

# Cortical connectivity and sensory coding

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**The sensory cortex contains a wide array of neuronal types, which are connected together into complex but partially stereotyped circuits. Sensory stimuli trigger cascades of electrical activity through these circuits, causing specific features of sensory scenes to be encoded in the firing patterns of cortical populations. Recent research is beginning to reveal how the connectivity of individual neurons relates to the sensory features they encode, how differences in the connectivity patterns of different cortical cell classes enable them to encode information using different strategies, and how feedback connections from higher-order cortex allow sensory information to be integrated with behavioural context.**

Our senses are constantly bombarded with a vast amount of information. To guide behaviour, the brain must extract and amplify a relatively small number of features from this massive input; for example, features corresponding to the nature and location of objects in the world. In mammals, the cerebral cortex has a central role in this process. The cortex contains multiple hierarchically arranged areas devoted to each modality. Neuronal populations in these areas extract features of sensory scenes and integrate them with non-sensory cognitive and behavioural variables, in a progressively abstract manner<sup>1</sup>. Each sensory stimulus causes a complex pattern of activity in the neuronal populations of multiple cortical areas. The relationship between sensory stimuli, and the firing patterns they evoke, defines the ‘neural code’ of the corresponding populations.

Each cortical area contains a richly interconnected array of diverse cell types, whose patterns of connectivity underlie the cortex’s ability to extract sensory features. The circuits of different cortical regions and species share striking commonalities in their constituent cell types, their intrinsic properties, and the incidence and properties of synaptic connections between them<sup>2,3</sup>. Connections between cortex and other brain structures, and connections between cortical regions, also show a largely preserved relationship to cortical cell classes. These similarities suggest that there may be a set of general principles linking the common characteristics of cortical circuitry to the nature of cortical processing in multiple areas.

If such common principles exist, they are unlikely to describe which sensory features are encoded in particular cortical areas, but rather how these features are encoded. Cortical neurons detect complex and non-linear features from sensory scenes, whose precise character will obviously differ between sensory modalities. Nevertheless, there are notable commonalities in the strategies with which populations of different cortical areas encode diverse types of information, and in how these strategies differ between neuronal subtypes. An understanding of these strategies in turn enables us to consider why cortex might be organized in this way; for example, why the coding strategies used by each cell class are appropriate to their particular role in the circuit and their particular synaptic targets.

In recent years there has been a great acceleration in progress towards answering these questions, enabled by a number of newly developed experimental techniques. Advances in mouse genetics have provided tools to classify, identify and manipulate different classes of cortical neuron<sup>4–6</sup>. Optical and electrical techniques now allow scientists to simultaneously record the activity of large numbers of neurons in the living brain<sup>7,8</sup>. Advances in circuit mapping techniques allow neuronal

connections to be reliably identified<sup>9–11</sup>. Optogenetic techniques allow scientists to control neuronal activity with high temporal resolution using light-gated proteins<sup>12</sup>. Most importantly, recent studies have begun to apply these techniques in combination, directly relating cortical circuitry to sensory coding. Here we review some of the insights recently made with these techniques, with a specific focus on the visual, auditory and somatosensory cortices of rodents.

## The organization of cortical connectivity

Cortical neurons divide into two major classes. Principal cells are neurons that use the excitatory neurotransmitter glutamate. Usually pyramidal in shape, these cells respond selectively to specific features of sensory stimuli, and contact local and distant targets through extensive axonal projections. Principal cells comprise approximately 80% of cortical neurons in rodents, and fall into multiple classes distributed across and within cortical layers (Box 1). The remaining approximately 20% are interneurons that release the inhibitory neurotransmitter GABA and make mostly local connections (Box 2). Both principal cells and interneurons comprise multiple subclasses, whose classification is an active area of research.

The probability of connection between two neurons, and the physiological properties of the corresponding synapses, depends on the pre- and postsynaptic cell types (Boxes 1 and 2). Connectivity within a single cell class is also highly structured. Analysis of connections between principal cells reveals an overrepresentation of bidirectional connections between pairs, and of mutual interconnection motifs in larger sets of neurons<sup>13,14</sup> (although this was not seen in ref. 15). Such non-uniform connectivity occurs both within and between layers, with principal cells more likely to exhibit reciprocal connections if they receive common intra- or inter-laminar input<sup>16,17</sup>. These data suggest that each cortical area contains multiple interdigitated subnetworks of highly interconnected principal cells (Fig. 1). Note that although motifs such as bidirectional connections can occur several times more frequently than expected by chance, they do not occur with a probability of 1. This suggests that the subnetworks are not discrete: not every pair of neurons within a subnetwork is connected, and each principal cell can belong to multiple subnetworks. Unlike principal cell–principal cell connectivity, connectivity between principal cells and at least some interneuron classes seems to be non-specific. Although interneurons can show precise targeting of connections to specific cell classes and subcellular locations, their connection probability to neighbouring principal cells is close to 100%, at least for parvalbumin- and somatostatin-expressing interneurons<sup>18,19</sup>.

