Network Properties of Visual Cortex

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Abstract

Cortical neurons are arranged in a set of layers. Their position within these layers in large part determines with which other neurons they form connections with. Specifically, within a set of cortical layers, or laminar microcircuit, cortical neurons connect with neurons within the same layer, other layers, or other cortical and subcortical areas. Ultimately, the activity of these neurons and the functional interactions that arise as a result of this wiring or connectivity gives rise to what we call "network activity"—a term that attempts to capture the complexity of interactions between interconnected neurons. The focus of this chapter is the neuronal circuitry that yields network activity within primate - specifically, macaque – primary visual cortex (V1). We specifically focus on the neuronal circuitry of V1— cell types, connections within and between layers, and inputs and outputs to the microcircuit - that establish mesoscopic network activity.

Introduction

Humans, just like other primates, are predominantly guided by their visual sense (Kaas, 1992). Perhaps not surprisingly then, a majority (>50%) of the primate brain is devoted to processing visual information (Felleman and Van Essen, 1991; Wandell et al., 2007). The largest visual cortical area in the primate brain is the primary visual cortex, or area V1 (Lennie and Movshon, 2005). Area V1 is one of the most commonly studied cortical areas in primates, and much of what we know about neocortical organization more generally is based on studies from this area (Hubel and Wiesel, 1968).

V1 neurons, like those in other cortical areas, are arranged non-randomly in layers (**Fig. 1**). These neurons connect with other neurons within layers, between layers, and receive inputs from other cortical and subcortical areas. Ultimately, the activity of these neurons and the functional interactions that arise as a result of this wiring or connectivity gives rise to what we call "network activity"—a term that attempts to capture the complexity of interactions between interconnected neurons. The focus of this chapter will be the neuronal circuitry that yields network activity within primate - specifically, macaque - V1.

Before we delve deeper into the topic, it is important to note that neuroscientists are not immune to the zeitgeist when it comes to describing their data or forming hypotheses on how the brain works. The historic development of our understanding of brain function exemplifies this fact: during Roman times, when massive aqueducts began to cross the landscape to channel water from remote areas to the farmlands, ordinary people and scholars alike were in awe of these visual manifestations of human insight into the laws of physics. Given the impact of this technology, it may not be surprising that prominent thinkers of the time, such as Galen, thought of the brain as a complex, pneumatic system of fluid channels (Quin, 1994; Rocca, 1997). Although predominantly focused on blood vessels, Galen was one of the first who thought of brain function resting on a network, which he termed *rete mirabile* (wonderful net). Galen's ideas on brain function held authority until the late 1700s when Galvani discovered the electrochemical nature of neurons (Piccolino, 1998). During the ensuing age of electricity, descriptions of brain function began to use the jargon of electrical engineers, such as circuits, amplification and response gain. And when radio technology hit the stage, neurophysiologists started describing neurons and their activity in terms of filter properties, oscillations, bandwidth and modulation. As technology took another jump forward and electronics became miniaturized to microprocessors, neuroscientific jargon adopted terms like computations, neuronal codes and "algorithmic" levels of description. Modern day neuroscientists are obviously not immune to these trends as the current age of the internet and social media coincides with an effort to understand the brain in terms of interactions – and networks again. It is as if, realizing that a complete understanding of brain function is still beyond our grasp, humans tend to liken its function to the most sophisticated systems currently known.

