REVIEW

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Interneuron cell types are fit to function

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Understanding brain circuits begins with an appreciation of their component parts — the cells. Although GABAergic interneurons are a minority population within the brain, they are crucial for the control of inhibition. Determining the diversity of these interneurons has been a central goal of neurobiologists, but this amazing cell type has so far defied a generalized classification system. Interneuron complexity within the telencephalon could be simplified by viewing them as elaborations of a much more finite group of developmentally specified cardinal classes that become further specialized as they mature. Our perspective emphasizes that the ultimate goal is to dispense with classification criteria and directly define interneuron types by function.

Interneurons, of all the cells within the forebrain, are the most diverse in terms of morphology, connectivity and physiological properties[1]. Until 10 years ago, their classification, with a few notable exceptions[2], 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]. Studies from the past few years have coalesced into the surprising view that interneuron diversity may fundamentally be far more limited. When we consider their commonalities at a genetic, circuit or functional level, an argument can be made for condensing large subclasses of interneurons into more finite groups. In this Review, we suggest that, on the basis of both developmental and functional criteria, interneuron diversity can be simplified and addressed experimentally. The differences in connectivity, gene expression and physiological properties of interneurons found across the brain seem enormous (Fig. 1), nevertheless, we argue that this complexity arises from a small number of non-overlapping cardinal classes. These represent developmental genetic ground states that can 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 targeting specificity, coupled with the means to manipulate the *in vivo* activity of targeted neural populations this goal is becoming attainable.

Birth and specification of interneurons

How is neuronal diversity created? Developmental studies across various species[5,6] and systems[7,8] have suggested that cell diversity arises from specification programs established in progenitors that have been modified to varying extents by their subsequent post-mitotic interactions. The balance between genetic- and experience-dependent processes seems to represent a compromise dictated by the organizational constraints of the particular system. Within the cortex, 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 progenitors[9]. By contrast, interneuron progenitors of the telencephalon undergo incredibly complex patterns of dispersion. At the extremes, this could either be due to exquisitely precise pre-programs for migration to particular structures or plasticity mechanisms that allow the progenitors to adapt to local environments.

Until the late nineties, it was widely assumed that 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 zones[10]. This first came to light with landmark papers showing that the GABAergic populations from the ganglionic eminences migrated dorsally to populate the cortex[10], as well as to all other structures within the telencephalon[11,12]. Subsequent work in the spinal cord, led to the conjecture that an understanding of how specific subtypes are generated would come from a detailed analysis of gene expression within progenitors. It was assumed that combinatorial transcriptional codes in subpallial progentiors functioned to establish distinct cortical interneuron subtypes.

The connection between developmental origins and interneuron diversity has steadily expanded over the past 20 years. Almost all GABAergic interneurons within the telencephalon arise from one of two embryonic subcortical progenitor zones, the medial ganglionic eminence (MGE) and caudal ganglionic eminence (CGE; Fig. 2). Moreover, those arising from each structure represent complementary interneuron subtypes[6,11–15]. These major areas are augmented by specialized subpopulations from the lateral ganglionic eminence[9] and the preoptic region[8]. It also became clear that there is a strong correspondence between interneuron classes 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[13,16,17]. The CGE produces relatively rarer subtypes, including neurogliaform, bipolar and vasointestinal peptide (VIP)-expressing multipolar interneurons[14].

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, although in the cortex neurogliaform neurons are CGE-derived, a large proportion of the corresponding population in the hippocampus arises from the MGE[18]. Furthermore, whereas some classes, such as fast-spiking basket cells, show marked similarities across structures, others subclasses do not yet seem to have obvious paralogues. For instance, cholecystokinin basket cells, although a large population within the cortex and hippocampus, do not seem to be present within other brain areas[19]. Similarly, there seems to be at least two populations of the so called oriens/lacunosum-moleculare 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,

