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Cortical Circuits

Consistency and Variability across Cortical Areas and Species

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Abstract

Neurons in local circuits in the neocortex of mammals need both to extract reliably meaningful information from their dominant activating inputs and to modify their responses to these inputs in the context of inputs that are activating other local circuits. Neocortex has structural features to mediate both of these tasks. Neocortex is characterized by an arrangement of neurons with different types of inputs and outputs into six traditionally defined layers and a pattern of dense, vertical interconnections between neurons across these layers. This arrangement is consistent with the general conclusion that narrow, vertical columns of neurons interact intensely to form local-circuit processing units that reliably extract information from a small number of activating inputs that largely terminate in layer 4. In addition, neurons in these circuits are influenced by lateral connections that interconnect groups of columns, as well as by more widespread subcortical modulating inputs and feedback connections from other cortical areas. Some or all of these connections may provide contextual modifications within and dynamic coordination between the vertical arrays of cortical neurons. While basic features of columnar arrangements of cortical neurons and their connectional patterns with other columns are likely similar across cortical areas and mammalian taxa, they also clearly differ in ways that likely reflect areal and species requirements and specializations. Some of these differences are outlined here.

Introduction

The focus of this chapter is on the structural features of neocortex of mammals that allow information to be extracted from inputs to narrow vertical arrays of highly interactive neurons, the cortical columns or modules (Mountcastle 1997; DeFelipe 2005; Douglas and Martin 2007; Thomson and Lamy 2007), and on the features that allow neurons in different columns to interact dynamically.

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Across mammals and within most cortical areas, neocortex is subdivided into six traditionally defined layers (Figure 2.1). Neurons within these layers have different functional roles based, in part, on having different inputs and outputs (Peters and Jones 1984). In brief, cortical activation is highly dependent on thalamic or cortical inputs into layer 4; layer 3 has lateral connections within the cortical area and projects to other cortical areas; layer 5 provides mainly subcortical projections; and layer 6 provides feedback connections to the thalamic or cortical source of layer 4 activation. The vertical connections between neurons of different layers are both very dense and very restricted in lateral spread (Figure 2.2). However, more sparse distributions of axons spread out laterally from neurons in layers 1, 3, and 5 to contact nearby neurons in other vertical columns of highly interconnected neurons. These lateral intrinsic connections provide the structural framework for interacting across cortical columns, possibly by inducing temporal synchronies between neurons in different columns (Singer and Gray 1995). In addition, widely distributed inputs from the brainstem and thalamus modulate the activity patterns across cortical columns and feedback connections from higher cortical areas, which are generally less specific in their terminations than the feedforward connections and are likely to have an integrating role.

While this brief depiction of the basic processing circuitry of cortex serves as a useful guide, it does not take into account the variability that exists in this circuitry across cortical areas and across mammalian species. As such

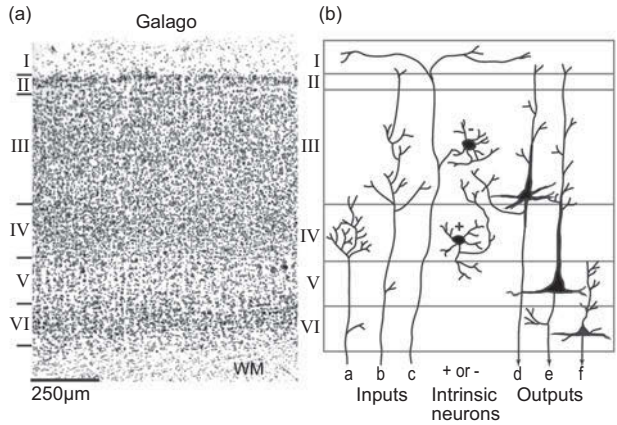

Figure 2.1 (a) The laminar arrangement of cells in the neocortex of a typical mammal (area 17 of a prosimian galago). Six layers are traditionally identified in most, but not all cortical areas. (b) The primary activating inputs from the thalamus or other areas of cortex, a, are to layer 4. Other thalamic and cortical inputs, b, are to other layers, while brainstem modulating inputs, c, are to layer 1. Intrinsic neurons are excitatory or inhibitory on other neurons, and they can be of several types. Output neurons are largely pyramidal neurons which project to other cortical areas, d, mainly subcortical targets, e, or provide feedback to thalamic nuclei or areas of cortex providing inputs.

