

The neocortical circuit: themes and variations

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Similarities in neocortical circuit organization across areas and species suggest a common strategy to process diverse types of information, including sensation from diverse modalities, motor control and higher cognitive processes. Cortical neurons belong to a small number of main classes. The properties of these classes, including their local and long-range connectivity, developmental history, gene expression, intrinsic physiology and *in vivo* activity patterns, are remarkably similar across areas. Each class contains subclasses; for a rapidly growing number of these, conserved patterns of input and output connections are also becoming evident. The ensemble of circuit connections constitutes a basic circuit pattern that appears to be repeated across neocortical areas, with area- and species-specific modifications. Such 'serially homologous' organization may adapt individual neocortical regions to the type of information each must process.

The neocortex is the brain structure most commonly believed to give us our unique cognitive abilities. Yet the cellular organization of the neocortex is broadly similar not only between species but also between cortical areas. This similarity has led to the idea of a common "canonical microcircuit," employing a similar computational strategy to process multiple types of information^{1–4}. If correct, this principle is very powerful for brain research, as understanding the organization of more tractable cortices such as the primary regions of experimentally accessible organisms would provide insight into the circuits responsible for our most complex cognitive abilities.

The type of relationship found between different regions of the neocortex is also seen elsewhere in the body. Different cortical areas are similar in the same way that hands are similar to feet or different bones are similar within the vertebral column. This type of relationship is termed "serial homology": a similarity in the organization of different structures within a single organism. (Unqualified, the word "homology" refers instead to a correspondence of structures between species, deriving from a common ancestral form.) Serially homologous structures consist of variations on a theme, containing similar classes of cells organized in the same basic pattern. Differences between serially homologous structures are typically quantitative: the sizes and relative positions of different substructures or the number and precise physiological parameters of cells of a given class. Quantitative differences, however, can allow serially homologous structures to serve very different functions: for example, the sizes and mechanical properties of bones and muscles in human hands and feet adapt them for grasping and walking, respectively.

To understand the serially homologous organization of the neocortex, it is necessary to characterize the classes of cortical neurons

consistently across multiple levels. Neurons can be classified according to different criteria: their morphology, their patterns of local and long-range connectivity, their developmental history and gene expression profile, their intrinsic physiology and the strategies they use to encode information *in vivo*. Finding a classification of cortical neurons that is consistent across these levels and that applies to neurons of multiple cortical regions would constitute a detailed understanding of the serially homologous neocortical circuit. As we shall see below, this goal has now been partly achieved in the form of a top-level classification of excitatory cells and interneurons (Tables 1 and 2). Nevertheless, these top-level classes contain distinct subclasses, for which the correspondence between the different classification criteria is not yet clear and the relationships between areas are not yet fully known.

Neocortical neurons are extensively interconnected, but in a highly specific manner. Indeed, a 1 mm³ volume spanning the layers of rodent neocortex—corresponding, for example, to a whisker barrel-related column in primary somatosensory cortex (S1)—contains ~10⁵ neurons, ~4 km of axon and ~0.4 km of dendrite^{5,6}. In contrast to the 10¹⁰ potential connections these cells could in principle form, there are 'only' ~10⁹ actual synapses⁵. Moreover, a substantial fraction of these synapses come from extrinsic axons (>50% in one estimate)⁷, and presynaptic axons typically connect to postsynaptic neurons via multiple (for example, 4 or 5) synapses⁸. Consistent with these calculations, paired recordings show that connectivity rates between excitatory neurons are in general low, rising to 10–20% or higher only for specific pre- and postsynaptic cells, such as functionally co-tuned neurons in primary visual cortex⁹. While most neuronal pairs in the local circuit are thus either unconnected or only weakly connected, the connections that do occur follow systematic patterns.

The past few years have seen a tremendous growth in knowledge of neocortical organization and function, accruing especially from newer experimental methods available primarily in rodents. We present here an updated view of cortical circuitry based on these recent results. We cannot comprehensively cover or adequately acknowledge a vast literature here, and we primarily review data on excitatory neurons

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Received 13 October 2014; accepted 4 December 2014; published online 27 January 2015; doi:10.1038/nn.3917

Table 1 Properties of top-level excitatory classes

| Top-level class: | IT | | PT | CT |
|---|--|--|---|--|
| Major subclass: | L4 | Other layers | | |
| Some characteristic genes: | <i>Rorb, Satb2</i> | <i>Satb2</i> | <i>Fezf2, Ctip2</i> | <i>Tbr1</i> |
| Inputs from other local excitatory classes: | Few | Many, including L4 IT and other IT | Many, mainly from IT | Few, mainly deep-layer (L5B/6) IT |
| Outputs to other local cell classes: | Mainly IT, especially in L3; in at least some cases, also PT | IT (but not L4 IT), PT, CT | Few | Some interconnectivity with IT, possibly PT |
| Long-range inputs: | Thalamus, lower order cortex | Thalamus, higher and lower order cortex | Thalamus, higher and lower order cortex | Higher order cortex |
| Long-range outputs: | Few | Many, but only within telencephalon (neocortex, striatum); the only ECs sending callosal/commissural projections | Many, to many subcortical and subcerebral regions (brainstem, tectum, spinal cord, thalamus, basal ganglia) | Thalamus; the only ECs to excite reticular nucleus and the only ECs without longer range corticocortical axons |
| Layer and morphology: | L4 pyramidal or stellate | L2/3, L5A, L5B, L6; pyramidal | L5B, thick tufted pyramidal | L6, pyramidal |
| Intrinsic physiology: | Regular spiking or bursting | Hyperpolarized (L2/3), little I_h , spike train adaption | Depolarized, strong I_h , little adaptation, bursting (subset) | Regular spiking |
| <i>In vivo</i> activity: | Rapid sensory response | Sparse code | Dense code | Very sparse |

See main text for references. The table entries are not intended to be comprehensive, but rather to provide key examples. Recurrent connections exist within each class (for example, IT to IT), which for simplicity are not listed. I_h , hyperpolarization-activated current.

of rodent sensory and motor cortex. We review the main classes of neurons and consider their local circuit and long-range connections. Drawing on examples from different cortical areas in rodent, we speculate on how quantitative differences in homologous circuitry may allow different functional specialization in different areas—for example, regarding how sensory processing is modulated by behavior. We suggest that a change of emphasis is now required to understand homologies between different cortical regions. In this view, lamination is not the sole or even primary organizing principle of neocortex. Instead, what different regions share is their hodology: the patterns of connection between different genetically defined cell classes. These connectivity rules can be highly conserved, whether the cell classes are intermingled or segregated into layers and sublayers. These rules are of course not immutable laws: the concept of serial homology means that circuit features (for example, cell classes and their connections) will generally be repurposed, rather than discarded or invented *de novo* between areas and species. The evolutionary success of mammals suggests that the conservation of a homologous neocortical circuit across species and its serialization across areas have provided an advantageous substrate for the evolution of diverse mammalian behaviors.