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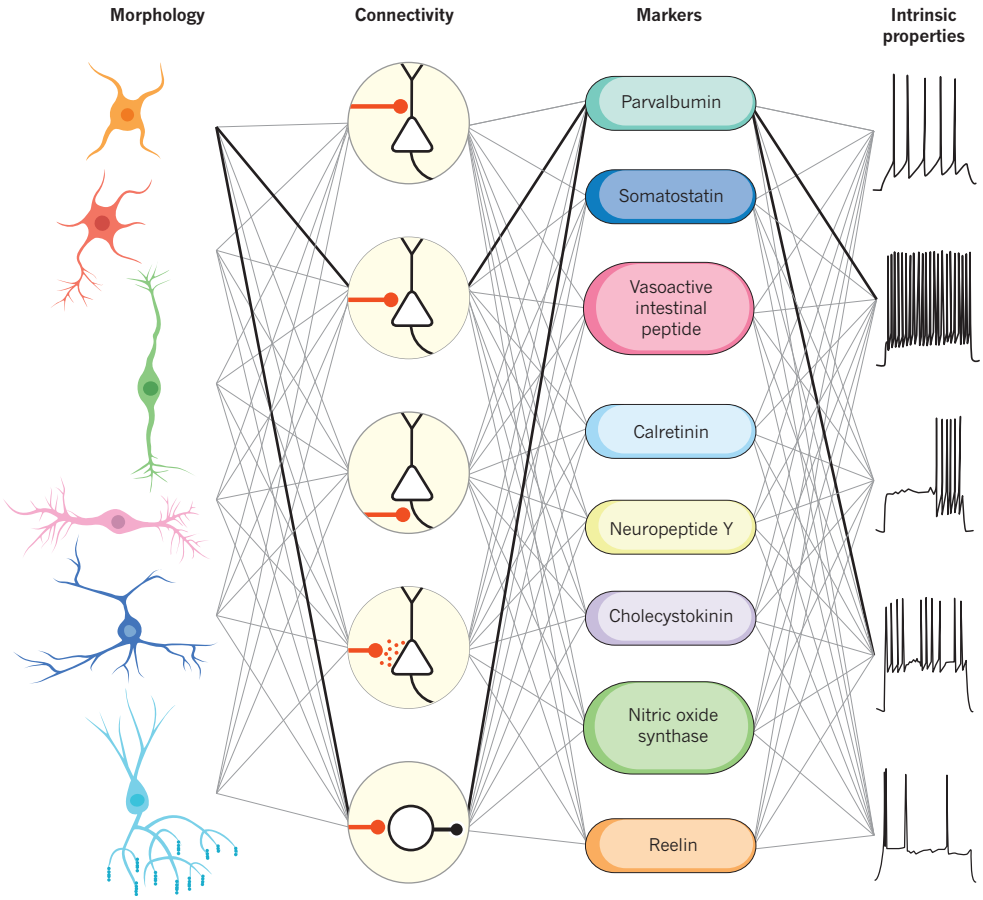

Figure 1 | Multiple dimensions of interneuron diversity. Interneuron cell types are usually defined using a combination of criteria based on morphology, connectivity pattern, synaptic properties, marker expression and intrinsic firing properties. The highlighted connections define fast-spiking cortical basket cells.

analysis of the basal ganglia suggests that only the MGE is a major source of interneuron populations within these structures[22].

These differences across areas raise two possibilities. First, there might be dedicated populations of interneuron progenitors that are committed to populating specific brain structures. Second, the notion of referring to an interneuron's 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 probably represent iterations produced by cardinal cousins or differential post-mitotic interactions by members of a single cardinal class.

These details emphasize the importance of mapping interneuron diversity onto molecular mechanisms. GABAergic lineages can be divided into those with long-range projections, such as those in the striatum or globus pallidus, and interneuron populations that largely project locally. A number of factors seem to be used within all GABAergic neurons (Fig. 2), most notably the transcription factors encoded by *Dlx1* and *Dlx2*, *Ascl2*, and *Gsx1* and *Gsx2* 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 those encoded by *Emx1*, *Neurog1* and *Neurog2*, and *Pax6*, function analogously in the specification of the excitatory populations[26].