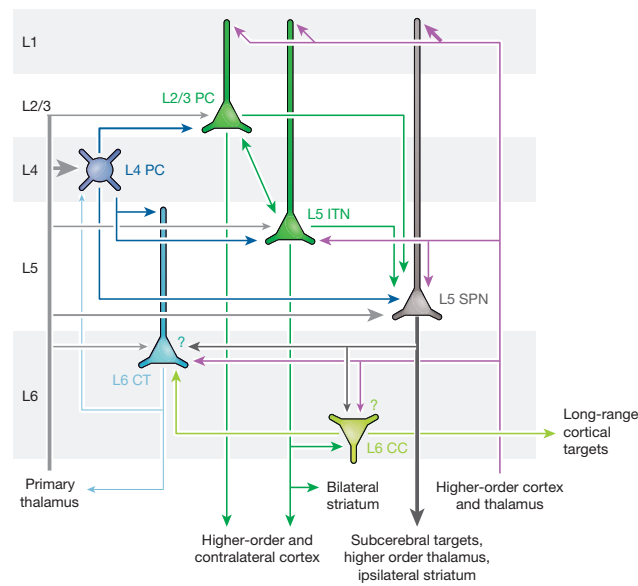
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## BOX 1

## Canonical connectivity of cortical principal cells

Sensory information arrives from primary thalamus into all cortical layers, but most densely into L4 and the L5–L6 border<sup>9,54,95</sup>. Contextual inputs from higher-order cortex and thalamus most densely target L1, L5 and L6, but avoid L4 (refs 2, 9). These inputs are integrated by a diverse array of cortical cell types. The figure shows a current understanding of the connectivity between the major principal cell classes of sensory cortex. Line thickness represents the strength of a pathway; question marks indicate connections that appear likely but have not yet been directly demonstrated.

L4 principal cells comprise two morphological classes, pyramidal and spiny stellate cells, whose intrinsic properties and coding strategies appear largely similar<sup>96</sup>. The architecture of L4 varies between species and modalities, which may reflect its developmental shaping by thalamic innervation and activity<sup>97,98</sup> in which the L4-specific gene *Rorb* has been implicated<sup>99</sup>. L4 principal cells project to all layers, but most strongly L2/3. However they receive little intracolumnar input in return, as evidenced both by paired recording



studies<sup>2,15</sup>, and the fact that optogenetic stimulation of L2/3 has little effect on L4 (ref. 46).

L2/3 principal cells are often considered homogeneous, but comprise as-yet incompletely classified subtypes, with different patterns of axonal targets, gene expression, and *in vivo* firing patterns<sup>100,101</sup>. Their major outputs are to higher order and contralateral cortices, as well as locally to L5.

L5 principal cells comprise two broad subclasses, whose fate is developmentally determined by suppressive interactions between the genes *Satb2*, *Fezf2* and *Ctip2* (ref. 102). ‘Intratelencephalic neurons’ (ITNs) are often found in upper L5 (ref. 103), and fire adapting spike trains at moderate rates. They project locally upward to L2/3 and distally to the ipsi- and contralateral cortex and striatum, but not to targets outside the telencephalon. ‘Subcerebral projection neurons’ (SPNs) are larger cells with prominent dendritic tufts in L1 and a periodic spatial organization<sup>104</sup>. SPNs show little spike train adaptation, and under some—but not all—conditions fire in bursts<sup>105</sup>. SPNs receive prolific inputs from multiple cortical cell classes, whose development depends on Shh signalling<sup>106</sup>. However, they give little local output in return<sup>52</sup>, therefore exhibiting the inverse connectivity pattern to L4 principal cells. SPNs of even primary sensory cortices project to subcerebral motor centres, and can directly drive movements<sup>107</sup>. Their axons send collaterals to ipsilateral striatum and higher-order thalamus with large, strong ‘driver’ synapses<sup>108,109</sup>. Together, these characteristics define a class of neuron that accumulates information from an entire cortical column, and broadcasts sustained, powerful outputs to distant targets.

L6 principal cells comprise at least two subclasses with distinct molecular identities and projection targets<sup>110</sup>, whose fate is partially determined by the gene *Tbr1* (ref. 102). Corticocortical cells (CCs) have small dendritic trees, long-range horizontal axons, and occasionally bizarre morphologies such as inverted somata<sup>111</sup>. Corticothalamic cells (CTs) send projections to thalamus which, unlike those of L5 SPNs, are weak, target the reticular and primary sensory thalamic nuclei<sup>108</sup>, and travel through slowly conducting fibres (as low as 0.5 m s<sup>-1</sup> in rabbit)<sup>90</sup>. Corticothalamic cells also project to cortical layer 4, where they strongly target interneurons<sup>111</sup>, as well as hyperpolarizing principal cells via group II mGluRs<sup>112</sup>. Consistent with this connectivity, optogenetic stimulation of L6 *in vivo* suppresses cortical activity, suggesting a role of this layer in gain control or translaminar inhibition<sup>113</sup>.