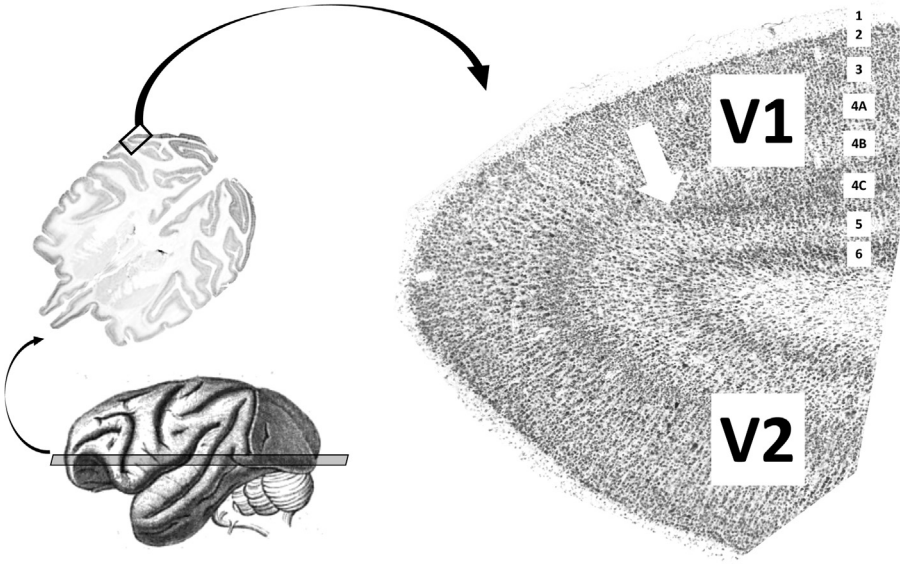

Figure 1 Histology (Nissl stain) of V1, demonstrating the laminar cortical layout. Left lower corner: Sketch of a side view of a (barbary) macaque brain by Paul Gervais (1816–1879). The brain is oriented such that the front is to the left and the visual cortex, which sits at the back of the brain, toward the right. The neocortex is indicated in dark gray and the cerebellum and brain stem below are shaded light gray and white, respectively. The shaded area that transects the brain horizontally indicated the slicing direction used for the axial slice shown right above (linked by the leftmost arrow). A small section of this histological section of a macaque brain (marked by a black box) is further magnified to the right (linked by the topmost arrow). This magnified section shows the transition zone from primary visual cortex (V1) to area V2. The histological (Nissl) stain reveals a marked striation that is more pronounced for V1 than V2. Arabian numerals indicate the laminar classification scheme for primate V1 that was first devised by Korbinian Brodmann (1868–1918), which equates layer 4 of other cortical areas with layer 4C in V1. The white arrow points out the transition between V1 and V2 and the associated visual appearance of layer 4. From Mikula et al. (2007),modified.

Although their voguish nature provides reason for caution, the above analogies and metaphors are all linked in one way or another to the concept of signal flow through a complex system. Neuronal network activity—the focus of this chapter—fits well into this overall theme. However, it is important to note that unlike pneumatic, electrical, computer or social networks, the brain is a biological system, so biological rules govern neuronal networks. First, neurons do not just integrate the excitation and inhibition elicited by neurotransmitters, but they also are affected by a manifold of neuromodulators. Second, recent evidence demonstrates that the central nervous system transmits information not just by rate code alone (James et al., 2019). There are also non-neuronal components such as glia cells (Araque et al., 1999) and changes in blood supply (Choi et al., 2015; Flores et al., 2016; Yew et al., 2017) that can impact neuronal function. Third, in contrast to most electronic and computational networks, neurons are almost always active, and their so-called spontaneous activity seems to be a crucial part of the inherent organization of the brain's network activity (Tsodyks et al., 1999; Kenet et al., 2003; He et al., 2010; Mennes et al., 2010; Larson-Prior et al., 2011; Raichle, 2015; Chen et al., 2020).

Due to space limits, we will mostly focus on the neuronal circuitry and the associated network activity *within* a single visual area (V1). In light of this, another caveat the reader should keep in mind is that neuronal connections between areas i.e., connections outside the local circuit, can be faster than connections within the local circuit itself (Angelucci and Bullier, 2003). This fact alone shows that neuronal networks heavily intersect and that cross-area circuits might form functional units similar to those that we deem to be of a cortical area (Liang et al., 2017). In other words, neurons in distant parts of the brain may sometimes form a closer connection or loop than physical neighbors. Hence, network activity intrinsic to V1 only captures part of V1's overall network architecture.