Dlx1 and *Dlx2*, in particular, function at multiple stages of GABAergic maturation: in the acquisition of GABAergic identity[27], the initiation and cessation of tangential migration[4,28,29], and in the morphological and physiological maturation of specific subclasses[29]. The specific role of *Dlx1* and *Dlx2* in these disparate developmental activities has become clearer as their transcription targets have been identified. These include *Elmo1*, *Dlx5* and *Dlx6*, *Arx* and *Gemin2* (or *Zep2*), each of which has been shown to be required in the control of migration and regional identity[30–33]. Moreover, mutations of these genes, presumably through their requirement for interneuron function, contribute to a variety of affective psychiatric disorders[30].

In addition, a number of factors seem to be 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[34,35]. Moreover, in the clearest 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 (embryonic day 15 to 18 in mice) from a population of *Nkx2-1* progenitors[36,37]. In addition, *Nkx2-1* is a gene with both activator and repressor function. Its repressor function attenuates the expression of CGE-specific genes, whereas its activator function induces the expression of Lhx6 (ref. 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* (refs 38, 39) the products of which selectively affect the development of both PV- and SST-expressing interneurons. By contrast, so far only a few genes have proven to be specific to the CGE-derived lineages. Collectively, the specific functions of these transcription factors and their targets are still a work in progress, but the tools to tackle this challenge are at hand.

Although the emerging picture is exhilarating, rather than coalescing into an explanation for the myriad distinct subtypes that populate all areas of the forebrain (Fig. 1), it seems to only reveal a handful of genetic cascades. If the goal were simply to account for the neuronal markers