## Functional specificity of excitatory subnetworks

Synaptically connected principal cells tend to process similar types of information. In mouse visual cortex, the connection probability between nearby superficial principal cells is higher for neurons that respond to similar visual features<sup>20</sup>. Connection probability is elevated for neurons sharing the same orientation preference, but is higher still for neurons responding similarly to natural movies. This suggests that connection probability mirrors similarities in the complex and as-yet poorly understood feature combinations extracted by visual cortical neurons. The relationship between connectivity and sensory tuning is preferential but not exclusive: not all neurons that respond to similar features are connected, and not all connected neurons respond to identical features. This indicates that the neuronal populations that respond to different sensory features are not discrete and disconnected from each other, but interconnected and overlapping. Consistent with functionally specific recurrent connectivity, whole-cell recordings *in vivo* indicate that the excitation principal cells receive from their cortical neighbours is tuned similarly to their direct thalamic input, at least with regard to simple features such as visual orientation and sound frequency<sup>21–24</sup>. Functionally

specific principal cell connectivity may be a general feature of at least visual cortex, as long-range horizontal excitatory projections in carnivores are also biased towards neurons with similar stimulus preferences<sup>25</sup>. In contrast to principal cells, local excitatory connections onto interneurons (at least, onto parvalbumin-expressing interneurons) seem unrelated to feature preference<sup>10,26</sup>.

These data suggest that the interconnected subnetworks postulated in the previous section consist of neurons that are largely, but not exclusively, tuned for similar sensory features. This organization may provide several benefits. First, recurrent excitation amplifies cortical responses<sup>21–24,27</sup>. By reinforcing thalamic inputs, recurrent excitation can increase the spiking probability of individual neurons, and increase the number of neurons responding to a given stimulus. This will reduce susceptibility to noise and boost the efficiency with which they can drive downstream targets. Second, recurrent excitation prolongs sensory responses<sup>21–24</sup>. This will again boost the efficacy of sensory responses, and may allow responses to brief stimuli to be maintained for long enough to interact with subsequent sensory inputs as well as later-arriving feedback from higher-order regions. Third, recurrent excitation may allow for

**BOX 2**

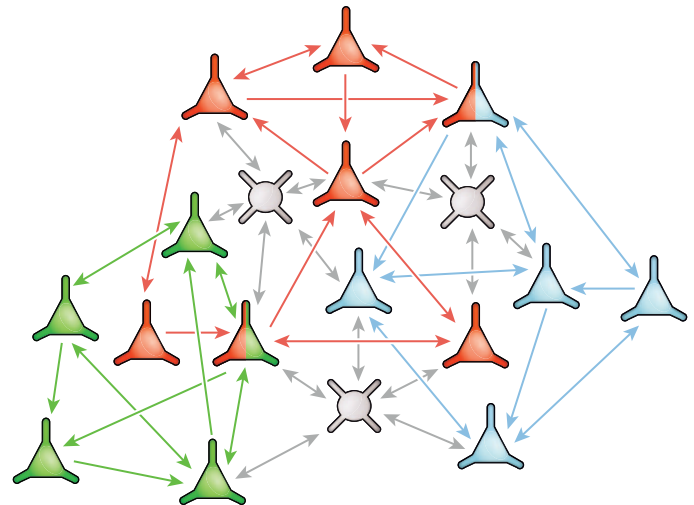
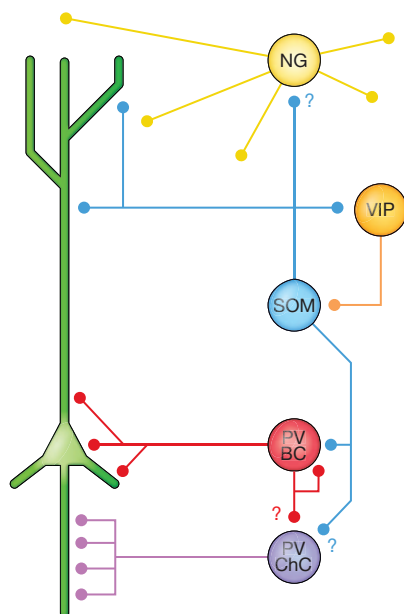
## Classes of inhibitory interneuron

The cortex contains three major families of interneuron, each of which divides into multiple subclasses. The figure shows a current understanding of the synaptic targets of five classes of cortical interneuron, with the green neuron representing a principal cell. Question marks indicate connections that appear likely but have not yet been directly demonstrated.

Parvalbumin-expressing interneurons (PVs) are capable of firing rapidly and with high temporal precision. They consist of two main subgroups: basket cells (BCs) that target the soma and proximal dendrites of principal cells, and chandelier cells (ChCs) that target the axon initial segment. PV cells receive strong excitatory inputs from thalamus and cortex<sup>114</sup>, as well as inhibition from other PVs<sup>115</sup>. A key role of these cells is to stabilize the activity of cortical networks: their absence leads to epileptiform activity, whereas more moderate chronic dysfunction of these cells has been implicated in diseases such as schizophrenia<sup>116</sup>.