Laminar Architecture of Neocortex

Our earliest understanding of cortical network organization comes from anatomy studies, in which scientists use histological stains to label cells, or associated features (Brodmann, 1909). One of the most commonly used stains is Nissl, which marks cell bodies. If one—expert or non-expert alike—were to look at a section of V1 tissue stained with Nissl, the first feature that would pop out, besides the tiny dots marking cells or the purple color, would be the stripes that run east-to-west (**Fig. 1**). These stripes are called layers, or laminae. The reason for visible stripes is that each layer is made of a distinct combination of neurons.

In fact, the primary visual cortex, or striate cortex, was named for one of its stripes. During the late part of the 17th century, Francesco Gennari, a medical student at the University of Parma, observed that there is a thin white band - or line - that runs through the corresponding section of the occipital lobe of primates (Bakkum, 2015). This *stria of Gennari* was evidence that cortex is not homogenous, but features local specializations (see arrow in **Fig. 1**).

The exact number of layers described for a cortical area depends on the type of histological stain and varies between cortical areas and individual species (DeFelipe et al., 2002). The resulting variability in layer count has prompted neuroanatomists to propose a variety of slightly altered labeling schemes (Billings-Gagliardi et al., 1974; Marín-Padilla, 1998). However, broad consensus follows neuroanatomist Korbinian Brodmann's scheme (Brodmann, 1909), dividing the neocortex into six major laminae. These six layers are often grouped into three major laminar domains. In particular, layer 4 and its various sublayers are commonly referred to as the "granular layers" due to their fine-grained appearance in some histological stains. Accordingly, superficial layers 1–3 are referred to as "supragranular", while deeper layers 5–6 are referred to as "infragranular" layers (note that some cortical areas seem to be void of a granulated layer 4 and thus are called "agranular cortex" (Shipp, 2005)).[1]

Interlaminar Connectivity and the Canonical Microcircuit Model

The three main laminar domains (supragranular, granular, and infragranular layers) are not entirely segregated but are connected in a stereotyped way (Callaway, 1998). Cortical neurons not only project to neurons within the same layer but also innervate neurons in other layers (Casagrande and Marion, 2011). These interlaminar connections are formed by both excitatory and inhibitory neurons. The resulting neuronal microcircuitry is complex in anatomical detail with almost all layers, except layer 1, sharing mutual excitatory and inhibitory connections with each other (**Fig. 2**) (Binzegger et al., 2004). Several interlaminar connections are worth explicitly mentioning due to their relative prominence. For example, L4 projects heavily to L2/3. There is a strong reciprocal projection between L2/3 and L5, as well as a heavy projection from L6 to L4.

Based on these connections and neurophysiological observations that will be discussed below, a more generalized and simplified schematic of signal flow across cortical layers has been described (Singer and Aldenhoff, 1987; Nowak et al., 1995). In this model, primary sensory nuclei of the thalamus (or other cortical structures if not a primary sensory area) project "bottom up", or "feedforward", signals primarily to layer 4 (layer 4C in V1) (Hubel and Wiesel, 1972; Blasdel and Lund 1983; Douglas et al., 1989; Felleman and Van Essen, 1991; Douglas and Martin 2004; Bannister 2005; Lübke and Feldmeyer 2007). Many granular layer neurons in turn project to neurons in the supragranular layers directly above (**Fig. 2**) (Rockland and Pandya, 1979; Gilbert, 1983; Rockland and Virga, 1989; Anderson and Martin, 2009). Certain layer 2/3 efferents then project to infragranular layers. Some layer 5/6 neurons back-project to the supragranular layers, thus forming a reverberating loop between the superficial and deep cortical layers. Other layer 5/6 neurons project to thalamic nuclei and other subcortical structures (Thomson and Bannister, 2003).