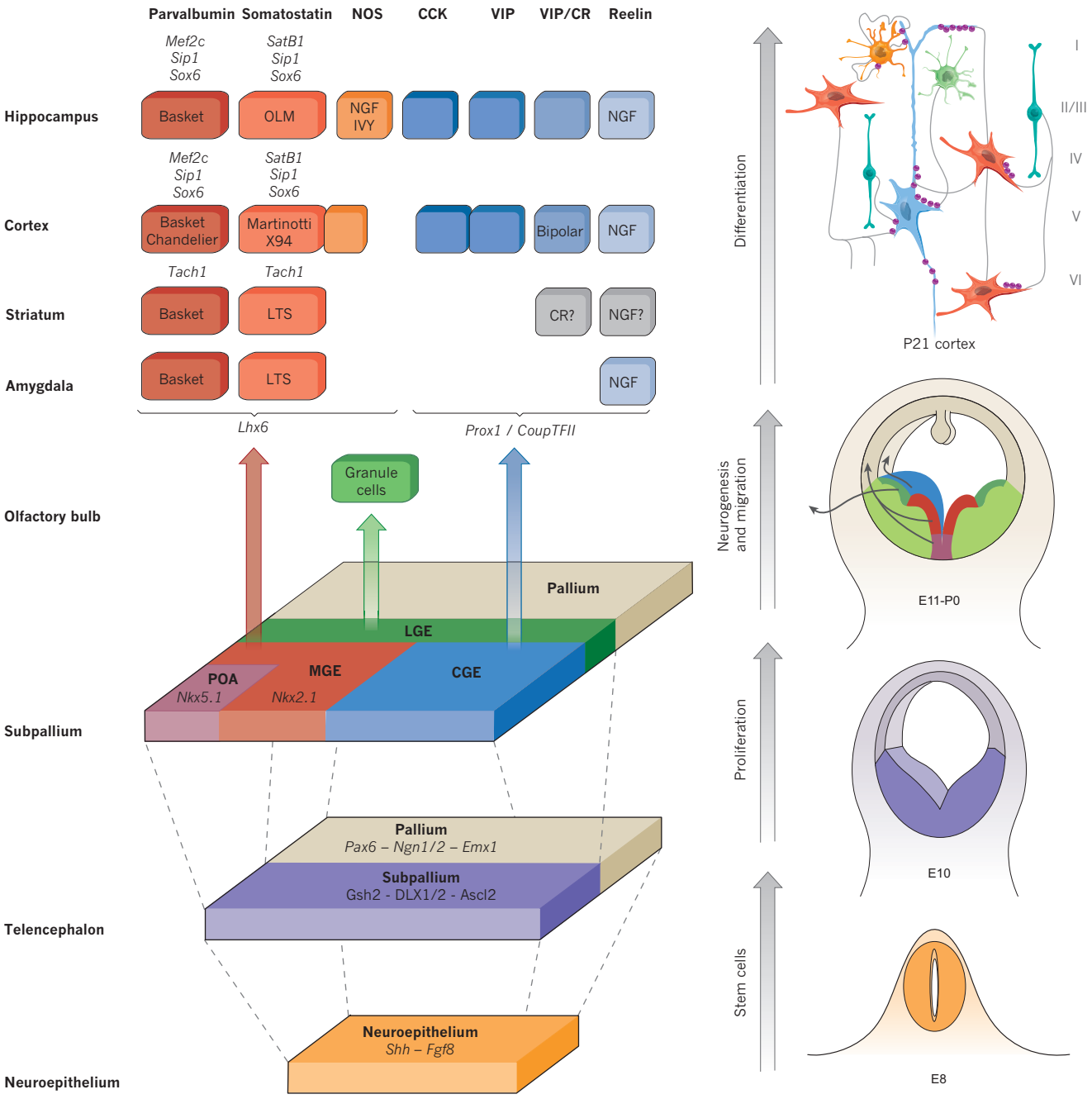

Figure 2 | Interneuron subtypes are generated from discrete proliferative regions within the subpallium. The progressive development of the telencephalon from an undifferentiated epithelium into discrete proliferative zones that produce particular interneuron populations and the specific genes involved at each stage. On the right are more anatomically accurate cross-sections of the progenitor zones from embryonic day 8 to 11, and a schematic of interneuron diversity in the cortex. Interestingly, although common proliferative zones 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. CCK, cholecystokinin; CR, calretinin; CGE, caudal ganglionic eminence; LGE, lateral ganglionic eminence; LTS, low threshold spike; MGE, medial ganglionic eminence; NGF, nerve growth factor; NOS, nitric oxide synthase; OLM, oriens/lacunosum moleculare; POA, pre-optic area; VIP, vasointestinal peptide.

that have conventionally been used to categorize interneurons, then a mere six (PV, SST, VIP, nitric oxide synthase, reelin and calretinin) could divide most 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 have been discovered in the cortex, and more will probably be found. Although we believe that the cardinal specification of interneurons is only the first, albeit crucial, 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. Complex maps showing intricate embryonic patterns of gene expression within the subpallium have been posited to combinatorially specify different cell types[40]. However, we think that the cell types generated by developmental programs are unlikely to explain all of 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 various structures, arguing against

the existence of progenitor populations dedicated to the generation-specific interneuron classes. That said, it is possible to 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 lineage analysis.

Interneuron lineages

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[41,42]. Both have shown that clonally related progenitors seem 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[43,44], it was stunning that clones could collectively target particular parts of the cortex. 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 invertebrates[45], as well as in the vertebrate retina[31] and spinal cord[32], indicates that neuronal lineages, although stereotyped, do not generally 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[33,46]. If they are dispersed, it will be intriguing to assess the afferent and efferent connectivity of such clones, as this would help address the question: to what extent do intrinsic compared with local cues direct the connectivity of interneurons?