Somatostatin-expressing interneurons (SOMs) consist largely, but not exclusively, of Martinotti cells that target the tuft dendrites of principal cells, as well as inhibiting other interneurons<sup>115,117</sup>. Consistent with their targeting of dendritic tufts, these cells have been implicated in behaviour-dependent control of dendritic integration<sup>88,118</sup>, as well as in more general lateral inhibition<sup>47</sup>. Connections from principal cells to SOMs show facilitating synapses<sup>119,120</sup>, whose establishment depends on postsynaptic expression of the cell-surface protein Efn1 (ref. 121). In contrast to PVs, SOMs receive the majority of their input from local principal cells but little inhibition or thalamic drive<sup>47,115,117</sup>.

5HT3A-receptor-expressing interneurons are the most numerous interneuron of the superficial layers<sup>122</sup>. Although the classification of these neurons is still incomplete, they contain two prominent subgroups: neurogliaform cells (NGs), which are thought to release GABA by volume transmission<sup>123</sup>; and cells that express vasoactive intestinal peptide (VIP) and preferentially target SOMs<sup>89,115</sup>. Putative 5HT3A-receptor-expressing cells have been implicated in learning<sup>124</sup> and control of cortical circuits by higher-order cortex and thalamus<sup>89,125</sup>.



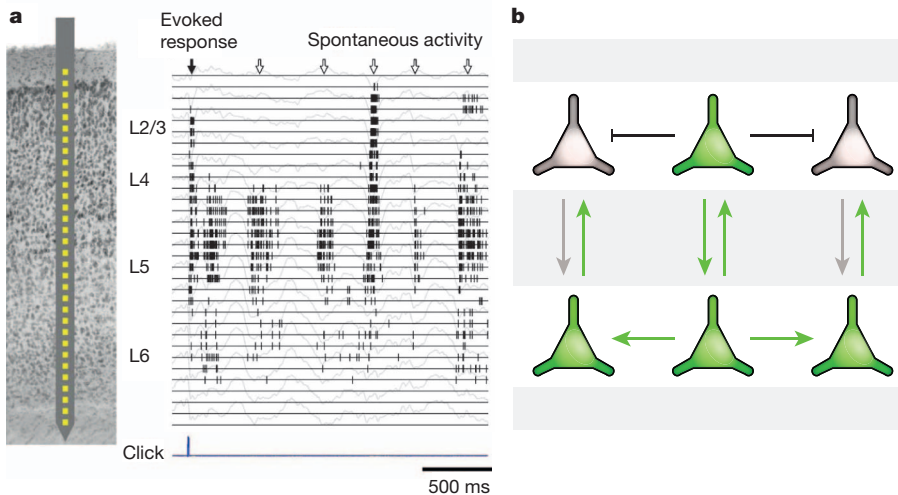
**Figure 1 | Proposed fine structure of neocortical connections.** Connectivity analyses suggest that cortical circuits contain multiple interdigitated subnetworks of highly interconnected principal cells. Red, blue and green triangles represent principal cells in three subnetworks; arrows of the corresponding colour represent synaptic connections within each subnetwork. Not all cells within a subnetwork are connected, and any cell can belong to more than one subnetwork (striped triangles). Unlike principal cells, parvalbumin-expressing interneurons (grey circles) connect nonspecifically to principal cells in their local area.

more complex feature integration in sensory scenes. Although connection probabilities are elevated between neurons of the same feature preference, substantial connectivity also exists among neurons with different feature preference. If these connections link neurons driven by features whose combination is of particular behavioural relevance (for example, features forming extended visual contours or spectrally complex sounds), recurrent connectivity may allow the subnetwork to specifically amplify responses to these combinations.

### Establishment of cortical connectivity patterns

Cortical circuits are wired by a combination of molecular cues and activity-dependent synaptic plasticity. Recent research is beginning to reveal the molecular signals governing the incidence and synaptic properties of connections between specific cell classes (Box 1). However, a key question is what determines the non-uniform connectivity patterns within a principal cell class. The first possibility is that interconnected subnetworks reflect still-undiscovered neuronal subtypes. For example, connection probabilities within the apparently uniform class of callosally projecting layer 5 (L5) principal cells could be predicted by similarity of physiological characteristics<sup>17</sup>, suggesting preferential connectivity between cryptic subclasses. Recent work suggests that clonal sister neurons (that is, neurons arising from divisions of a common progenitor cell) are more likely to be synaptically connected and share orientation preference than unrelated cells<sup>28</sup>. A single progenitor can give rise to preferentially connected principal cells of multiple subclasses, suggesting that early developmental processes beyond subclass specification contribute to wiring intracortical circuits. Transient electrical synapses between clonal sisters before eye opening have been implicated in this process<sup>29</sup>.