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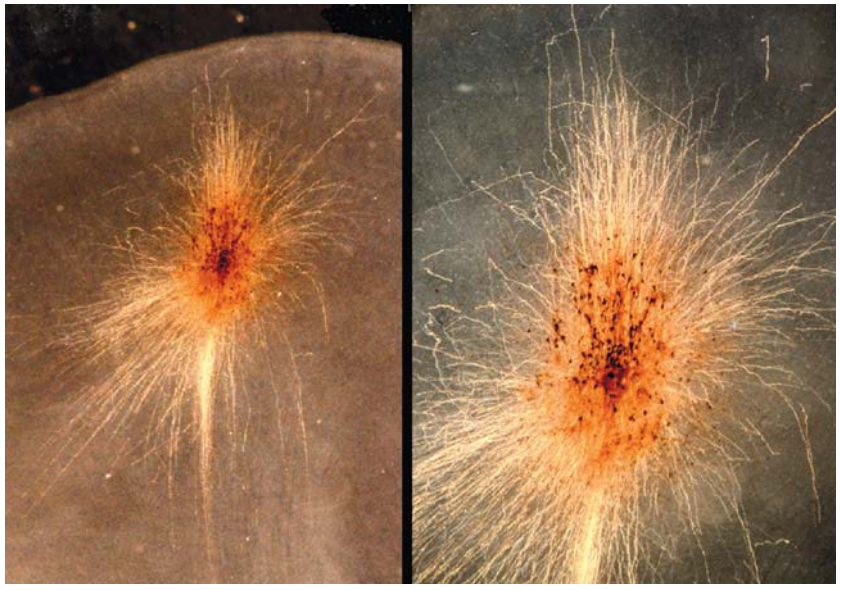

Figure 2.2 Neurons and axons labeled by an injection of a tracer into deeper cortical layers in a slice of neocortex of an owl monkey. Note the dense spread of axons to the more superficial layers immediately over the injection site (dense core of labeled neurons—dark spots), the sparseness of long lateral connections, and the bundles of output axons to the thalamus and brainstem, as well as to other areas of cortex.

variability in structure implies variability in function, some of the structural variability that occurs is reviewed here.

Cortical Layers Vary in Distinctiveness and Differentiation

Comparative studies suggest that early mammals had few cortical areas, on the order of 20–25, and that these areas were not very distinct architectonically from each other (Kaas 2007). In addition, cortical layers, although apparent, were not markedly different in cellular makeup or in histochemistry. No specialized agranular motor cortex was present (Beck et al. 1996). In sensory areas, layer 4 was populated mainly with intrinsic neurons rather than pyramidal neurons; however, because of their size, these layer 4 neurons could more appropriately be called stellate cells, rather than granule or powder (koniocellular) neurons, which are tiny cells found in the highly specialized sensory cortex of some mammals. The six main layers did not have very distinct sublayers. Overall, there were relatively few classes of neurons, the morphological and histochemical variations across neurons of a class were small, and the intrinsic connections in cortex were similar across areas in early mammalian species. Thus, except for functional differences imposed by the distinct activating

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inputs to areas of cortex, and the differing targets for outputs, the basic computations in the vertical cortical processing units across most cortical areas in early mammalian species were likely to be highly similar.

In many cortical areas of numerous mammals, this ancestral pattern of weak cortical lamination and limited cellular differentiation appears to have changed very little. There are, however, mammals where there clearly have been major modifications. In one example, the neocortex of whales and other Cetacea is so modified, and to some extent regressed, that some investigators have postulated that they had retained structural features of the "initial" mammalian brains (Glezer et al. 1988). More likely, their brains have been severely modified as an adaptation to their unusual marine lifestyle (Marino 2007). The cytoarchitecture of neocortex of Cetacea is unique in not having a detectable layer 4 (or possibly having a very meager layer 4), while layer 1 is very thick, layer 2 is pronounced, and other layers are very indistinct. Additionally, there is little difference from region to region that would suggest morphological specializations for different kinds of processing in different cortical areas (e.g., Hof and Van der Gucht 2007). Unlike other mammals, the majority of afferents from the thalamus, and presumably those that are feedforward from area to area, appear to go to layer 1 rather than layer 4. Thus, cortical circuits in these marine mammals appear to be quite different from those in most mammals.