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 seem to explain is how interneurons from the same cardinal class are able to form connections with such a wide variety of synaptic partners. In favour of a role for local cues contributing to this process, various studies have suggested that both excitatory and inhibitory signals may influence the migration and positioning of developing interneurons[47,48]. Recent data have shown that attenuating the activity of specific interneuron populations affects both their migration and morphological development[49]. Although the activity is class specific, whether it is instructive rather than simply permissive has yet to be demonstrated. That said, there seems 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 *Zep2*, *Dlx1*, *Elmo1* and *Mef2c*, the last three of which are activity regulated[30,49–52]. Although 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 in ref. 53). It is the failure at present 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 of 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 various synaptic partners. How interneurons form functional circuits in a variety of structures is a crucial question that remains to be answered.

So far we have taken a bottom-up developmental view that is aimed at examining events by which interneuron subtypes are integrated into functional circuits. In the next section, we 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. Although the data so far are in nascent stages, the availability of genetic driver lines[57,58] to reliably target particular interneuron cohorts, has provided the means to test this hypothesis.

How interneurons function

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 to which they contribute. There are two complementary ways of approaching the question of what an interneuron does: by examining when and how they are recruited to fire or by determining the impact of their firing on the circuit (Fig. 3). First, understanding recruitment requires us to determine under what circuit and brain-state configurations or behavioural contingencies is a given neuron active? This is strongly constrained by a neuron's afferent connectivity, which in turn is probably dictated by its 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, to understand their recruitment we must take into account a large number of factors. The classic idea is that interneurons

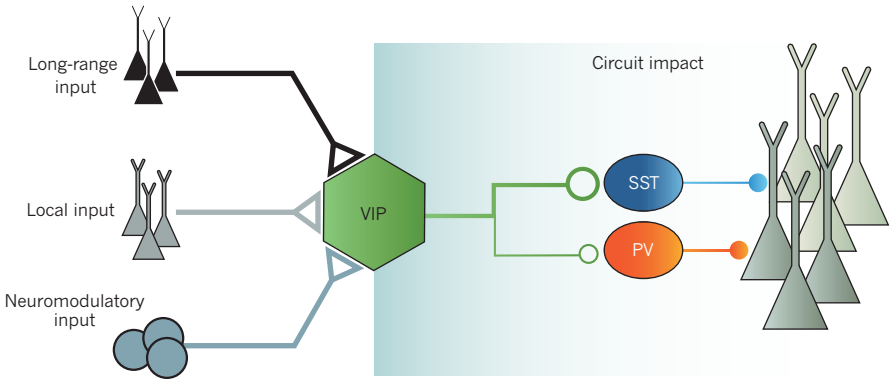

Figure 3 | Two faces of interneuron function. A cortical circuit from the perspective of a vasointestinal peptide (VIP) interneuron. The recruitment of VIP interneurons is constrained by the inputs they receive. The afferents can be local, long range from other cortical areas as well as neuromodulatory from the dorsal raphe and nucleus basalis through ionotropic receptors. The circuit impact of VIP interneurons is constrained by their outputs. The efferents are mostly to somatostatin (SST) interneurons and to a smaller degree to parvalbumin (PV) interneurons, which lead to the disinhibition of a functional subset of principal cells[85,101,102].

coordinate networks, such that their recruitment is best understood in reference to the local population activity (Fig. 4a). We also consider an alternative view that we term the flow-control hypothesis, whereby interneurons gate information flow within a given circuit and are excited at precise moments in reference to specific behavioural events (Fig. 4b). 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 its developmental genetic program. In addition, the impact of 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 types[59]. Perhaps because inhibitory interneurons are largely local, they have generally been considered to simply guard excitatory networks against runaway excitation[60]. Recently, our understanding of their function has become significantly more sophisticated. Among other lessons, we learned that interneurons could normalize the activity of local excitatory networks as well as provide feedforward inhibition. The latter strongly influences the timing of signals and allows excitatory signals to remain sub-threshold 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 that can generate elevated activity. It has become clear that there are at least as many inhibitory circuit motifs as there are cell types.