These early developmental processes, however, seem to simply provide a starting point for activity-dependent refinement of cortical circuitry after the onset of sensory experience. Indeed, studies in superficial visual cortex suggest the relationship between principal cell connectivity and visual feature preference is weak at eye-opening, only becoming strong after visual experience, which suggests that sensory input leads to the formation of functionally specific subnetworks<sup>30</sup>. An intuitive argument suggests that Hebbian plasticity—strengthening of connections between principal cells that fire together—should lead to interconnected subnetworks of cells tuned to similar or commonly co-occurring features;



**Figure 2 | Coding strategies of different cortical layers.** **a**, Cortical activity is sparse in superficial layers but dense in deep layers. Left, inferred location of a multisite electrode in rat auditory cortex, with recording sites indicated by yellow squares. Right, raster plot of activity, with tick marks indicating spike times of simultaneously recorded neurons at the corresponding cortical depths. **b**, Cell-type-specific coding may result from stronger inhibition in superficial and stronger excitation in deep layers. Green-filled triangles represent active neurons; empty triangles represent silent neurons. Arrows represent net excitation, thick black lines represent net inhibition. Part **a** is adapted from ref. 40.

indeed, this is the essence of Hebb's original 'cell assembly' hypothesis<sup>31</sup>. Understanding how more complex cortical plasticity processes sculpt cortical networks to detect salient sensory features, is an important topic of research in computational and experimental neuroscience<sup>30,32–35</sup>.

### Coding strategies differ between cell classes

Different cortical cell classes encode information differently. The major difference is not in what information is encoded (for example, preference for a particular sensory feature), but in the manner in which it is encoded. The best-understood difference in coding strategy between cell classes is in their 'sparseness'. For neuronal classes employing a 'sparse code', information is encoded at any instant by the spiking of a small subset of cells within the population. At the other end of the spectrum (a 'dense code'), most neurons are active at any moment, with information encoded by variations in their firing rates. Sparse coding is typically associated with low mean firing rates and high selectivity of individual neurons for sensory features, although in principle this association is not absolute<sup>36</sup>. Sparse codes are considered efficient, because they are able to transfer information with fewer spikes<sup>37</sup>. In addition, sparse codes may also increase information storage capacity at the level of neuronal populations, because of a smaller overlap in representations for different stimuli<sup>38</sup>. However, sparse coding imposes a different type of cost, as the large number of neurons required to support sparse codes must occupy a significant spatial volume. This cost would be particularly acute for physically larger neurons, such as those that must support long-range axonal projections.

### Principal cells

Recordings in multiple modalities indicate that L2/3 principal cells encode information sparsely (Fig. 2a). L2/3 principal cells have low spontaneous and evoked firing rates (usually <1 spike per s in rodents), and respond selectively only to a narrow range of stimulus features<sup>39–42</sup>. This sparseness is likely to result from a combination of strong, unselective inhibitory connections, and functionally specific excitation. L2/3 contains large numbers of densely connected interneurons<sup>43</sup>, which provide powerful synaptic inhibition, particularly in awake animals<sup>44</sup>. Both *in vitro* and *in vivo*, optogenetic stimulation of L2/3 principal cells causes predominant inhibition rather than excitation in other L2/3 principal cells<sup>45–48</sup> (Fig. 2b). Consistent with strong lateral inhibition, recent work suggests that at least in auditory cortex, superficial layer activity *in vivo* is sparse and patchy at a spatial scale of <200  $\mu\text{m}$ <sup>40,49</sup>.

In contrast, L5 principal cells—in particular subcerebral projection neurons (SPNs; see Box 1)—encode information densely, firing at relatively high rates (5–15 spikes per s) and responding to a broad range of stimuli in a graded manner<sup>39–42,50</sup> (Fig. 2a). This firing pattern again mirrors their connectivity, as L5 SPNs integrate thalamic and intracortical

excitatory input from diverse principal cell classes and subnetworks, while receiving weaker inhibition<sup>9,51–55</sup>. Again consistent with this connectivity, *in vivo* estimates of synaptic currents suggest putative SPNs receive broadly tuned excitatory drive, compared both to the excitation received by other cell classes and to the inhibition they themselves receive<sup>21,46</sup>. Furthermore, optogenetic stimulation of L5 *in vivo*—unlike stimulation of L2/3—causes self-sustaining activity, consistent with strong recurrent excitation in L5 circuits<sup>48,56</sup> (Fig. 2b).