Excitatory circuits

Neocortical excitatory cells (ECs) constitute ~80% or more of cortical neurons. ECs have been divided into three main classes on the basis of their axonal projection patterns (Fig. 1 and Table 1), with each class containing subclasses whose classification is a topic of active research^{10–13}. The first main class comprises the intratelencephalic (IT) neurons, which are found in layers (L) 2–6 and project axons only within the telencephalon (neocortex, striatum and corticoid structures such as the amygdala and claustrum). IT neurons are the only ECs that project to contralateral cortex, their axons extensively interconnecting the two hemispheres via the corpus callosum and anterior commissure. IT neurons are numerous and diverse, with hodologically distinct subclasses such as L4 ITs. The second main class, the pyramidal tract (PT) neurons, also known as subcerebral projection neurons, are large pyramidal neurons of L5B; indeed, L5B is traditionally defined as the layer containing these neurons¹⁴, a convention we follow here. PT neurons project to subcerebral destinations, including brainstem, spinal cord and midbrain, and also send axonal branches to the ipsilateral cortex, striatum and thalamus. Finally, corticothalamic (CT) neurons, found in L6, project primarily to the ipsilateral thalamus. Each projection class has a characteristic laminar distribution, but

Table 2 Main classes of interneurons and their properties

| Top-level class: | Htr3a | | Pvalb | | Sst | |
|--------------------------|---|--------------------------|--|--|---|---|
| Subclass: | Vip | Neurogliaform | Basket | Chandelier | Martinotti | L4 Sst |
| Local outputs: | Descending axon, inhibiting Sst and Pvalb | Nonsynaptic GABA release | Inhibiting ECs (soma), other Pvalb | Inhibiting axon initial segment of ECs | Inhibiting Pvalb, EC dendrites including tufts | Inhibiting L4 Pvalb |
| Local inputs: | Excited by ECs | Excited by ECs | Excited by ECs, inhibited by Pvalb, Sst, Vip | Excited by ECs | Excited by ECs, inhibited by Vip | Excited by ECs |
| Long-range input: | Higher order cortex | ? | Thalamus, lower order cortex | ? | ? | ? |
| Intrinsic physiology: | Irregular spiking | Late spiking | Fast spiking | Fast spiking | Low threshold spiking | Intermediate fast/low-threshold pattern |
| <i>In vivo</i> activity: | Driven by behavior | ? | Dense code, weakly tuned | ? | Modulated by motor activity; wide visual receptive fields | ? |

See main text for references.

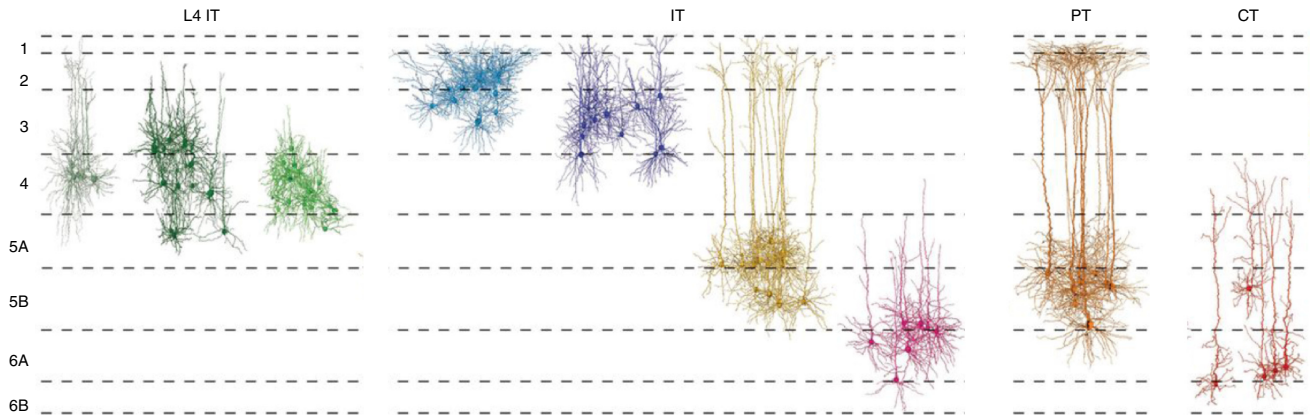


Figure 1 Dendritic morphology of excitatory neurons in S1 barrel cortex. L4 IT shows the three morphological classes of L4 intratelencephalic (IT) neurons: pyramidal, star pyramidal and spiny stellate cells. Under IT are other intratelencephalic neurons of L2, L3, 5A/B and 6. PT shows pyramidal tract neurons of L5B. CT shows corticothalamic neurons of L6. (Adapted from Marcel Oberlaender, Christiaan P.J. de Kock, Randy M. Bruno, Alejandro Ramirez, Hanno S. Meyer, Vincent J. Dercksen, Moritz Helmstaedter and Bert Sakmann, Cell Type-Specific Three-Dimensional Structure of Thalamocortical Circuits in a Column of Rat Vibrissal Cortex, *Cerebral Cortex*, 2012, Vol. 22, issue 10, pp. 2375–2391, by permission of Oxford University Press⁶).

these overlap, such that two layers have mixed composition: IT and PT neurons are intermingled in L5B, and IT and CT neurons in L6.

The hodology of cortical ECs is complex, but it appears governed by some basic principles that are conserved across areas. All classes of EC form recurrent connections with local neurons of the same class. Connectivity across EC classes is asymmetric, and results of research in frontal, visual, barrel and motor cortex are consistent with the hypothesis of a common sequential organization within the local circuit (**Fig. 2**)^{2,3,8,15–19}. We emphasize, however, that this sequential organization does not constrain the flow of information to a single linear, feedforward pathway: because all EC classes receive external inputs, there are multiple entry points into this circuit; and because ECs are usually projection neurons, there are also multiple exit points—a key principle of cortical circuit organization^{2,20,21} often lost in simplified schematics. The remainder of this section will review the organization of the main excitatory circuits, following the sequential hodology from thalamus through L4 ITs, IT neurons of other layers and then PT neurons. Finally, we discuss the connectivity of CT neurons, whose role in the cortical circuit is still largely uncertain.

Thalamocortical axons innervate multiple cell types. Most subcortical inputs to neocortex come from the thalamus. The rules governing the projections from the brain’s many thalamic nuclei to its many cortical areas are complex and still not fully understood. Nevertheless, there is a useful working model based on a division of thalamocortical (TC) projections into distinct patterns arising from types of relay cell known as “core” and “matrix”^{22,23} (**Fig. 3**).

Core-type relay neurons are believed to be carriers of rapid sensory or motor information and are located mainly in the primary (first-order) relay nuclei. Their axons project in a topographic manner to primary sensory cortices, chiefly to L4 and also (with areal and species variability) to L3 and L5B/6. Matrix-type relay neurons, occurring predominantly in higher order thalamic nuclei, project to L1 but avoid L4 of primary sensory cortex, and have been further divided into subclasses according to whether they target a single cortical area or project more broadly²³. The information conveyed by matrix-type afferents is poorly understood. In addition to these two main classes of TC neuron, a third proposed class, IL-type relay cells (primarily found in the intralaminar nuclei),

innervate striatum and other subcortical structures but also project to L5/6 of mainly motor and frontal cortex^{23,24}.