Computing with interneurons

How then does the diversity of interneurons contribute to neural computations? First, it is worth noting that it would be difficult to imagine networks with only excitation. In fact, from an engineering standpoint, such networks would have to have extremely time-limited dynamics or they would become intrinsically unstable. Moreover, inhibition not only provides balance, it also ensures richness in the possible dynamics within networks of principal neurons. These considerations led to the idea that interneuron diversity allows for a vast increase in the computational power of cortical circuits[61,62]. 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[63,64]. 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 its 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[65,66]. Such gain modulation might result from shunting[67], synchronous[68] or balanced[69] inhibition. Originally proposed to explain early visual cortical responses[65], normalization has become one of the most studied cortical computations[70,71].

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 responses[71]. Indeed, cortical recordings often reveal finely balanced excitation and inhibition[72–75], consistent with these models. When inhibition precisely tracks excitation, it can also increase temporal precision[72,76] or decorrelate networks[77].

Circuit impact of identified interneuron types

To understand how computations are implemented in neural networks requires an appreciation of how distinct interneuron subtypes affect local networks. Although conventionally studied *in vitro*, we focus mostly on recent *in vivo* work using transgenic mice for targeting interneurons on the basis of markers, such as PV, SST and VIP[57,58]. It should be noted that 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 delineate distinct non-overlapping populations and in aggregate can label around 85% of all cortical interneurons[13,78,79]. When combined with optogenetic modulators[80,81], they have allowed 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[82–86]. Recent studies have shown that this population controls the timing of spikes with respect to theta oscillations in the hippocampus[87–89]. In the visual cortex, optogenetic control

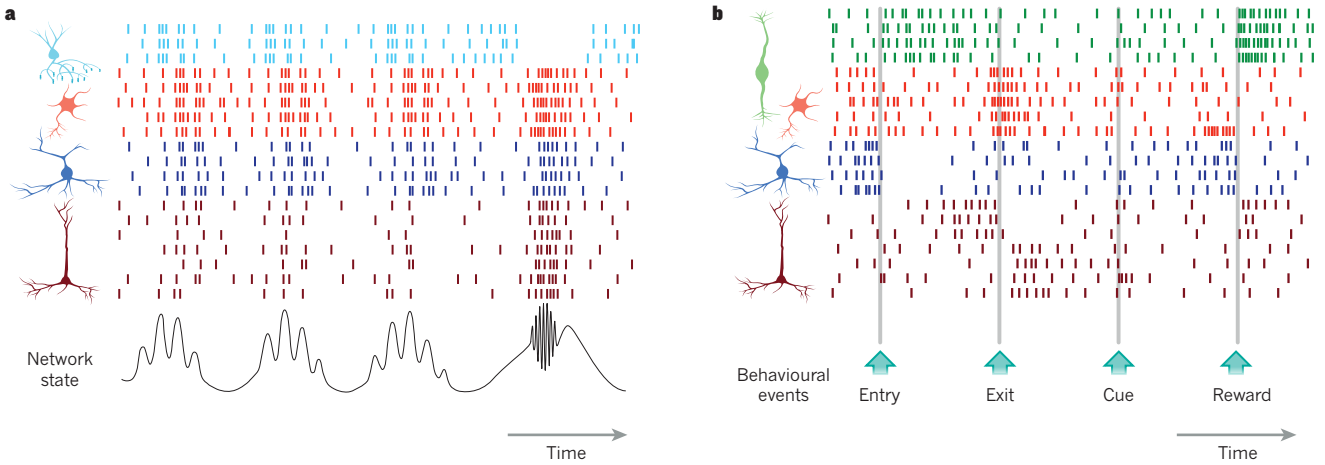

Figure 4 | Coordination and flow control hypotheses of recruitment. **a**, Coordination hypothesis. The bottom trace shows a local field potential representing the network state in the hippocampus. The firing of different neuron types (chandelier cell, light blue; basket cell, red; OLM cell, blue; pyramidal cell, brown) can be described in reference to the local field potential, both in terms of overall activity level and phase relationship[87,107,113]. **b**, Flow control hypothesis. The bottom arrows mark the timing of four behavioural events: entry, exit, cue and reward. The firing of different neuron types (vasointestinal peptide, green; parvalbumin, red; somatostatin, blue; pyramidal cell brown) can be described in reference to these events[84,102].

of PV-expressing interneurons can bidirectionally modulate the gain of visual responses[90,91]. Under some conditions, optogenetic activation of this population can even sharpen the tuning of cortical responses[92].