The lamination pattern of primary visual cortex (V1) of tarsiers is perhaps at the other extreme of differentiation (Collins et al. 2005). In Nissl-stained sections, layer 3 has three distinct sublayers that differ in cell packing and cell sizes; layer 4 also has three distinct sublayers; layer 5 has two; and layer 6 has two (using the numbering of layers according to Hässler 1967, which places layers 4A and 4B of Brodmann in layer 3). The overall laminar appearance of area 17 is reminiscent of the distinct lamination of the optic tectum of predatory birds. Surely these morphological distinctions reflect functionally significant modifications of the basic circuitry of primary visual cortex in these highly visual predators.

These two extremes of cortical lamination patterns only hint at the great variability that exists in cortical lamination features across cortical areas and across mammals. Using histochemical, immunohistochemical, and receptor binding procedures, it is now possible to reveal laminar, areal, and species differences in a great number of factors that are likely to be important in neuronal circuit functions. For example, the monoclonal antibody Cat-301, which reacts with neurons associated with the magnocellular visual processing stream of primates, reveals different laminar patterns of antigen expression in primary visual cortex of cats, monkeys, and tree shrews (Jain et al. 1994). Layers across cortical areas vary in such features as the expression of synaptic zinc, cytochrome oxidase, parvalbumin, calbindin, vesicular glutamate transporters, and neurofilament markers. While layers in homologous cortical areas across species often have similar relative levels of expression of these markers, there is considerable variability (Hof et al. 1999; Wong and Kaas 2008, 2009a, b).

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Layers and cortical areas differ in the patterns of expression of the various neurotransmitter receptors such that cortical areas can be recognized by a "fingerprint" of their neurotransmitter profile (Zilles et al. 2002). Although the functional significance of such structural and histochemical variability in cortical layers is not always clear, it suggests that the operations of cortical circuits likely vary with such features.

Neuron Densities and Proportions to Glia and Other Nonneural Cells Vary across Areas and Species

A frequent assumption among neuroscientists is that cortical modules contain approximately the same numbers of neurons (for a brief review, see Rakic 2008). In one study that is often cited in support of this assumption, Rockel et al. (1980) counted the number of neurons in a narrow strip (30 μm) of cortex through the depth of cortex for several areas and five species; he reported that these were a fairly constant number (about 110) as studied in all areas and species, except for the primary visual cortex of macaque and humans (about 270). The results of more recent studies do not support the conclusion that neuron density is constant, but instead indicate that there is considerable variation in neuronal density across cortical areas and across species. If all of neocortex is considered, one recent estimate is that the average number of neurons underneath 1 mm^2 of cortical surface varies by about three times across primate species (Herculano-Houzel et al. 2008). Furthermore, primate brains consistently have a larger number of neurons than rodent brains of a matching size (Herculano-Houzel et al. 2007). Consistent with the early observations of Rockel et al. (1980) on macaques and humans, all primates appear to have a much higher density of neurons in primary visual cortex than in other areas of cortex (Collins and Kaas, unpublished). Yet, this density varies with species, and other visual areas, especially V2, have higher values than most cortical areas. In macaques, primary somatosensory cortex (area 3b) also has an elevated density of neurons. If one makes the assumption that cortical processing columns are of the same width across areas and species, the numbers of neurons within such columns vary greatly. This would certainly impact the processing within a column.