Most TC projections to primary sensory cortex can be classified as core or matrix type. In barrel cortex, core-type axons from the ventral posterior medial (VPM) nucleus project primarily to L4 barrels and to L5B, and matrix-type axons from the medial subdivision of the posterior nucleus (POm) project to L1 and L5A (and in rats to the L4 septa between barrels)^{8,25}, with excitatory synaptic connections forming onto postsynaptic dendrites located in those layers¹⁶ (**Fig. 3c**). In primary auditory cortex (A1), core-type axons from the ventral part of the medial geniculate nucleus (MGN) project to L4 and the L5/6 border, while matrix-type afferents from dorsal and medial MGN project to L1 and subgranular layers but avoid L4 (refs. 26,27). In primary visual cortex (V1), core-type projections from TC neurons in the dorsal part of the lateral geniculate nucleus (LGN) project heavily to L4, and

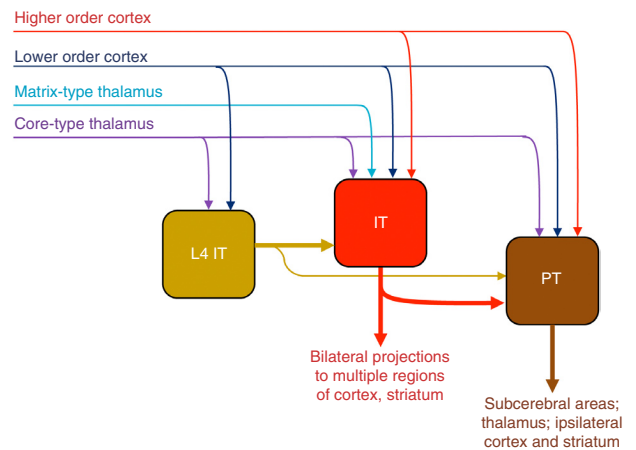
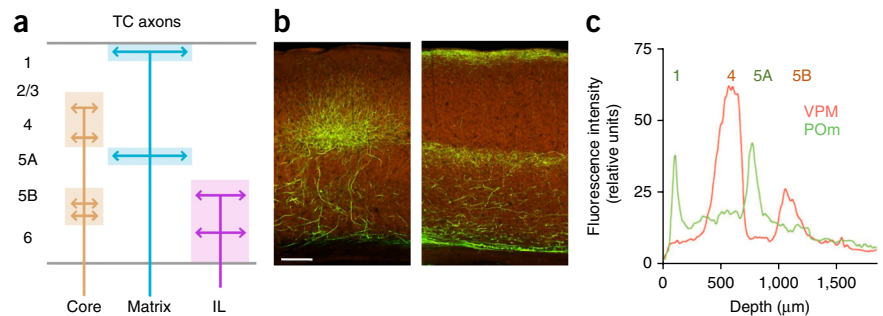


Figure 2 Excitatory hodology of ECs in layers 2–5, including intratelencephalic neurons in layer 4 (L4 IT), IT neurons of other layers (L2/3, L5A, L5B; grouped as IT here) and pyramidal tract (PT) neurons. L4 IT neurons project mostly unidirectionally to other IT neurons, which in turn project mostly unidirectionally to PT neurons. Each class receives extrinsic inputs, but information flows across classes in a largely directional manner owing to asymmetric interclass connectivity. All classes have recurrent connections with other members of their own class (not shown). The relationship of CT neurons and IT neurons in L6 to this stratified hodology is not yet established.

Figure 3 Thalamocortical (TC) input streams.

(a) The layers of termination of matrix-, core- and intralaminar (IL)-type TC projections. (b) Projections to V1 from dorsal LGN (left) and from lateral posterior and adjoining nuclei (right). Images from Allen Connectivity Atlas (<http://connectivity.brain-map.org/>, experiments 293914766 and 267608343). Scale bar, 140 μm . (c) Interdigitating laminar profiles in barrel cortex of matrix-type TC axons (green; from POM in thalamus) and core-type TC axons (red; from the ventral posterior medial nucleus (VPM) in the thalamus). (Reproduced from Verena C. Wimmer, Randy M. Bruno, Christiaan P.J. de Kock, Thomas Kuner and Bert Sakmann, Dimensions of a Projection Column and Architecture of VPM and POM Axons in Rat Vibrissal Cortex, *Cerebral Cortex*, 2010, Vol. 20, issue 10, pp. 2265–2276, by permission of Oxford University Press²⁵.)



in some species also L6 (refs. 2,28), whereas matrix-type projections from TC neurons in the lateral posterior (LP) and lateral dorsal (LD) nuclei project to L1 and L5A (ref. 29) (Fig. 3). Not all projections from primary relay nuclei are of core type: in primates, matrix-type cells of LGN project heavily to L1 and L2/3 (ref. 28); in mice, a subdivision of dorsal LGN conveys information from directionally selective retinal ganglion cells to L1/2 but avoids L4 (ref. 30).

The applicability of the core/matrix scheme beyond primary sensory cortex is not yet fully clear. Thalamic projections to primary motor cortex (M1) appear, at least in rodents, to follow a rough core/matrix organization: TC axons relaying cerebellar information project to the L3/L5A border, while TC axons relaying basal ganglia information project more heavily to L1, consistent with core- and matrix-type patterns, respectively³¹; upper-layer neurons in M1 can also receive matrix-type inputs from POM³². Thalamocortical inputs to secondary sensory and association cortex come from nuclei containing chiefly matrix-type neurons²³. However, at least in secondary somatosensory and auditory cortex, these inputs terminate heavily in L4, suggesting they strongly drive secondary cortical areas, in contrast to their modulatory effects on primary areas^{26,33,34}. Thus, the concepts of core- and matrix-type projections may need to be extended to manage the full complexity of thalamic projections to higher order cortex.

L4 neurons process extrinsic input in an area-specific manner.

Excitatory neurons in L4 can be considered a special class of IT neurons. As a result of their predominantly asymmetric local connectivity with other ECs, L4 neurons appear to be situated upstream in the local excitatory network. They project heavily to L2/3 and also to L5A/B, but receive little excitatory input in return (see, for example, ref. 8). Excitatory connectivity between L4 and L6 appears to be common in some species and areas but scarce in others^{2,35,36}; in rodent, L6→4 excitatory projections often appear weak as compared to other interlaminar projections^{19,37–40} and are proposed to have modulatory or inhibitory functions^{36,40–42}.

L4 IT neurons comprise multiple morphological subclasses (pyramidal, star-pyramidal, spiny stellate; Fig. 1), but these appear to have broadly similar circuit properties, at least in barrel cortex^{8,39,43}. Although spiny stellate cells have traditionally been considered the prototypical L4 excitatory neuron, their occurrence varies markedly between areas and species: they are found in V1 of cat and monkey but not rodent^{2,28,44} and are generally absent in A1 (ref. 45).

L4 can be greatly expanded in sensory cortices, with marked architectural differences among cortical areas and species. In primary sensory regions, L4 receives massive core-type thalamic input but very few inputs from other thalamic or cortical areas. It thus appears that L4 circuits are specialized for sensory processing, structured in a manner

appropriate to each modality^{2,8,28}. Consistent with their predominantly sensory-related inputs, L4 neurons in A1 are not modulated by behavior (unlike their L2/3 counterparts)⁴⁶, while in primate V1, L4 neurons show less of the trial-to-trial variability and noise correlation that might reflect common modulation by nonsensory inputs^{47,48}.

Consistent with a modality-specific role, functional studies have yielded different perspectives on L4 processing in different modalities and species. In cat V1, for example, the spatial structure of visual receptive fields arises from the arrangement of TC inputs onto L4 IT neurons. These cells respond to stimuli of a particular orientation, which are derived by integrating inputs from a subset of LGN neurons with spatially aligned circular receptive fields of both on- and off-center polarity⁴⁹. In tree shrews, however, L4 contains sublayers that receive inputs of different polarity, which are only integrated to form orientation-selective responses further downstream in L2/3 (ref. 50).