SST-expressing cortical Martinotti neurons are dendritic-targeting interneurons that project to layer 1 of the cerebral cortex and provide inhibition to the tufts of deep-layer pyramidal cells. Inhibition by Martinotti cells strongly suppresses dendritic calcium spikes and bursting[93], and can mediate di-synaptic inhibition between neighbouring pyramidal cells[94,95]. Similarly, in the hippocampus, dendritic inhibition by SST neurons controls burst firing[87,88,96]. In the cortex, SST-expressing interneurons have broader spatial tuning and can mediate surround suppression of visual responses[70,97]. However, SST-expressing neurons are anatomically diverse, with some subtypes specializing in disinhibition of local principal cells[98].

VIP demarcates the third major class of interneurons, which constitute around 15% of all interneurons[78,79] and are mostly located in the superficial layers of cortex. VIP-expressing interneurons have long been proposed to mediate disinhibition[99,100]. Recent studies have shown that in four different cortical regions, VIP interneurons tend to inhibit most SST and a smaller fraction of PV-expressing interneurons[85,101,102]. Inhibition of these interneurons in turn disinhibits principle cells *in vivo,* providing a form of gain control[102]. These results demonstrate that VIP-expressing neurons form a disinhibitory microcircuit that is conserved across cortical regions with shared computational functions (Fig. 3).

A final example is provided by layer 1 neurons, which are almost all inhibitory interneurons[103]. Recent results have shown that two major interneuron types have opposing functions: neurogliaform cells inhibit layer 2/3 pyramids, whereas single bouquet cells inhibit other interneurons within layer 2/3, and may provide disinhibition *in vivo*[104,105].

These studies injected great excitement into the field as they provided, at last, the causal testing of hypotheses using optogenetics. In addition, they provided support for the hypothesis that cardinal classes of interneurons have defined circuit functions. However, they carry the caveat that they assume that these populations are synchronously activated under physiological conditions. Although often this is a reasonable assumption, it needs to be tested on a case-by-case basis by recording the requisite neural population during behaviour.

Coordination and flow control during recruitment

What are the brain-state and behaviour-dependent contingencies that determine when a specific interneuron type is activated? At the broadest scale, different behavioural 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[106–109]. 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 behavioural contingency?

Network recruitment of interneurons

One idea is that interneurons coordinate the precise timing of principal cell activation, such as network oscillations. There is a long history of experimental and theoretical investigations proposing that the diversity of interneuronal subtypes underlies a division of labour for organizing cortical population activity at different time scales[61,110–112].

The best-studied examples of the contribution of different interneurons come from the hippocampus, in which recordings from targeted cells have been used to correlate their firing to network oscillations[107,113–116]. These studies, mostly in anaesthetized animals, revealed that distinct interneuron subtypes fire during different rhythms (for example, theta, gamma and ripple) and with distinct phase relationships, suggesting that they differentially contribute to network dynamics. Thus it seems that the spike timing of different interneuron types can be referenced to specific network events[61,107,117] (Fig. 4a). More generally, this work supports the coordination hypothesis, whereby each interneuron subtype performs as a temporal specialist within a 'distributed clock system' that coordinates pyramidal cell ensembles[112].

These observations set the stage for testing the causal role of different interneuron subtypes in generating oscillations[106,107]. Recently, two studies probed the role of PV interneurons using either optogenetic activation[118] or suppression[119], and found increased and decreased gamma oscillations, respectively, suggesting that interneurons are indeed actively involved in their generation.

