect local network activity, which itself is tied to specific behavioral contingencies. We suspect that this

explains the homogeneous activation of deep layer PV neurons. Nevertheless their function is most parsimoniously described by temporal reference to specific behavioral events. Alternatively, specific classes of interneurons may be activated by strong long-range inputs. For instance, neuromodulatory systems can provide behavior-dependent inputs to specific interneuron classes. Interestingly, VIP neurons have ionotropic receptors for the neuromodulators acetylcholine and serotonin, which likely drive reinforcement signals in these neurons^{98,124}.

At present, the behavioral recruitment of many interneuron types remains unexplored and different mechanisms may apply to each type. In contrast to the coordination hypothesis, these early results support the “flow control” hypothesis (Figure 4) proposing that distinct interneuron types specialize in controlling information flow in and out of a local circuits by suppressing or boosting principal cell pathways and modulating response gain during specific behavioral contingencies and thus acting much like controllers to a state-machine. This suggests that the recruitment of an interneuron type is linked with behavioral scale requirements of local circuits. Moreover, the observations that genetically-targeted interneuron classes show similar recruitment suggests they do indeed act as functional units, supporting the existence of a small number of cardinal interneuron types.

7. Conclusions and Outlook

We are in the midst of an exciting era where new data on the development and function of interneurons are being weekly brought to light. In our perspective we suggest that the large diversity in interneuron classes may originate from a handful of cardinal cell types. Such an assertion could be misinterpreted as a statement claiming that interneuron classes are in fact not diverse or that divisions into further subtypes is not warranted. The incredible work in areas such as the hippocampus show us that this is patently incorrect. What we are trying to provide is a framework that will help direct future studies by consolidating interneuron diversity into cardinal classes with specific ground states. Therefore if one wishes to explore questions such as the intrinsic physiological properties, axonal targeting or general target selection then understanding the ground state established in progenitors is a good place to start. However, if one wishes to explore the circuit properties, connectivity or computational contributions of a subclass of interneurons, one needs to consider the interplay between cardinal cells and the local cues received from the circuits they contribute to. From a functional point of view, if we confine ourselves to specific circuits, such as VIP interneurons, a cardinal class will share important aspects of their function. Hence the tools to genetically target cardinal classes will prove invaluable for parsing the function of the different and quite exotic interneuron subtypes they ultimately give rise to.

It is intriguing to contemplate why such a mechanism is used to create cellular diversity. It may be that the strategy used by natural selection favors simple programs to provide stability, and combinatorial assembly to provide complexity. Although they are ultimately incorporated in a wide breadth of circuits, cardinal interneuron classes share critical combinations of features that enable their function. Genetic program direct the receptors they express, the cell types and subcellular compartment they innervate, as well as their firing properties. These features in turn strongly constrain their recruitment and circuit

impact. In short, we may ultimately find interneurons exist as cardinal classes because nature has conspired to bestow on them generalized computational function that necessitated the presence of common biophysical and hodological properties. Despite these commonalities, it is self-evident that neural circuits allow for a remarkable array of behavioral outcomes. Harnessing biology's ability to use limited set of building blocks, to create enormous diversity circuits holds the real promise that we may soon begin understand the means by which brain circuits self-assemble and initiate function.