A complementary example comes from rodent S1 and A1, where L4 processing of TC inputs appears to depend critically on the precise timing of excitation and inhibition. TC inputs excite not only L4 IT neurons but also interneurons, resulting in rapid and powerful feedforward inhibition of ECs (for example, refs. 51,52). Because this inhibition arrives with a slight delay relative to excitation, it creates a narrow ‘window of opportunity’ for ECs to fire an accurately timed spike; furthermore, stimulus-dependent differences in the timing of excitatory input allow L4 IT neurons to respond selectively to specific stimuli^{53,54}. These examples suggest that the spatial and temporal properties of TC and intracortical circuits are tuned to produce receptive fields in L4 neurons that are appropriate for particular sensory modalities and species.

L4 neurons have received less attention outside of primary sensory areas. Although ‘agranular’ areas such as motor cortex lack spiny stellate cells, they may nevertheless possess a rudimentary L4, as based on the expression of L4-associated molecular markers at the expected laminar zone^{31,38,55–58}. L4 neurons in higher order sensory areas receive long-range inputs from different thalamic sources, as well as corticocortical inputs from lower order areas^{59–61}, a pattern that is used to define hierarchical relationships between areas (discussed further below). In summary, IT neurons in L4 appear to be specialized for receiving external input from thalamus or lower order cortex and processing it in a manner adapted to the specific input types each area receives.

IT neurons interconnect and project widely within the cerebral hemispheres.

Whereas L4 IT cells appear specialized for processing of extrinsic inputs, IT neurons of other layers integrate signals from L4 with multiple TC and cortical inputs. These neurons thus constitute the second stage of the local excitatory circuit. In contrast to the largely unidirectional projections out of L4, connections among IT

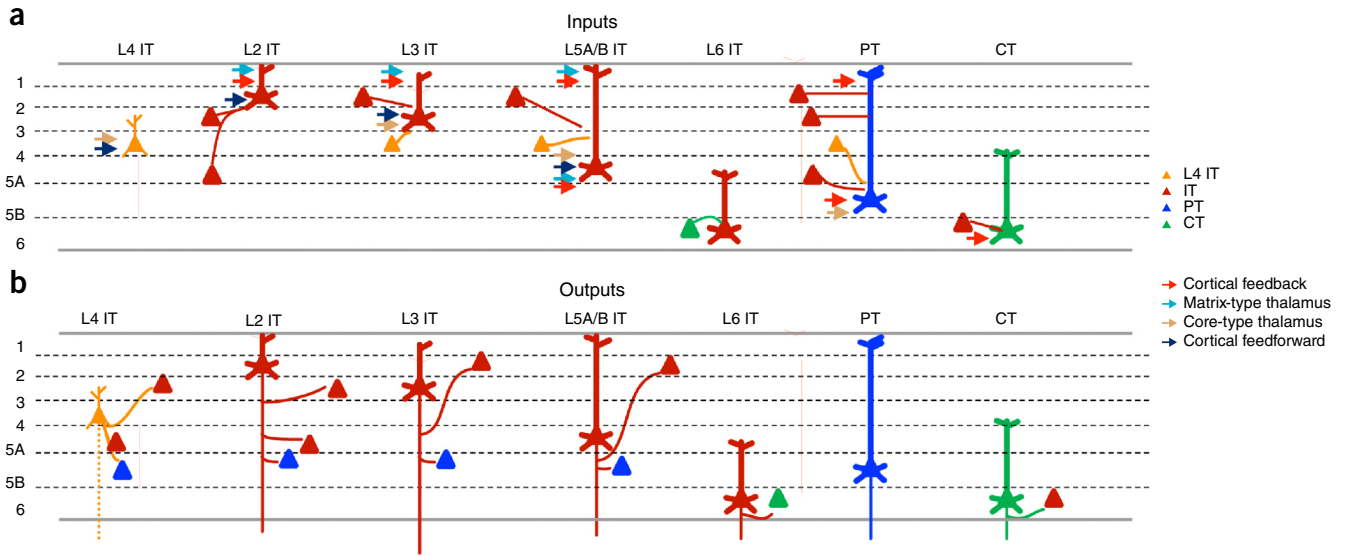


Figure 4 Hypothesized excitatory hodology of the main EC classes. For clarity, intraclass (recurrent) connections are omitted, but these exist for all cell types. This connectivity scheme is derived primarily from rodent barrel and motor cortex (see main text), and the existence of many of these connections in other regions remains to be tested. L5A ITs and L5B ITs have been represented together for simplicity. Additional connections for which only limited and/or conflicting evidence is available or whose connectivity rates have often been found to be low (for example, L4 IT to L6 IT and CT) have been omitted. (a) Hypothesized patterns of excitatory input to each main cortical excitatory class. For clarity, many connections are drawn as going to the dendrites of the postsynaptic neurons in the same layer as the presynaptic neurons; however, available evidence suggests that inputs tend to go mostly to the perisomatic dendrites¹⁶. (b) Hypothesized patterns of output from each excitatory class onto other excitatory classes.

neurons in other layers tend to be bidirectional. Their outputs go to distant neocortex and striatum, as well as locally to PT and probably CT neurons. IT neurons are a diverse cell class whose connectivity and physiology differ between and within layers.

L2/3 IT neurons send a major descending interlaminar axonal projection that branches extensively and densely in L5A and L5B, but not in L4. This L2/3→5A/B pathway appears to be a particularly prominent and consistent feature of cortical circuits across areas and species^{2,3,37,38,62} and is mirrored at a functional level: optogenetic stimulation of L2/3 IT neurons has been shown to generate strong oscillatory activity in L2/3 and L5A/B, but not L4 or L6 (ref. 63).

It is increasingly evident on the basis of gene expression, projection target and firing patterns that L2/3 IT neurons comprise multiple subclasses^{11,64–66}. Although the supragranular layers are often studied as a single entity, hodological distinctions between sublayers are an important aspect of inter-areal connectivity in primate neocortex⁶¹, and recent work in rodent is also revealing increasing distinctions between L2 and L3 (for example, refs. 8,67,68).

L2 IT neurons receive matrix-type TC input both monosynaptically and indirectly via ascending projections. In mouse barrel cortex, L2 ITs receive matrix-type input from POM¹⁶, but they receive little core-type input as their basal dendrites overlap little with these TC axons (Figs. 3b and 4a)³². L2 ITs also receive substantial input from L5A as well as L4 (refs. 19,38), particularly (in rat) for L2 ITs located above septa^{8,67–69}. The main local interlaminar target of L2 ITs is IT neurons of lower L5A and PT neurons of upper L5B (at least in motor cortex⁷⁰).

L3 IT neurons, in contrast, receive core-type TC input on their basal dendrites, matrix-type and higher order cortical input on their apical dendrites¹⁶, many inputs from local L4 ITs and relatively weaker input from local L5A ITs^{19,38,67} (Fig. 4a). Locally, L3 ITs project primarily within the superficial layers as well to L5A/B, where they preferentially innervate PT rather than IT neurons (at least in motor cortex⁷⁰) (Fig. 4b).

Despite receiving extensive excitatory input from L4, L2/3 ITs fire sparsely (that is, at low rates) *in vivo*, with L2 ITs exhibiting sparser firing than L3 (refs. 71–75). This sparse firing may arise from their hyperpolarized resting potentials¹⁹, as well as strong activation of L2/3 interneurons⁷⁶. Theoretical considerations suggest that sparse firing is advantageous for efficient learning in neural networks, and L2/3 is indeed a site of high plasticity in sensory cortex^{77,78}.

IT neurons of L5A/B are generally interconnected with those of L2/3 (Fig. 4a,b)^{19,38,79}. L5A/B ITs are smaller than PT neurons, with thin-tufted apical dendrites stretching to L1. *In vivo*, they are more active than L2/3 ITs, but less so than PT neurons^{71,72,75}. Their long-range projections broadly resemble those of L2/3 ITs, but with more extensive connections to striatum^{10,12}.