Dendritic Arbors of Cortical Pyramidal Cells Vary in Extent across Cortical Areas and Species

Some of the best evidence for how pyramidal cell morphology varies across cortical areas and species comes from a series of studies by Elston and his coworkers. By injecting layer 3 pyramidal neurons with Lucifer Yellow and viewing labeled dendritic arbors in tangential cortical slices, these researchers

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have been able to demonstrate great variability in the sizes of the basal dendritic fields. In macaque monkeys, for example, basal arbors of layer 3 pyramidal cells were smallest in primary visual cortex and were progressively larger across visual areas V2, V4, TEO and TE; the largest arbors were for neurons in prefrontal cortex (Figure 2.3) (Elston 2003; Elston et al. 1999). In contrast, the layer 3 pyramidal cells in tree shrews had larger arbors in V1, while V2 and temporal visual cortex had neurons with progressively smaller arbors. Other features of dendrites are also variable (Elston et al. 2005). For example, the pyramidal cells in V1 of tree shrews had twice the number of dendritic spines as those of primates. In addition, Elston et al. (1999) reported that peak spine density, reflecting synaptic contacts, was over three times higher for layer 3 pyramidal cells in higher-order visual area TE than in primary visual cortex of macaque monkeys. Elston (2003:1134) proposed that such regional variations in pyramidal cell structure "are likely to underlie fundamental differences in cortical circuitry," leading to "different functional capacities." If the widths of cortical columns correspond to the widths of the fields of basal dendrites, columns with neurons that have widespread basal dendritic arbors would be larger than those having neurons with restricted arbors. Columns that are larger in diameter would typically have greater numbers of neurons, although this is not necessarily the case, as neuronal densities vary.

Pyramidal neuron sizes vary as well. The specialized Betz pyramidal neurons of primary motor cortex and Meynert pyramidal neurons of primary visual cortex are known for their extra large size, which appears to be a specialization for fast conduction of axon potentials over long distances. Meynert neurons project cortically to visual area MT (middle temporal) and subcortically to superior colliculus, whereas Betz cells project to motorneuron pools in the brainstem and spinal cord. Both Betz and Meynert neurons also have long widespread basal dendrites that summarize information over a larger expanse

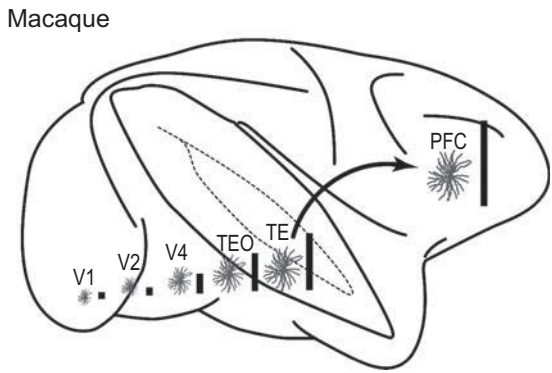

Figure 2.3 A dorsolateral view of the brain of a macaque monkey showing the relative sizes of the basal dendritic arbors of layer 3 pyramidal neurons in progressively higher-order visual areas (V1–TE) and in prefrontal cortex (PFC). Modified after Elston (2003).

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of cortex than other pyramidal neurons. In a comparative study of Betz and Meynert neurons, Sherwood et al. (2003) found that terrestrial patas monkeys had larger Betz neurons than any of the great apes, even though patus monkey brains are about four times smaller. As Betz and Meynert neurons tend to be larger overall in larger brains, the authors suggested that the large Meynert neurons might be a terrestrial adaptation for visually detecting predators, a problem that could be more pronounced for patus monkeys, since they live in the open savannah. Also, several primates, including tarsiers, had larger Betz neurons than predicted from brain size. As small, nocturnal visual predators, tarsiers might benefit from rapid grasping as well as escape movements. Betz cells are smaller than expected in the relatively slow moving prosimian galagos (Otolemur). The large dendrite arbors of Betz and Meynert neurons suggest that they integrate information over several cortical columns to form a hypercolumn. Thus, cortical circuit processing would differ in cortical areas that have the large Betz or Meynert neurons.

As another modification of cortical pyramidal cells, humans, but not apes or monkeys, have a novel mesh of dendrites in layer 3 (Brodmann's layer IVA) of primary visual cortex (Preuss and Coleman 2002; Preuss et al. 1999). Because this meshwork is related to the magnocellular pathway, Preuss and Coleman (2002) suggest that this modification in cortical circuitry subserves the visual perception of rapid orofacial consequences of speech.