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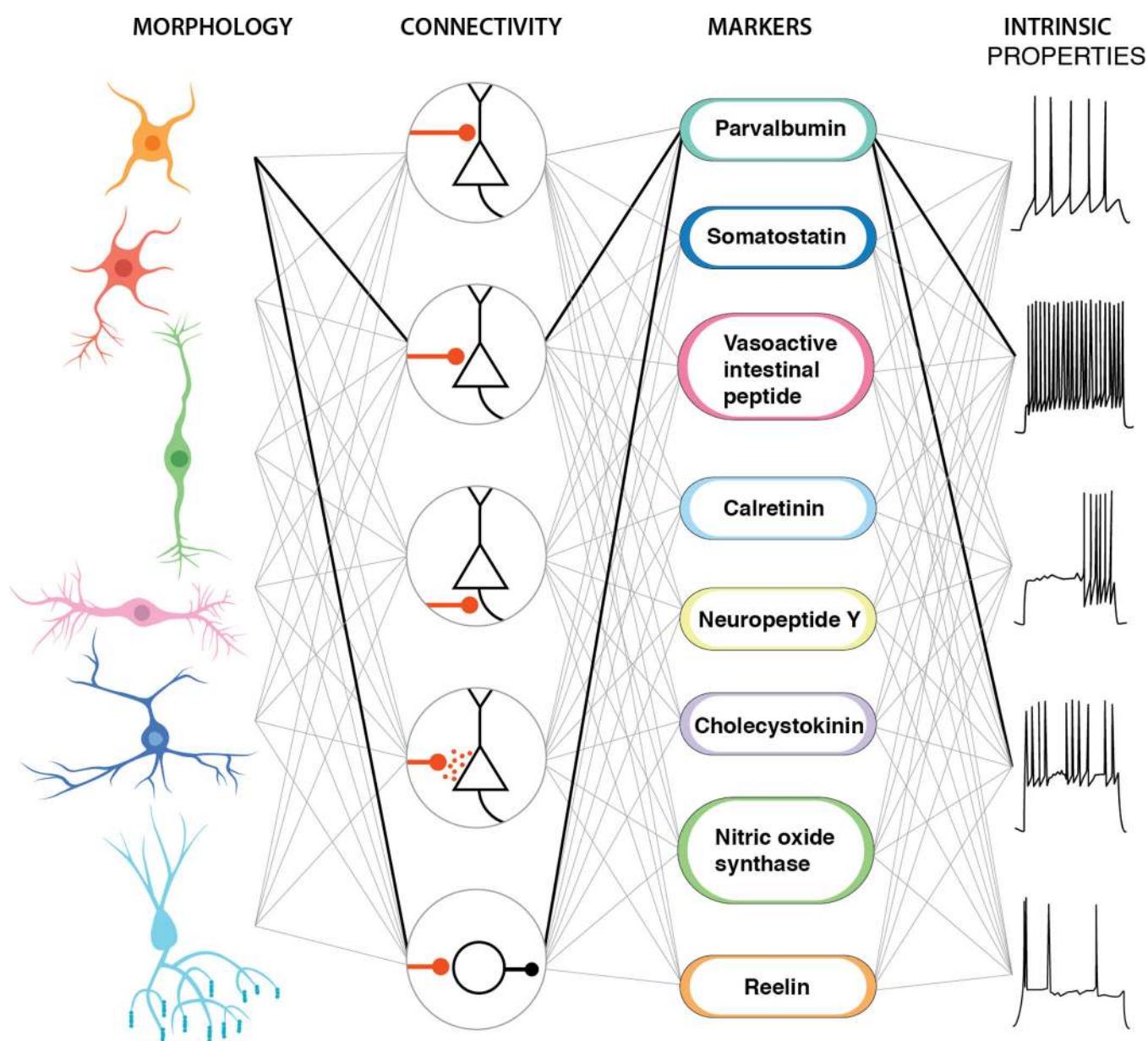


Figure 1. Schematic of interneuron diversity across the brain

Within each of the distinct anatomical regions of the brain exist discrete interneuron populations. In some of these cases the paralog relationships between subtypes within specific regions are obvious (such as the fast-spiking basket cells), while in others such as the hippocampal CCK basket populations they appear to uniquely population specific structures.