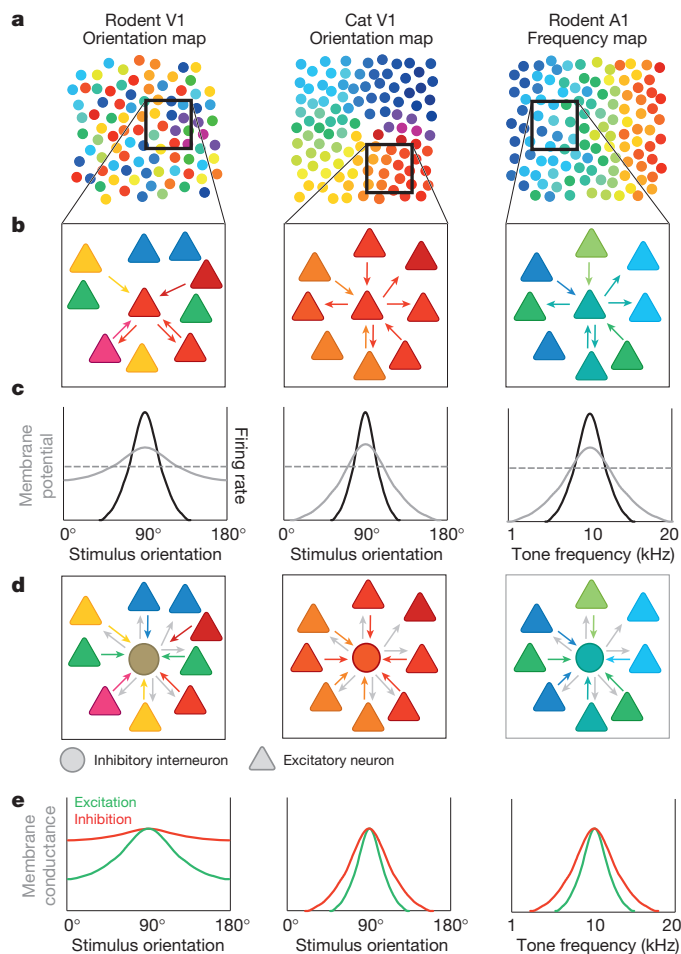
By using different coding strategies in different populations, the cortex may have found a way to balance the benefits and costs of sparse coding. We propose that sparse coding in a large number of physically smaller, intracortically projecting neurons (L2/3 principal cells) may allow efficient information storage in local synapses; the use of dense coding in a smaller number of large, long-range projection cells (L5 SPNs) may allow efficient broadcast of the results of cortical computations to distant structures, without requiring excessive physical volume. Thus, the differential coding schemes of L2/3 and L5 principal cells appear tailored for the targets their axons innervate.

### Interneurons

The way information is encoded in the cortex's multiple interneuron classes is a topic of active research and some controversy<sup>26,57–60</sup>. Interneuron activity can be strongly and diversely modulated by non-sensory factors such as ongoing behaviour (see below), but interneurons are also driven by sensory input. Unlike principal cells, interneurons (at least, parvalbumin-expressing interneurons) receive functionally unspecific inputs from nearly every principal cell in the local area<sup>10,26</sup>. Consistent with this broad connectivity, interneuron sensory tuning seems to approximate the average of the principal cells in their local neighbourhood<sup>57</sup>. As a consequence, even superficial interneurons seem to use a dense coding strategy more similar to deep principal cells than to their superficial principal cell neighbours<sup>40</sup>. However, this coding strategy is intimately related to the way activity is organized across the cortical surface, as discussed below.

### Connectivity, coding and cortical maps

One of the most prominent differences in cortical organization between modalities and species is in the spatial mapping of information on the cortical surface. Often, the cortical surface maps the organization of primary receptor surfaces in the sense organs (such as the retinotopic, cochleotopic and somatotopic mapping of visual, auditory and somatosensory cortices). However, when sensory features are mapped in a manner not inherited from the receptor surface, differences between species can be seen. For example, the visual cortices of carnivorans and primates, but not rodents, show a functionally organized and periodic arrangement of orientation preference<sup>61,62</sup> (Fig. 3a). This may be unavoidable in rodents



**Figure 3 | Proposed relationship between feature mapping and coding in rodent visual cortex, cat visual cortex and rodent auditory cortex.** **a**, Non-topographic arrangement of orientation preference in rodent V1 contrasts with spatially contiguous arrangement of orientation preference in cat V1 and of frequency preference in rodent A1. **b**, In all cases, principal cells receive inputs preferentially from neurons with similar feature preference. **c**, Incomplete functional specificity of connections for non-mapped features such as orientation in rodent V1 leads to broader subthreshold tuning. This is converted to sharp tuning of firing output by nonlinear neuronal amplification and synaptic inhibition. **d**, Inhibitory interneurons receive dense and unselective input from all neighbouring neurons. **e**, The inhibitory and excitatory synaptic inputs received by a principal cell are both strongest for the same preferred stimulus, but inhibition is more broadly tuned than excitation, leading to sharpened tuning of spiking output.

given the small size of their visual cortex: if mice had orientation columns similar in size to carnivorans, they would be able to see only one orientation in any part of the visual field.

Differences in cortical maps lead to differences in the tuning of synaptic input for sensory features. Although connections in rodent primary visual cortex (V1) are biased to cells of similar orientation preference, this bias is not complete<sup>20</sup> (Fig. 3b). Accordingly, whole-cell recordings in individual neurons show substantial subthreshold depolarization also in response to non-preferred orientations<sup>22,24,62,63</sup> (Fig. 3c). When features are mapped in a more orderly manner across the cortical surface, such as in iso-orientation domains of carnivoran visual cortex and iso-frequency bands in rodent auditory cortex, subthreshold tuning is sharper<sup>64–66</sup>, consistent with the dominance of local inputs of similar feature preference (Fig. 3b, c). In carnivoran V1, subthreshold tuning is also broader at ‘pinwheel centres’ (where neighbouring neurons exhibit a diverse range of orientation preferences) than in iso-orientation domains<sup>64</sup>, again reflecting the importance of functional map organization in determining subthreshold tuning.