L6 IT neurons are the least studied IT type. Their inputs arise mainly from local deep layer neurons, at least in V1 (ref. 80). L6 ITs make extensive long-range horizontal connections within neocortex, and some project to claustrum³⁶. L6 ITs contain neurochemically distinct subclasses whose sublamination patterns can vary between areas^{81,82}. A distinct class of neurons found in the deepest stratum of neocortex, referred to as L6B, L7 or subgriseal neurons, constitute the surviving remnants of the subplate, a structure that is essential for cortical development but whose neurons largely die before adulthood⁸³. This sublayer contains excitatory neurons but also long-range GABAergic projection neurons, and its neuronal composition and function remains to be fully elucidated^{83,84}.

In summary, IT neurons are a highly diverse class whose local and long-range connectivity forms the backbone of communication within and between cortical areas and hemispheres. There is as yet no clear evidence for areal differences in the local-circuit hodology of IT neurons. However, much remains to be learned about the connectivity and function of different subclasses of IT neurons, and it is possible that such investigations will reveal differences in not only the long-range but also local connectivity of IT subtypes between cortical areas.

PTs integrate cortical and TC inputs and broadcast to subcerebral structures. PT neurons represent the third and final stage of the local excitatory circuit. These large neurons receive extensive inputs from local IT neurons of multiple layers but give little back locally, a result that has been seen in several cortical regions^{15,17,18} (Fig. 4a,b). They receive direct TC inputs, which are strong enough to drive them even without inputs from local L2/3 IT cells⁸⁵. Their TC inputs appear to be primarily core type, at least in barrel cortex: although PT tuft dendrites in L1 receive corticocortical inputs from motor cortex, they receive very little matrix-type TC input from POM¹⁶.

PT neurons are found across the neocortex. PT neurons in any particular area often project to a characteristic subcerebral target—for example corticospinal neurons in motor cortex and corticotectal neurons in visual cortex. Nevertheless, PT axons tend to be multi-projectional, branching to multiple subcerebral destinations as well as cortex, striatum and thalamus. Their specific projection targets vary considerably from cell to cell, even for PT neurons within the same cortical area (for example, ref. 86; reviewed in ref. 10). The intracortical axons of PT neurons are ipsilateral only and contribute, together with IT neurons, to inter-areal corticocortical projections between areas. Cortical PT collaterals have mostly been observed only in feedback-type projections^{87–89}; their laminar termination differs from those of IT axons, at least for projections from motor cortex to S1 (ref. 89). The extent to which these patterns generalize for all intracortical branches of PT axons remains to be assessed.

The physiology of PT neurons is broadly consistent across areas and is distinct from that of neighboring IT neurons. PT neurons have relatively depolarized resting membrane potentials, non-adapting spike trains, relatively narrow spikes, strong expression of hyperpolarization-activated currents and distinct neuromodulatory properties^{10,90–92}. These properties have been observed in multiple regions, although some properties, such as expression of Kv1-type voltage-gated potassium currents, are area specific⁹³. Subclasses of PT neurons have been distinguished within an area on the basis of electrophysiological properties such as action potential conduction velocity^{94,95}. Although PTs have been associated with intrinsic bursting firing patterns, they do not always display this property⁹⁶, and they are not the only cells that can burst *in vivo*^{85,97}. Notably, PTs have the highest *in vivo* firing rates of all EC classes^{71–73,75,95,98,99}; such ‘dense coding’ may provide an information-theoretic advantage to the broadcast of cortical output through a relatively small number of long-range projection fibers⁴.

Data so far thus suggest that PTs in many regions act as downstream elements in the local circuit: integrating the results of local computations with direct thalamic inputs and efficiently broadcasting the results, mainly to distant subcortical structures. PTs of different regions send these outputs to different places; furthermore, PT neurons with diverse projection patterns may exist even within a single area, integrating particular combinations of local and long-range input and routing them to distinct sets of subcortical targets.

CT neurons: mysterious creatures of the deep. CT neurons are a distinct class of L6 cell, with unique developmental history and molecular characteristics^{11,36}. They are distinct from L6 IT neurons, with which they are intermingled, and also from PT neurons that send axonal branches to the thalamus. Anatomically, they are positioned to receive inputs from the many axon classes crossing their dendritic span, including local L4, IT and PT neurons; matrix-, IL- and core-type TC inputs; and long-range projections from many cortical regions and claustrum^{31,36}. Nevertheless, CT neurons appear to receive a general paucity of thalamic and local input^{8,36,80,100}. Studies in

several cortical areas have indicated that they are instead innervated by high-order cortical areas^{32,80,101}.

CT neurons in sensory areas generally project back mostly to the thalamic relay nucleus providing their own cortical area with core-type TC input. However, a subclass of CT neurons found in lower L6 of several sensory areas projects also to higher order thalamic nuclei¹⁰². The thalamic nuclei targeted by CT neurons in motor and associative areas are poorly understood. CT projections can be extremely slow, with delays of up to 30 ms reported in rabbit S1 (ref. 99). Their synapses on thalamic relay cells are small, distal and relatively weak, with a major metabotropic component, leading to their classification as “modulators” as opposed to the “drivers” conveying input to thalamus from the sense organs and from cortical PT neurons¹⁰³.

The intracortical axons of CT neurons are limited to sparse, locally ascending branches^{36,104}. In rats, the upper and lower CT subclasses give off local branches in L4 and L5A, respectively¹⁰⁴. Similarly, in tree shrew V1, the axons of different CT subclasses target different sublayers in L4 (ref. 35). In mouse S1, CT neurons innervate IT neurons in L5A but not those in L4, which they instead indirectly inhibit⁴⁰, whereas in V1 they exert a predominantly inhibitory effect on all other layers, via a subclass of parvalbumin (Pvalb)-positive interneurons^{42,105}.

The function of CT neurons remains enigmatic³⁶. While CT connections have been proposed to close excitatory thalamocortical loops, the dominance of corticocortical over local excitatory inputs suggests a specialization for integrating long-range signals to modulate thalamocortical activity. Indeed, optogenetic experiments suggest that CT neurons, through their strong inhibitory influences on neurons in other cortical layers and in thalamus, can provide gain control in perceptual processing^{42,106}. Puzzlingly, but consistent with their paucity of local inputs, most CT neurons *in vivo* are remarkably silent, even during various behaviors^{75,80,98,107}. Thus, even though L6 occupies a substantial fraction of cortical volume, the role of CT neurons remains largely a mystery.

IT subclasses may explain inter-areal connection patterns

The neocortex’s many areas are elaborately interconnected through the axons of primarily IT neurons. Inter-areal connectivity is complex, and large-scale studies of primate and rodent have suggested the existence of subnetworks showing elevated interconnection, linked together by diversely connected hub regions^{61,108–110}. The connectivity of N cortical areas can be summarized by a matrix of N^2 numbers; but a more intuitive understanding of these connections could be gained if there exist simpler organizing principles governing connections of multiple regions. One such principle is the cortical hierarchy, which arose from primate studies showing that the layers of origin and termination of inter-areal projections differ between ‘feedforward’ and ‘feedback’ projections^{60,61} (Fig. 5a). In rodents, evidence for hierarchical organization also exists, but its relation to lamination is less clear, with the primary laminar feature described being the avoidance of L4 by feedback projections in visual cortex⁵⁹. Cells giving rise to feedforward and feedback projections can form distinct populations, but they do not always occupy different layers¹¹¹ (Fig. 5b); furthermore, these subclasses can receive different patterns of long-range synaptic input¹¹². The existence of genetically distinct subclasses of IT neuron with characteristic long-range projections might provide a cellular explanation for inter-areal connectivity patterns in rodents, including but not limited to its hierarchical organization.