Other Neuron Types Also Vary with Cortical Area and Species

Perhaps the neuron type currently receiving the most attention by neuroscientists and other readers is the Von Economo neuron: a spindle-shaped neuron with a simplified dendrite arbor. These neurons were once thought to be found only in humans and certain great apes (Nimchinsky et al. 1999; Allman et al. 2002), but they now have been described in elephant and whale brains (Hof and Van der Gucht 2007). Von Economo neurons are unusual in that they are considerably larger than nearby pyramidal cells, while having a large apical dendrite extending toward the cortical surface and a single basal dendrite extending toward the white matter. They appear to be restricted to the anterior cingulate cortex and frontal insular cortex of great apes, humans, whales and elephants. One suggestion is that these spindle cells or von Economo neurons have a special role in neural mechanisms related to social and emotional functions (Seeley et al. 2006). Whatever the case may be, their presence, in only a few cortical areas of a few taxa with very large brains, indicates that all cortical circuits are not the same.

There is some suggestion that another rare type of pyramidal neuron—the inverted pyramidal cell—is more frequent in large-brained mammals (Qi et al. 1999). This neuron type, however, is sometimes thought to be a result of errors in development, rather than being a functionally distinct type. This possibility

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has not been suggested for the Von Economo neuron, although their appearance in the very large brains of members of distantly related taxa suggests that they could reflect developmental factors associated with such large brains.

Other studies have demonstrated variations across areas and species in the distributions of inhibitory interneurons (DeFelipe et al. 1999; Hof et al. 1999; Sherwood and Hof 2007). The inhibitory double bouquet cell is present in the cortex of primates but not in rodents, lagomorphs, or ungulates. The impact of this anatomical difference is uncertain, but this inhibitory neuron could be critical in constraining and forming receptive field response properties to sensory stimuli. Inhibitory neurons also vary in distribution across species and the thalamic nuclei that project to neocortex (Arcelli et al. 1997; Penny et al. 1984). For example, GABAergic neurons are typically found in the visual lateral geniculate nucleus, but often not in the somatosensory ventroposterior nucleus. Furthermore, in mammals with few GABAergic neurons in the thalamus, intrinsic and projecting neurons vary little in size, whereas intrinsic neurons are smaller than projecting neurons in species where thalamic intrinsic neurons are widespread.

Patterns of Intrinsic Horizontal Areal Connections Vary across Areas and Taxa

Horizontal cortical connections that link various vertical arrays of cells within cortical areas appear to exist in all mammals and in all cortical areas. Although those connections are most dense near their cells of origin, the sparser, longer horizontal connections seem well suited for the role of coordinating the activities of groups of columns of cortical neurons, as widely proposed (Gilbert 1992; Singer and Gray 1995). The surface-view patterns of the distributions of these horizontal connections, however, are quite variable, apparently in ways related to the functional organization of cortical areas. The differences in the patterns of intrinsic horizontal connections in primary visual cortex of tree shrews and squirrels are, perhaps, the most dramatic in this regard. Squirrels and tree shrews are highly similar, visually dominated, diurnal mammals with well-developed visual systems. They are also members of the same major branch of mammalian evolution (Euarchontoglires). Tree shrews, however, have a remarkably widespread, patchy distribution of intrinsic horizontal connections with any location in V1 (Rockland and Lund 1982; Sesma et al. 1984), whereas the distribution pattern in squirrels is diffuse and even, rather than patchy (Van Hooser et al. 2006). The reason for this difference appears to relate to how neurons selective for stimulus orientation are distributed in V1, as cells with similar preferences are adjacent in V1 of tree shrews but distributed in squirrels. Thus, the long-range horizontal connections in V1 of tree shrews (and some other mammals, including primates) are patchy as they interconnect distributed patches of neurons with matching orientation preferences, but they

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are not in squirrels (and most other mammals) where orientation selective cells are not grouped by preference similarity (for a review, see Van Hooser 2007).