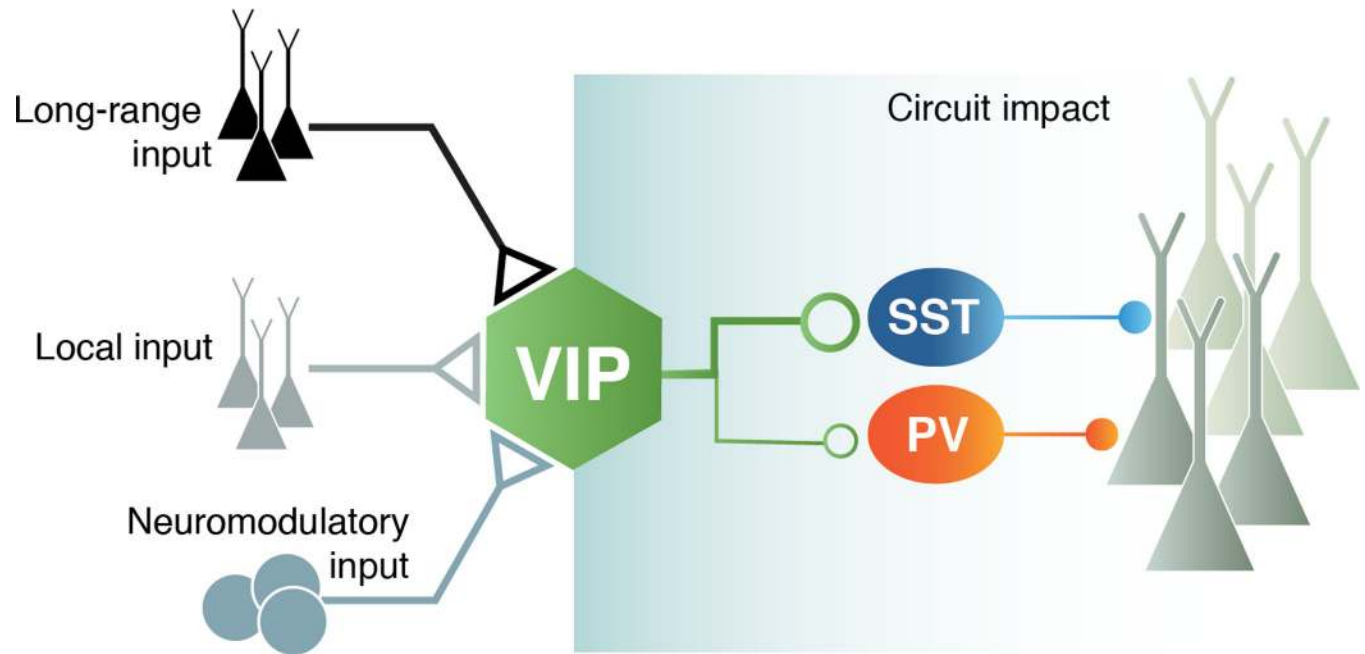


Figure 2. Interneurons subtypes are generated from discrete proliferative regions within the subpallium

On the **Left side** of this figure we show the progressive development of the telencephalon from being an undifferentiated epithelium to being divided up into discrete proliferative zones that produce particular interneuron populations. On the **Right side** we show a more anatomically accurate cross-section of the progenitor zones and then for illustration show a schematic of interneuron diversity in the cortex in the top panel. Interestingly, while common proliferative zone produce the entire diversity of interneurons across all telencephalic structures, unique cell types and gene expression are seen in interneuron populations that reside in particular telencephalic structures.