One example of subclass-specific inter-areal IT projections comes from a study of deep-layer neurons in the rat⁸² (Fig. 5c). In secondary visual, auditory and somatosensory cortices, a molecularly distinct

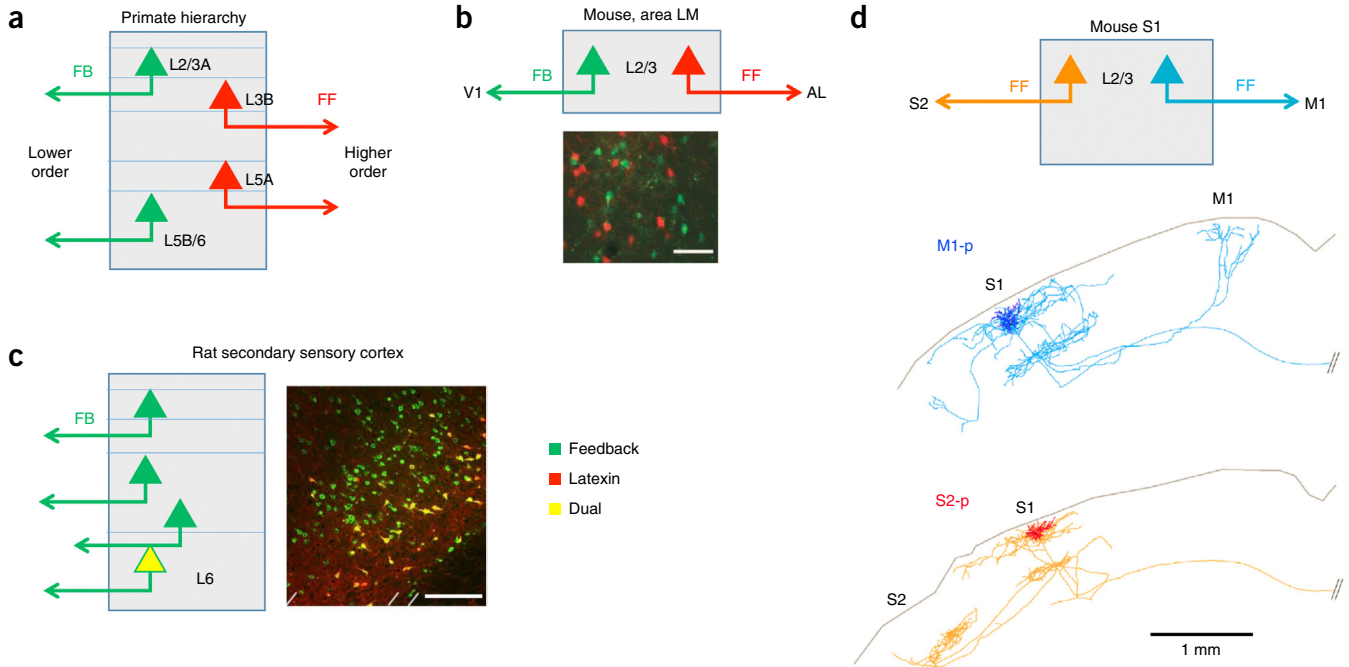


Figure 5 Hypothesized homologous hodology of inter-areal connectivity. (a) In primate neocortex, feedforward (FF) and feedback (FB) streams have characteristic layers of origin and termination. (b) In mouse visual cortex, FF and FB projections from an intermediate area (LM) arise from distinct IT subclasses that are intermingled in L2/3, as demonstrated by retrograde tracer injections into the upstream (V1) and downstream (anterolateral; AL) areas (image adapted with permission from ref. 111, John Wiley & Sons). Scale bar, 50 μ m. (c) In rat secondary sensory cortices, a subclass of L6 neurons expressing latexin projects back to the corresponding primary sensory region, but not to thalamus, higher order cortex or contralateral cortex (image reproduced with permission from ref. 82, Elsevier). Scale bar, 200 μ m. (d) In mouse S1, two distinct subclasses of L2/3 neurons project to M1 and S2, both of which would be considered FF projections (reconstructed neurons reproduced with permission from ref. 66, Cell Press). Note the collosally projecting axons of both neurons (branches to the right), a defining feature of IT neurons. S2, secondary somatosensory cortex; M1, primary motor cortex; M1-p, M1-projecting; S2-p, S2-projecting.

subset of deep-layer neurons expressing latexin and Nr4a2 sends feedback-type projections to the corresponding primary areas, but rarely to higher order cortex, thalamus or the contralateral hemisphere. It thus appears likely that these cells express a gene module including not only latexin and Nr4a2 but also other molecules that during development direct their axonal projections toward primary cortex.

Extrapolating from this relatively clear example, one might hypothesize that the apparently complex global pattern of corticocortical connections could be explained by the existence of a relatively small number of IT subclasses that are homologous across regions. Analogously to the way common gene modules guide the differentiation of top-level EC classes (PT versus IT versus CT), these IT subclasses would express common gene modules enforcing common characteristics, including long-range axon targets, input connectivity, intrinsic physiology, somatodendritic morphology and, in some cases, sublamination of both somata and axon terminals. Similarly, just as area-specific genes modulate the top-level EC classes by directing the precise subcortical structures they target (see below), area-specific genes might regionally diversify the common IT subtypes—for example, by guiding top-down projections from V2 to V1, rather than to A1. Importantly, the IT subclasses giving rise to feedforward and feedback projections need not occupy different layers in all species. Thus, even though the organization of inter-areal projections might appear different between primate and rodent at the laminar level, it may be homologous at the level of cellular subclasses.

If such homologous IT subclasses exist, they are unlikely to be restricted to subclasses producing feedforward and feedback projections.

For example, within superficial barrel cortex, distinct subclasses of IT neurons project to motor cortex and secondary somatosensory cortex (Fig. 5d), although both would be considered feedforward pathways. These subclasses have differences in intrinsic physiology and encode information differently *in vivo*^{64–66}. While present data do not rule out these subclasses being specific to barrel cortex, it has been hypothesized that these two output streams are homologous to the dorsal and ventral streams of the visual and auditory pathways, specialized for processing information on stimulus location and identity, respectively⁶⁶. Indeed, the dorsal and ventral projection streams of primate visual cortex also originate from neurons with different firing patterns, presumably corresponding to different IT subclasses^{28,113}. It is therefore conceivable that a common set of genes control the long-range projections, physiology and possibly information coding of dorsal-type and ventral-type IT neurons across areas and species. Combinatorial expression of a relatively small set of genetic modules like those just hypothesized could be sufficient to define the complex set of subtype- and area-specific corticocortical projections found in the mammalian brain.