This idealized model of laminar connectivity, termed the *canonical cortical microcircuit* (CCM), is not unique to V1 but can be found across many other cortical areas (Maunsell and Van Essen 1983; Bastos et al. 2012; Beul and Hilgetag 2015; Godlove et al. 2014). It thus forms the basis of more macroscopic models of cortical connectivity. Following the logic outlined above,

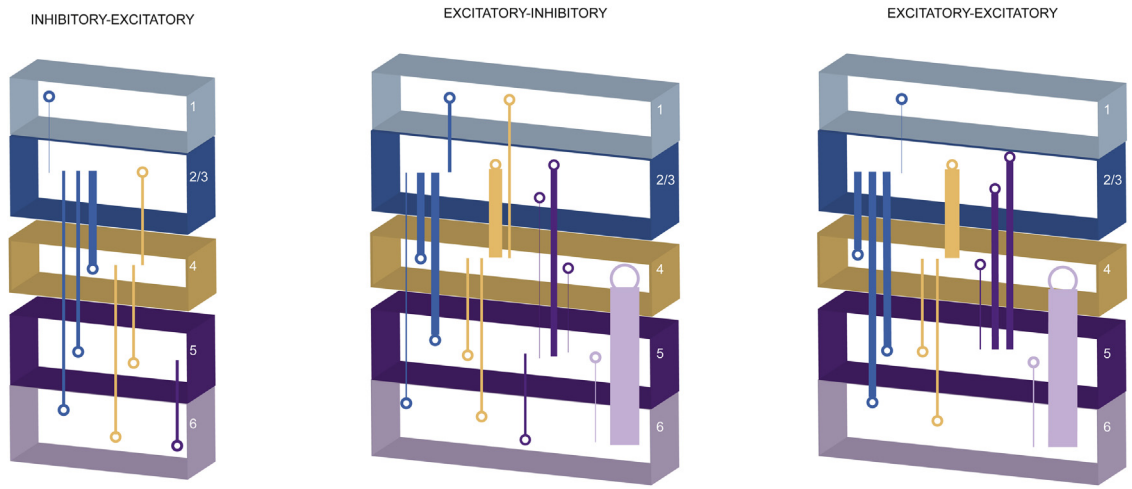

Figure 2 Intrinsic Connectivity of V1: Interlaminar connectivity of primary visual cortex of the cat (to the authors' knowledge, no comparable data is currently available for primates). The three columns represent the interlaminar connectivity of inhibitory neurons projecting onto excitatory neurons (leftmost), excitatory neurons projecting onto inhibitory neurons (center) and excitatory neurons projecting from one layer synapsing onto excitatory neurons in other layers. The topmost layer of cortex is shaded in light blue, layers 2, 3 are represented by a dark blue box. Layer 4 is shown in gold. Layer 5 is depicted in dark purple and layer 6 in light purple. The thickness of each line roughly scales with the relative number of synapses for each type of connection. From Binzegger et al. (2004), modified.

[1]Brodmann extended Gennari's work, and a little over a hundred years after Gennari, while naming distinct areas across the neocortex, redefined striate cortex as area 17 in 1909 (Brodmann, 1909). Brodmann also labeled layers of area 17. Of note, he labeled the lower parts of layer 3 as layer 4A and layer 4B. As a consequence, the "granular"-looking middle layer that corresponds to layer 4 in other areas, is labeled layer 4C in Brodmann's scheme of primate V1. This likely mistake of Brodmann's can add a certain degree of confusion to the labeling scheme of V1 (Balaram and Kaas, 2014).

inter-cortical projections from one area that terminate in layer 4 of another area are defined as ascending or "feedforward". Indeed, neurophysiological studies found that visual activation of V1 generally evokes a fixed sequence of laminar activation, with granular layer 4C dominating the earliest part of the response, followed by activation of the supragranular layers and then the infragranular layers (Mitzdorf, 1985). Projections that innervate another area by sparing layer 4, are characterized as descending or "feedback" (Rockland and Drash, 1996). Accordingly, extraretinal activation of visual cortex involving input to V1 descending from other areas of cortex (e.g., when an animal starts to attend a visual stimulus), first emerges within V1 extragranular layers (Maier, 2013; Self et al., 2013; van Kerkoerle et al., 2014, 2017).