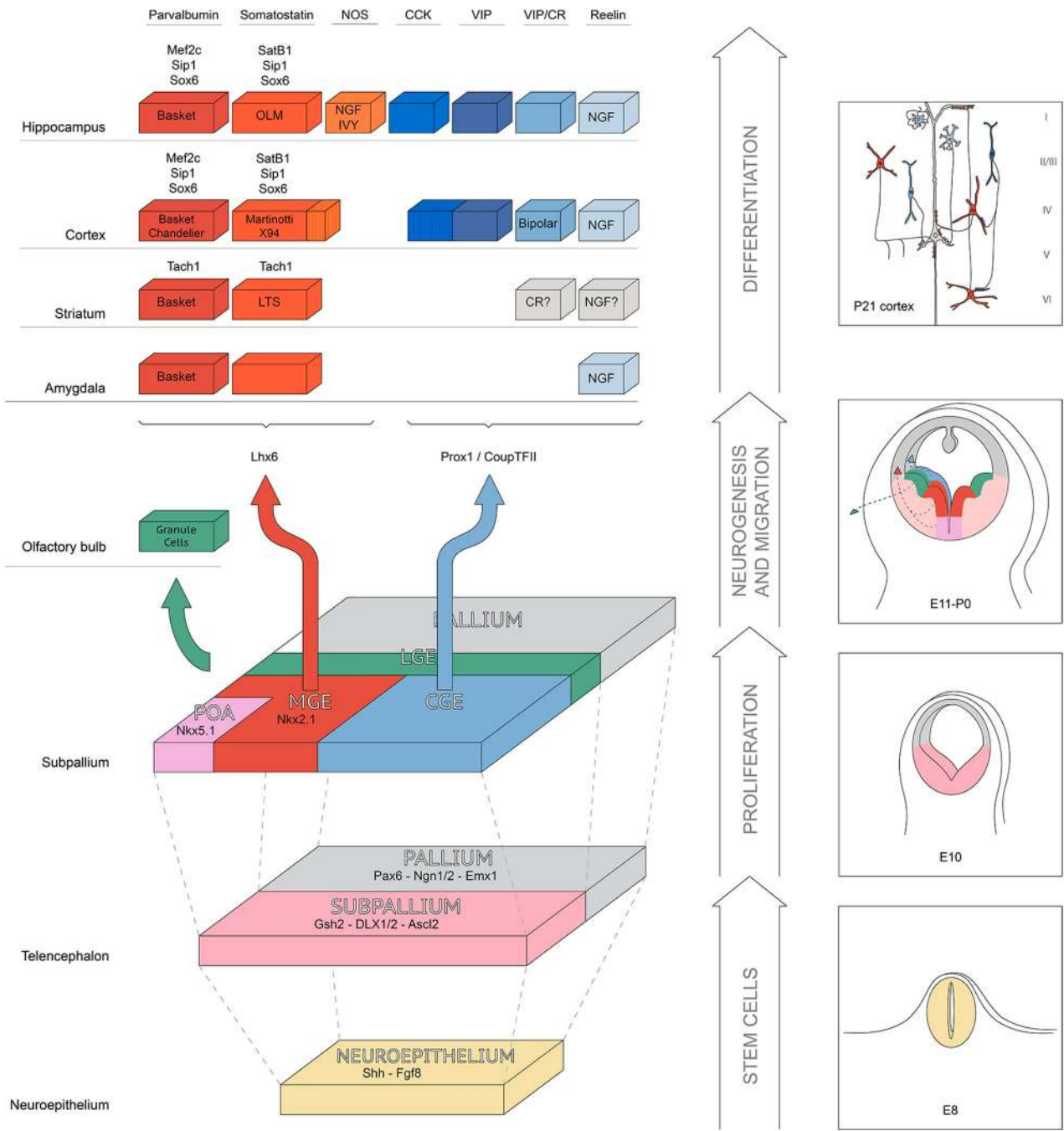


Figure 3. Two faces of interneuron function
A cortical circuit from the perspective of a VIP interneuron. The recruitment of VIP interneurons is constrained by the inputs it receives. The afferents can be long-range from other cortical areas and also neuromodulatory from the dorsal raphe (DR) and nucleus basalis (NB) via ionotropic receptors. The circuit impact of VIP interneurons is constrained by its outputs. The efferents are mostly to SST interneurons and to a smaller degree to PV interneurons, which lead to the disinhibition of a functional subset of principal cells (black).

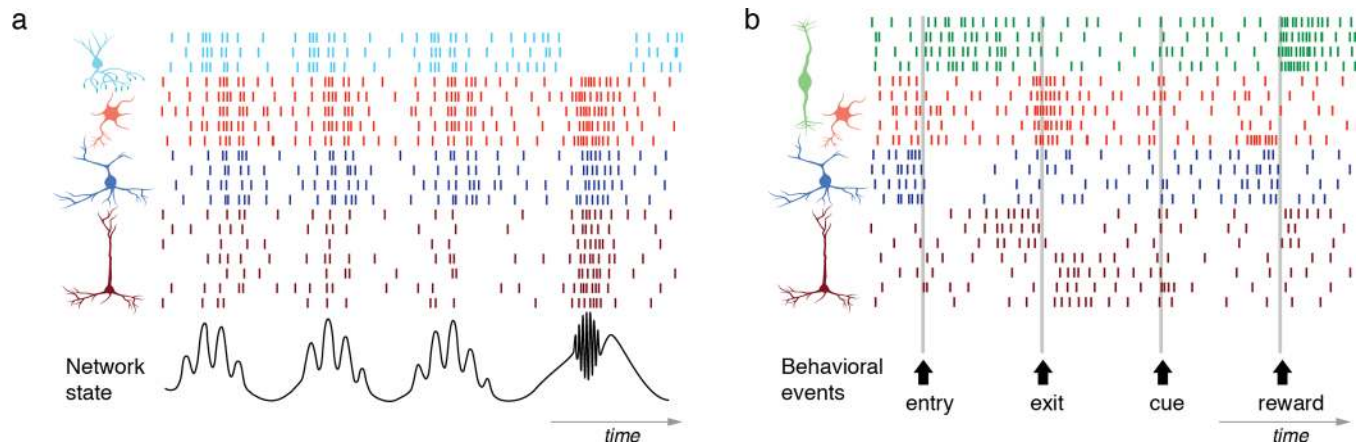


Figure 4. Coordination and flow control hypotheses of recruitment

Left, Coordination hypothesis. The bottom trace shows a local field potential representing the network state in the hippocampus. The firing of different neuron types can be described in reference to the LFP, both in terms of overall activity level and phase-relationship. *Right*, Flow control hypothesis. The bottom arrows mark the timing of three behavioral events, exit, entry and reward. The firing of different neurons can be described in reference to these events.