Homologous inhibitory circuits mediate diverse effects

Recent research has greatly elucidated the development, connectivity and function of different types of cortical interneurons. Their classification remains an actively pursued issue (for example, ref. 114), but in an increasingly adopted scheme they can be grouped into three genetically defined top-level classes, expressing Pvalb, somatostatin (Sst) or serotonin receptor type 3a (Htr3a) (Table 2)¹¹⁵. These classes contain many subtypes, which are outside the scope of this

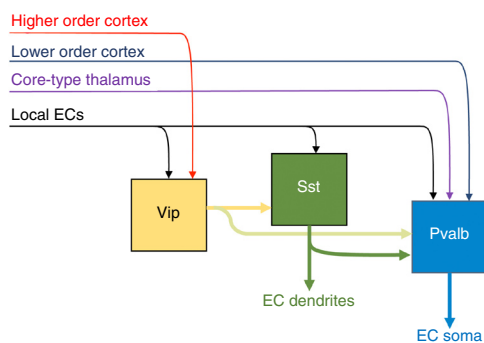


Figure 6 Sequential hodology of three main inhibitory cell classes. All classes receive inputs from local ECs. Vip cells (a subclass of Htr3a interneurons) receive input from higher order cortex and inhibit primarily other interneuron classes. Sst cells inhibit Pvalb cells and the dendrites of ECs. Pvalb cells receive strong feedforward inputs from thalamus and lower order cortex, and inhibit ECs perisomatically. More interneuron classes exist whose hodology is not yet fully established.

Review and have been extensively reviewed elsewhere (for example, refs. 13,116–118). We focus here on one particular aspect: how serially homologous inhibitory circuits may mediate diverse control of cortical processing during behavior.

Classes of interneurons, like classes of ECs, form systematically asymmetric connections that define a sequentially organized network, and recent evidence indicates that this organization is conserved between multiple areas (Fig. 6). The overall most upstream interneurons in this inhibitory network are those expressing vasoactive intestinal peptide (Vip), a major subclass of Htr3a neurons^{119–122}. These cells are most abundant in L2/3 and are characterized by a narrowly focused descending axon, a trait shared with a class of interneurons of lower L1 that have been termed single-bouquet cells¹²². Both Vip and lower L1 interneurons receive strong excitatory input from corticocortical axons in L1, as well as local ECs^{120,123–125}, and are also excited by ionotropic receptors for acetylcholine and serotonin^{116,120,124}.

The primary targets of Vip and single-bouquet cells are other interneurons, especially Sst interneurons as well as Pvalb-positive basket cells^{119–122}. Sst and Pvalb cells receive excitatory input from local neurons, with Pvalb cells also receiving strong inputs from core-type thalamic and feedforward corticocortical axons^{51,126}. Sst and Pvalb interneurons inhibit ECs on their dendrites and somata respectively, and Sst cells also inhibit Pvalb cells in a largely unidirectional manner^{121,127}.

The activity of different interneuron classes is modulated by behavior, in a manner that appears to differ between cortical regions. In barrel cortex, whisking leads to increased Vip cell firing, primarily through projections from motor cortex¹²⁰. Consistent with the strong inhibition of Sst cells by Vip cells, whisking hyperpolarizes Sst cells¹²⁸, which in turn causes EC neurons' apical dendrites to be released from inhibition, potentially explaining the enhanced dendritic calcium activity seen during active whisking^{128,129}.

In V1, locomotion excites Vip cells¹²⁴ and causes diverse speed-dependent changes in the activity of ECs¹³⁰, including increased visually driven activity in superficial layers^{124,131–133} that again appears to result from Vip cell-mediated disinhibition¹²⁴. In A1, however, locomotion decreases sensory responses in L2/3 IT and Pvalb neurons^{46,134}, even though locomotion again increases the activity of A1 Vip cells¹²⁴, which again inhibit Sst and Pvalb interneurons¹¹⁹. Thus, the effects of locomotion on the different sensory cortices can be quite different,

despite their apparently conserved hodology. Intriguingly, these opposing effects of locomotion on sensory responses in superficial visual and auditory cortex can both be mimicked by optogenetic stimulation of inputs from higher order cortices^{125,134}.

How could two cortical circuits with apparently identical hodology show opposite modulation by behavior and top-down cortical input? Such a phenomenon is not unprecedented: in electronics, for example, a circuit of a single topology can act as an amplifier or an attenuator, depending on the precise relative impedances of its constituent components. Analogously, quantitative differences in the parameters of serially homologous cortical circuits might explain how activation of one input pathway causes opposite-signed effects on the activity of a single cell class in different areas. For example, the differing effects of locomotion on superficial EC neurons of V1 and A1 might be explained by differences in the strength of inhibition that EC, Sst and Pvalb cells receive from Vip cells; by differences in the susceptibility of different interneuron classes to neuromodulation; or by differences in the strengths of local and top-down inputs received by different interneuron classes. More generally, quantitative differences among areas may control how animals integrate top-down and bottom-up information in a manner appropriate to each modality and behavior. For example, enhanced integration of top-down and bottom-up information during active whisking has been hypothesized to allow for computation of object locations by the interaction of whisker position and touch^{129,135}. Integration of optic flow and running speed has been proposed to allow V1 neurons to estimate an animal's velocity through the world¹³⁰. Finally, suppression of auditory cortical activity during running might enable the animal to focus more on the visual and somatosensory modalities critical to rodent navigation^{46,134}. Thus, quantitative variations in serially homologous circuits might adapt different cortical regions to the ethological role of each sense.

Developmental basis of serially homologous circuits

The serially homologous organization of neocortex, like serial homology throughout the body, occurs because the developmental precursor populations of different regions follow homologous genetic programs, leading to similar cell types arranged in a similar organization. We refer the reader to other recent reviews of the vast developmental literature^{11,13,116,136}. The top-level EC classes are developmentally specified by mutually suppressive interactions between transcription factors including *Fezf2* and *Ctip2* for PT, *Satb2* for IT and *Tbr1* for CT neurons. The relationship between gene expression and top-level cell classes appears to be conserved between cortical regions¹¹. Genetic modules downstream of these top-level transcription factors control receptors and molecular pathways involved in axon guidance and synapse formation, giving each class its characteristic connectivity profile^{11,137,138}. Experimental manipulation of these transcription factors in postmigratory neurons changes their connectivity and physiological properties, confirming that it is the genetically specified cell class, rather than laminar location *per se*, that is the fundamental determinant of cortical connectivity^{139–141}.

What developmental mechanisms account for differences between cortical regions? The developing neocortex shows graded expression of some transcription factors across its surface, through which neocortical arealization is developmentally orchestrated (for example, refs. 56,142). These gradations modulate the common cortical developmental plan, resulting, for example, in differences in long-range axon targeting and the attraction of different types of thalamic input^{11,56,136}. Thalamocortical innervation in turn sculpts cortical organization and appears to underlie inter-areal differences in L4 architecture. Indeed, in primary sensory cortex, TC innervation and activity is developmentally

required for expression of L4-specific genes such as the M2 muscarinic receptor¹⁴³, for the formation of whisker barrels¹⁴⁴ and for the retraction of apical dendrites to form spiny stellate cells¹⁴⁵. The characteristic architectural features of L4 appear to be controlled by the patterns of sensory innervation the neocortex receives, as evidenced, for example, by the adaptation of barrel cortex to the number of intact whiskers¹⁴⁴. Such input-driven malleability of L4 might help accelerate the evolution of new sensory strategies.

Outside L4, there is as yet little evidence for major inter-areal differences in local circuit hodology. However, as noted above, hodologically similar circuits can evidently operate differently in different cortical areas. We have suggested that such differences can result from relatively small changes in quantitative parameters, such as the number of cells of particular classes or their precise intrinsic and synaptic parameters. Although the developmental basis for such differences is not yet known, the existence of physiological differences between areas is supported not only by differences in cell counts, but also by differences in ion channel expression between regions in neurons of a single cell class⁹³. Such quantitative differences may in turn be imposed by areal differences in gene expression, as well as the differing electrical activity patterns of multiple regions.