The intrinsic connections in V1 of primates reflect another pattern that indicates that other functional classes of neurons are sometimes selectively interconnected. Primates have a distribution of cytochrome oxidase patches, called blobs, which are missing from V1 of most mammals. Neurons in the blob regions are thought to be especially involved in color processing, and not in mediating sensitivity to stimulus orientation. Overall, blob regions are connected over the long intrinsic connections with other blob regions, and interblob regions with the interblob regions (Yabuta and Callaway 1998); however, significant differences in these patterns exist such that in galagos, and likely other prosimian primates, the extra long intrinsic connections involve blobs (Cusick and Kaas 1988). Furthermore, in galagos even the callosal connections between blob regions of V1 are rather extensive, including blobs quite distant from the outer border of V1 representing the vertical meridian (Cusick et al. 1984). Thus, the intrinsic connection system involving blobs can be more widespread than that for interblobs, and species differ in the extents of these widespread connections between blobs.

As for V1, where intrinsic horizontal connections may or may not be patchy, motor cortex of cats has an even distribution of horizontal connections, leading to the conclusion that these connections "bind together" the representations of a variety of muscles (Capaday et al. 2009). In contrast, intrinsic horizontal connections are patchy in primary motor cortex of macaque monkeys (Lund et al. 1993), suggesting that motor cortex functions differently in monkeys than it does in cats. Finally, and for uncertain reasons, the intrinsic connections of prefrontal cortex in macaques terminate in stripes rather than patches (Levitt et al. 1993).

Distributions of intrinsic connections are influenced in other ways by the somatotopy of primary somatosensory cortex (S1 or area 3b). In the S1 representation of the whiskers of the face in rats, intrinsic horizontal connections are more extensive between the representations of anterior-posterior rows of whiskers than vertical arches of whiskers (Kim and Ebner 1999). In a similar manner, intrinsic connections in the hand representation in area 3b of monkeys are more extensive along the length of the representation of individual digits, than across these representations (Fang et al. 2002). In addition, although the face representation adjoins that of digit 1, there are few connections across the hand–face border.

Although there could be many more examples, these few illustrate the point that the universally present intrinsic connections are quite variable in extent and distribution pattern. This variability implies that cortical areas within and across species vary in the ways cortical columns interact with each other. Overall, it appears likely that patchy and stripe-like patterns of intrinsic connections in cortical areas signify a like-to-like pattern of connections between groups of neurons with similar response properties, while diffuse, evenly

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distributed (at comparable distances from origin) patterns suggest a lack of specificity in such connections.

Feedback Connections

Connections from higher to lower areas in hierarchies of cortical areas provide another source of widespread neuronal interactions, as feedback connections are generally thought to be more widespread and less specific than feedforward connections (e.g., Krubitzer and Kaas 1990). Thus, patchiness is less pronounced than in feedforward connections and can participate in the coordination of processing in different processing streams. Nevertheless, feedback connections are generally more dense in the matching than non-matching feedforward modules, and thus vary in ways that reflect the modular organization of target areas (Salin and Bullier 1995).

Conclusions

One of the great temptations for overworked neuroscientists is to ignore, deny, or oversimplify the complex variability within and across nervous systems. In initial stages of development, models of nervous systems need obviously to depend on a few simplifying assumptions, but ultimately realistic models must reflect the organizations of real nervous systems. If we focus on mammalian neocortex, it is useful to remember that mammals with neocortex emerged at least 250 million years ago, and since that time formed the many branches of the mammalian radiation. A cladistic analysis, together with evidence from the fossil record, suggests that neocortex of early mammals occupied proportionally little of the brain, and that it was divided into few cortical areas, perhaps 20–25, that were poorly differentiated in cellular structure and rather similar (Kaas 2007). No present-day mammals have completely retained their ancestral organization, although the brains of some extant mammals have clearly changed much more than others. Perhaps human brains have changed the most, with human cortex now having more neurons than any other mammal, and having perhaps 200 functionally and structurally distinct processing areas. In addition to variably increasing the numbers of cortical areas across species (and in some cases, reducing them), cortical areas variably become more different in laminar and cellular structure. Thus, it is now unreasonable to assume that all cortical local circuits are the same, and that cortex varies simply in numbers of such circuits and types of inputs and outputs. Instead, we should explore and document this variability further, and use this variability as experiments of nature to understand how local circuits function and interact.

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