Despite broad subthreshold tuning, the spiking output of principal cells can still be highly selective for non-mapped features<sup>62–64</sup>. This seems to reflect a combination of nonlinear neuronal integration, which can convert subtle differences in membrane potential to large differences in spiking<sup>67</sup>, and synaptic inhibition. Consistent with their nonspecific local connectivity, parvalbumin-expressing interneurons are selective for smoothly mapped features such as orientation in cat visual cortex<sup>68</sup>, tone frequency in rodent auditory cortex<sup>65</sup> and spatial position in rodent visual cortex<sup>59</sup>, but are unselective or broadly tuned for unmapped features such as orientation in mouse V1 (refs 26, 57–59) (Fig. 3d, e). *In vivo* patch-clamp experiments and models suggest that broadly tuned synaptic inhibition has an important role in producing sharp output selectivity for orientation in mouse V1 and in pinwheel centres of carnivoran V1 (refs 64, 69). Thus, selective tuning of excitatory neurons can occur irrespective of whether a stimulus feature is mapped smoothly on the cortical surface, due to functional biases in connectivity, nonlinear neuronal integration, and appropriately tuned inhibition.

These data suggest two hypotheses regarding the relationship between connectivity and coding across areas and species. First, certain features of cortical connectivity appear to be preserved across multiple systems: principal cells receive functionally selective excitatory inputs both locally and from distant regions, while the connectivity of many interneurons is local but nonspecific. Second, although the selectivity of subthreshold responses of principal cells and spiking responses of local interneurons will depend on how a particular stimulus parameter is mapped across the cortical surface, the firing of principal cells—the cortex’s final output—is highly selective even without feature mapping. Indeed, unmapped orientation is found in even highly visual rodents such as squirrels<sup>62</sup>, suggesting mapping is not essential for accurate sensory function.

### Redundant coding in cortical populations

Current experimental techniques allow recordings of up to a few hundred neurons simultaneously. One of the most notable findings from these experiments is that cortical population codes are redundant. The firing pattern of a neuronal population can be summarized (to a first approximation) by the subset of neurons that are active at any moment. In principle, the number of potential subsets of even a moderately-sized neural population is vast. In practice however, only a much smaller number of firing patterns can actually occur. The existence of preserved constraints on population activity indicates that cortical coding is redundant, as the firing of any one neuron can be partially inferred from the activity of its peers<sup>39,49,70</sup>. Redundant coding is found in many other domains: written language is redundant, for example, because only a small fraction of potential letter combinations spell actual words. This redundancy allows words to still be understood if letters are missing or misprinted.

The nature of cortical redundancy can be studied by considering patterns of neuronal correlation. The firing of neighbouring neurons is often correlated, and the structure of correlations in a population is broadly similar when considering the mean responses to different stimuli (‘signal correlations’), the variability of responses to multiple presentations of a single stimulus (‘noise correlations’), as well as activity occurring without sensory stimulation (‘spontaneous correlations’)<sup>26,70,71</sup>. This preservation of correlation structure suggests that cortical redundancy arises from constraints imposed by cortical wiring. Although individual pairwise correlations are typically weak (approximately <0.1), even weak pairwise correlations indicate strong constraints on the subsets of neurons that may be co-active at the population level<sup>72</sup>.

A natural hypothesis is that the restricted subsets of neurons that can in practice fire together correspond to the interconnected subnetworks suggested by connectivity analyses. Although at present this remains conjecture, several pieces of evidence suggest it may be the case. Correlations are stronger between synaptically connected principal cells<sup>20</sup>, at least in visual L2/3. These correlations do not reflect the direct driving of one cell by the other, as synaptic connections between principal cells are typically weak (approximately <1 mV)<sup>15,20</sup>; rather, they indicate that synaptically connected neurons frequently fire together as part of larger

neuronal subsets that provide correlated input to both. Both noise and signal correlations are higher between connected neurons, suggesting a direct relationship between connectivity and the constraints on co-active neuronal subsets<sup>20</sup>. Finally, the structure of correlations matches that of connectivity patterns across layers and cell classes. For L2/3 principal cells, correlations are typically weak and fall off steeply with anatomical distance<sup>26,40,49</sup>, consistent with their local and functionally-specific connectivity profiles. Correlations among pairs of fast spiking interneurons and pairs of L5 principal cells are stronger and persist over larger distances<sup>26,40</sup>, consistent with denser and more widespread connectivity<sup>26,55</sup>, and therefore larger fractions of shared input.