These observations suggest a hypothesis for how a common cortical circuit plan is modulated between areas. First, intrinsic differences in gene expression give each area its characteristic long-range patterns of input and output, as well as establishing quantitative differences in circuit parameters that fine-tune local circuit dynamics for the type of information processing that will occur there. Second, differences in extrinsic innervation and afferent activity patterns sculpt the circuits of thalamorecipient neurons, particularly in L4 sensory cortex, to adapt their architecture to particular classes of inputs.

Is cortical organization homologous across species?

How similar is cortical architecture between species? A comparison of the rodent literature, reviewed here, with cat, tree shrew and primate studies might give the impression that the hodology of these species is very different. In fact, there are as yet few data that indicate major differences in hodology between species. Evidence for the sequential hodology illustrated in **Figures 2, 4 and 6**, for example, comes largely from experimental techniques as yet applied only in rodents; so far, there are insufficient data to know whether this organization also holds in other mammals. Similarly, while modern genetic methods allow detailed study of rodent inhibitory circuits, most such techniques are not yet available in other species.

As with differences between areas of mouse neocortex, the greatest differences between species appear to be in L4. L4 has a deep homology across species: it is found in marsupials¹⁴⁶, and even nonmammalian vertebrates such as birds and turtles, which lack neocortex, contain cells proposed as homologous to L4 neurons on the basis of gene expression patterns¹⁴⁷. The cytoarchitectural idiosyncrasies of L4 appear strongest in areas devoted to ethologically important modalities. Rodents rely heavily on their vibrissae, and their S1 barrels have striking specializations as compared to other sensory areas. In highly visual primates and humans, L4 in V1 is stratified into distinct sublayers receiving different input streams²⁸. By contrast, the star-nosed mole's somatosensory L4 contains a map of its nose¹⁴⁸.

The question of how primate and especially human neocortex differs from that of other mammals has long intrigued neuroscientists. There is evidence that primate neocortex has a different developmental profile from that of rodent¹³⁶. In primates, L2/3 appears expanded relative to those of carnivorans and rodents, which has been suggested to arise from increased proliferation that may in turn be allowed

by longer gestation¹⁴⁹. Expansion of L2/3 has thus been suggested as one of the key evolutionary features of primate neocortex, but the intriguing implication—that L2/3 IT neurons' circuits have somehow been modified with this adaptation—remains largely unexplored.

Outlook

Recent years have seen tremendous advances in our understanding of neocortical function, but an increasing fraction of this work is focused on a handful of cortical areas in a very specific model organism: the C57BL/6 strain of *Mus musculus*. This intense focus is likely to facilitate progress, as did the focus on *Escherichia coli* in the early days of molecular biology. The serially homologous nature of cortical circuits suggests that what we learn in the mouse will guide us toward general organizing principles, which can then be tested by more targeted investigations in other mammalian species. However, while recent work has suggested the broad outlines of how homologous connectivity may lead to common processing strategies in multiple areas, a great deal more work needs to be done before such principles are firmly established.

First, we must continue to work toward a consensus about the cell types that make up cortical circuits. For the top-level classification of ECs and interneurons, such a consensus is now emerging. It is now apparent that most, if not all, cortical regions contain homologous cell classes generated through similar cell-fate specification mechanisms: for excitatory neurons, the IT, PT and CT classes; and for inhibitory neurons, the Pvalb, Sst and Htr3a classes. This classification provides a unified framework that is consistent at many levels, including development, molecular biology, local and long-range connectivity, intrinsic physiology and *in vivo* activity, all of which appear to be broadly conserved across areas. The next frontier is to understand the extent to which the subclasses of these top-level classes are also homologously specified. Progress on this question will be accelerated by continued development of molecular markers, transgenic mice and other tools that systematically and reliably identify and manipulate neuronal subclasses across areas (for example, refs. 12,150).

Second, we must continue to clarify the input and output connectivity of these cell types at all length scales. While the local connectivity and long-range outputs of top-level EC and interneuron classes appear homologous across many areas, it is not yet clear whether the same will be true for subclasses. Furthermore, it is not yet known whether the long-range inputs of even the top-level classes are homologous across areas. For example, PT neurons of barrel cortex receive very little input from P_{Om} thalamus¹⁶; do PT neurons elsewhere also not receive matrix-type thalamic input? The recent development of optogenetic circuit tracing⁶² has enabled studies of long-range inputs to different cortical cell classes; when this technique is systematically applied to numerous areas, this question and many others can be answered, providing general principles of cortical connectivity across multiple regions.

Third, the relationship of IT subclasses to inter-areal connectivity must be established. Cortical areas are interconnected through seemingly myriad long-range projections. Conceivably, this complexity could arise from a small number of basic genetically specified IT subclasses, modulated by area-specific molecular gradients or other factors. Understanding the projection patterns of IT subclasses thus holds the potential to illuminate the cellular basis of inter-areal connectivity, including but not limited to the hierarchical organization seen at a macroscopic scale. CT neurons, lacking inter-areal branches, seem to be receivers but not senders in these corticocortical networks. How PT axons' intracortical projections contribute to this organization needs to be further evaluated, particularly the possibility that

they systematically provide feedback signals. A cellular understanding of IT subclasses would give information on not just the anatomical connections of the different subclasses but also their physiological properties and provide a framework to understand the types of information transmitted by different projection classes *in vivo*.

Fourth, how does the specific connectivity and physiology of different cell classes contribute to their *in vivo* firing patterns? The *in vivo* coding strategies of top-level EC and interneuron classes seem broadly homologous across regions, as do their profiles of connectivity and intrinsic physiology. Understanding how each cell class's connectivity and physiology shapes its coding strategy—and understanding whether and how this differs between further subclasses—will be critical to understanding cortical information processing.

Fifth, in what ways are serially homologous circuit patterns modified among cortical areas? What are the developmental mechanisms that specify these differences, and what are their functional consequences? We have suggested that the primary differences between areas are quantitative rather than qualitative. Assessing this will entail quantitative comparisons between areas at multiple levels, ranging from functional synaptic connectivity and intrinsic physiology to cell densities and morphology. Relatively few genes show different expression patterns between cortical regions; understanding how these modify the development of cortical connectivity and physiology will be important to understand its adult function. Understanding how quantitative differences in circuit patterns underlie different *in vivo* functions will require comparisons of recordings between multiple areas, most likely during several types of behaviors.

Finally, how similar is the cortical organization of different species? In this short Review, we have not attempted a systematic phylogenetic comparison, but simply drawn on a few examples of homologous organization. A large number of observations made in individual species remain to be evaluated in others. For example, two observations for which there is good evidence for serial homology in the rodent—the sequential homology of local excitatory and inhibitory circuits and the cell-type dependence of firing sparseness—remain to be thoroughly tested in other species. Comparative studies will remain essential for understanding exactly what is similar and specialized about neocortical circuits across different areas and mammalian species, and exactly how circuit organization relates to behavior.

ACKNOWLEDGMENTS

We thank K. Svoboda, N. Steinmetz, N. Yamawaki and M. Carandini for comments. K.D.H. is supported by grants from the Wellcome Trust (095668), Engineering and Physical Sciences Research Council (I005102, K015141) and Simons Foundation. G.M.G.S. is supported by grants from the US National Institutes of Health (NS061963, NS087479, DC013272, EB017695) and the Whitehall Foundation.

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

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