Behavioural recruitment of interneurons

An alternative view is that the function of some interneuron types is better described with reference to behavioural events. Although interneuronal identity has long been inferred in behaving animals on the basis of spike waveform and firing pattern[110,120,121], it is only recently that this could be directly ascertained for a handful of genetically defined interneurons during well-controlled behaviours. For instance, a recent study in the anterior cingulate cortex of mice reported the surprising observation that deep-layer PV-expressing and narrow-spiking SST-expressing interneurons responded in a functionally homogeneous manner at specific behavioural epochs[84] (Fig. 4b). Similar observations were made in rat motor cortex using juxtacellular labelling in head-fixed rats: pyramidal cells responded heterogeneously, whereas all PV interneurons responded similarly at the moment of movement initiation[122]. This shows that PV interneurons, at least in mouse frontal regions, can be thought of 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 activity[82]. Therefore PV interneurons might fire in a behaviour- and region-dependent manner, which may be the 'leaving decision' in the anterior cingulate cortex, owing to its role in foraging behaviours[123], but movement initiation in the motor cortex.

Other examples of behaviourally activated responses come from the auditory cortex, in which a large fraction of interneurons in layer 1 are activated by negative reinforcers during auditory fear conditioning[105]. Similarly, VIP interneurons were observed to be strongly and uniformly recruited by negative- (air puff or mild shock) or positive- (water reward) reinforcement during an auditory discrimination task[102] (Fig. 4b). Although such reinforcement feedback-related signals may at first seem surprising in a primary sensory area, as VIP interneurons mediate disinhibition (discussed earlier) they are an ideal conduit for gating signals[99] (Fig. 3).

As we stated earlier, because interneurons are embedded in a highly interconnected network, their functions need to be understood in the context of local networks[124]. In light of this, the observations that some interneuron types are recruited at specific behavioural events may seem puzzling. Indeed, consistent with the coordination hypothesis[112,117], one would expect that most responses would be constrained by the state of the local network, on a time scale of milliseconds, and not by behavioural contingencies. Mechanistically, the observed behaviourally specific activation may reflect local network activity, which itself is tied to specific behavioural 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 behavioural events. Alternatively, some classes of interneurons may be activated by strong long-range inputs. For instance, neuromodulatory systems can provide behaviour-dependent inputs to specific interneuron classes. Interestingly, VIP neurons have ionotropic receptors for the neuromodulators acetylcholine and serotonin, which probably drive reinforcement signals in these neurons[99,125].

At present, the behavioural recruitment of many interneuron types remains unexplored and different mechanisms may apply to each type. In contrast to the coordination hypothesis, some early results support the flow-control hypothesis (Fig. 4), proposing that distinct interneuron types specialize in controlling information flow in and out of local circuits during specific behavioural contingencies, and thus acting much like controllers of a state machine. This suggests that the recruitment

of an interneuron type is linked with behavioural scale requirements of local circuits. Moreover, the observations that genetically defined interneuron classes show similar recruitment suggests they do act as functional units, supporting the existence of a small number of cardinal interneuron types.

Outlook

We are in the midst of an exciting era in which each week new data on the development and function of interneurons are being brought to light. In this Review, 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 not diverse or that divisions into further subtypes are not warranted. The incredible work in areas such as the hippocampus shows us that this is patently incorrect. We have provided a framework that we hope will help to direct future studies by consolidating interneuron diversity into cardinal classes with specific ground states. Therefore if one wishes to explore questions regarding intrinsic physiological properties, axonal targeting or general target selection, understanding the ground state established in progenitors is a good place to start. However, 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 that 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 more 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 favours 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 crucial combinations of features that enable their function. Genetic programs 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 interneuron recruitment and circuit impact. In short, we may ultimately find that 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 behavioural outcomes. Harnessing biology's ability to use a limited set of building blocks, to create enormous diversity circuits holds the real promise that we may soon begin to understand the means by which brain circuits self-assemble and initiate function. ■

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