Another important question is why the cortex might employ redundant coding. Redundant codes are inefficient, in that they require more neurons, more spikes, and thus more energy. Patterns of raw sensory input are redundant: much of the variance in natural image scenes, for example, reflects simple changes of luminance. Eliminating this redundancy seems to be a major function of the early sensory systems<sup>73,74</sup>, begging the question of why redundancy would be reintroduced in cortex. We suggest two reasons. First, redundant codes are robust. Neuronal activity is noisy; furthermore, long-range neuronal connections are divergent, implying that distal targets receive inputs from only a fraction of the neurons in any given cortical area. Redundant coding allows the noisy output of a small fraction of cells to convey a message close to that encoded by the whole population. Second, cortical redundancy may reflect selective amplification of important sensory features. One might expect the number of neurons used to encode a given feature to match the relevance of that feature for later neuronal processing. The retina might remove redundancy imposed by luminance changes because luminance is not usually behaviourally important; cortex may create new redundancy by allocating large subnetworks to subtle but important sensory features, which thereby gain greater potential control of the animal's behaviour.

### Top-down connections and contextual modulation

In the natural environment, animals must combine sensory and non-sensory information in diverse and novel ways according to changing behavioural demands. Neurons of even primary sensory cortex do not just encode sensory input, but integrate it with contextual information such as reward<sup>75</sup>, expectation<sup>76,77</sup>, attention<sup>78</sup> and motor action<sup>79–81</sup>.

Most inputs to primary sensory cortical areas come not from primary thalamus, but from higher-order structures. These 'top-down' inputs can carry detailed information about diverse behavioural and cognitive variables<sup>82</sup>. Top-down inputs project heavily to L1, where they synapse on interneurons, and on the apical tuft dendrites of principal cells. Although distal inputs may not alone drive principal cells to fire, they enable dendritic calcium spikes that increase the gain of a cell's responses to proximal synapses carrying sensory information<sup>83,84</sup>. By targeting subnetworks encoding sensory features of particular contextual relevance, top-down connections may thus amplify their sensory responses, and enhance contextually-appropriate behavioural outcomes. Consistent with top-down selection of subnetworks, experiments in primate area V4 show that attention to specific locations or features amplifies population responses to corresponding stimuli<sup>78,85</sup>. Furthermore, both the behavioural and neural correlates of spatial attention can be mimicked by electrical stimulation of a topographically-aligned area of the frontal eye fields<sup>86,87</sup>, consistent with a role for top-down inputs in this amplification.

Recent evidence from rodent cortex suggests that active behaviour can change the operating mode of sensory cortex in diverse ways, by modulating the activity of different interneuron classes. For example, active whisking hyperpolarizes somatostatin-expressing cells in superficial layers of barrel cortex<sup>88</sup>; this results from their inhibition by VIP-expressing interneurons, which are in turn excited by top-down afferents from motor cortex<sup>89</sup>. In visual cortex, by contrast, locomotion increases the activity of somatostatin-expressing cells<sup>90</sup>. As somatostatin-expressing cells inhibit apical tuft dendrites, these changes are in turn likely to differentially

impact the integration of top-down glutamergic input by principal cells. Understanding the way different active behaviours affect different neuronal classes in different cortical areas is an important topic of current research.

### Outlook

Recent progress has suggested how the coding strategies employed by several cortical cell classes may arise from their specific connectivity patterns. We end this review by outlining some of the major questions to be addressed in the near future, which will be aided by the development of emerging techniques.

First, despite extensive research, we still have only a rudimentary understanding of the diverse classes of cortical excitatory and inhibitory neurons. The answer is likely to be complex, with developmental and epigenetic factors defining a hierarchy of ever more subtly differing subclasses. An unbiased classification of cortical cells may be provided not only by rapid progress in developmental neuroscience, but also by new technologies such as single-cell transcriptome sequencing.

Second, the generic input–output connectivity profile of each cell class must be established. In addition to current methods such as multiple patch-clamp recordings *in vitro*, emerging techniques such as viral retrograde tracing<sup>91</sup>, large-volume electron microscopic reconstruction<sup>10,11</sup>, mGrasp<sup>92</sup>, and CLARITY<sup>93</sup> will help this endeavour. *In vivo* recordings of identified cells will allow each class's connectivity to be related to the coding strategy that it uses.

Third, although it is now established that activity correlations are higher between synaptically connected neurons<sup>20</sup>, the relationship between larger-scale population codes and circuit connectivity is still unclear. One question is whether co-active principal cell subsets<sup>70</sup> really correspond to the interconnected subnetworks suggested by connectivity analyses<sup>13,14</sup>. Answering this question will require large-scale connectomic analysis of populations whose activity has been previously recorded *in vivo*<sup>10</sup>.

A fourth question is how the top-down connectivity of a cell class, and of an individual neuron, relates to its encoding of nonsensory variables. To answer this question will require large-scale recordings in behaving animals, together with anatomical and functional characterization of top-down inputs, for example, by post-hoc tracing, or imaging of axons<sup>82</sup> and individual synaptic inputs<sup>8,63</sup>.

Finally, it is important to consider how cortical connections and codes are shaped by experience and learning. The recent availability of genetically encoded Ca<sup>2+</sup> indicators for long-term imaging now makes it possible to relate changes in an individual neuron's sensory responses to changes in its synapses as animals learn new information<sup>94</sup>. This technique, in combination with techniques to genetically manipulate synaptic plasticity, should provide a powerful tool to study how connectivity and coding develop into a form appropriate for an animal's experience.

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