Using the CCM framework, one can derive a rough diagram of a large-scale network between cortical areas based on their laminar interconnections (Felleman and Van Essen, 1991). This observation has given rise to the popular idea that there are stereotypical "columnar" elements that are repeated along the cortical sheet (Hubel and Wiesel, 1974, 1977; Rockel et al., 1980; Douglas et al., 1989; Lund et al., 1993; Mountcastle, 1997; Rockland, 1998) (but see (Nelson, 2002; Horton and Adams, 2005)). This idea is supported by both developmental studies (Rakic, 2003; Glover, 2009), as well as by the fact that V1 neurons share many functional properties in the radial (columnar) dimension (Tootell et al., 1988; Horton and Hocking, 1997; Hubel and Wiesel, 1998; Ringach et al., 2002; Gur et al., 2005; Cox et al., 2019; Dougherty et al., 2019), while varying systematically along the orthogonal, tangential dimension (Ts'o et al., 1990; Grinvald et al., 1991; Das and Gilbert, 1995; Roe and Ts'o 1999; Vnek et al., 1999; Slovin et al., 2002; Kaskan et al., 2007). It is important to keep in mind that the stereotypical template of laminar circuitry is an idealized concept (Silberberg et al., 2002; Herculano-Houzel et al., 2008), and it has yet to be determined how this idea of a modular cortical structure can be reconciled with the often stark regional anatomical differences (Haug 1987; Nelson, 2002; Horton and Adams, 2005; Herculano-Houzel et al., 2008; Rakic, 2008).

Cytoarchitecture of V1

The vast majority (~80%) of V1 neurons release the neurotransmitter glutamate, which is almost always excitatory in action (Fitzpatrick et al., 1987). Other neurons release the neurotransmitter GABA, which is almost always inhibitory in action. These two classes exhibit distinct morphological features. Glutamatergic cells come in two kinds (Salin and Bullier, 1995). The first type of glutamate-releasing cells are stellate cells, with a high density of dendritic spines. This special class of neurons is predominantly found in layer 4C, and has been labeled *spiny stellate cells* on the basis of their unique appearance. The second kind of glutamatergic neurons are the *pyramidal cells*, which make up the majority of cortical neurons that can be found throughout layers 2–6. Whereas spiny stellate cells only make contact with other local neurons, pyramidal cells also project to other cortical and subcortical structures. Excitatory pyramidal cells also feature a high density of dendritic spines. In contrast to these glutamatergic neurons, GABAergic neurons show few to no spines on their dendrites. GABAergic neurons are multipolar and feature dendritic arbors that come in a variety of shapes. One can distinguish different subclasses of GABAergic neurons based on physiology and histological dyes that stain for different kinds of proteins and peptides such as parvalbumin, calretinin or calbindin. With few exceptions, the histological markers of GABAergic cells are in many cases unrelated to their underlying morphology, synaptic organization such as targeting soma or dendrites of other neurons, intrinsic physiological characteristics such as spike waveforms or spike rate. Whether and how these histologically defined types of interneurons serve distinct functions remains the subject of ongoing research (Caputi et al., 2013; Harris and Mrsic-Flogel, 2013; Wood et al., 2017; Adesnik, 2018).

Inputs and Outputs of the V1 Microcircuit

Like in other primary sensory areas of cortex, in V1 the granular middle layer receives the primary input from the thalamus, specifically the dorsal lateral geniculate nucleus of the thalamus (LGN) (Sherman and Guillery, 1996; Sherman, 2001; Sherman and Guillery, 2002; Sillito and Jones, 2002; Sherman, 2005, 2017). As suggested in the previous paragraph, V1 neurons from the granular layer strongly project to the supragranular layers above and to the infragranular layers below. Neurons in these extragranular layers integrate these ascending, feedforward signals with ongoing activity and descending, feedback signals from other areas (Muckli and Petro, 2013). Neurons in superficial layers provide the bulk of V1's output to other visual areas (Sincich and Horton, 2005), whereas neurons in the deep layers are the main source for V1's signals to subcortical targets. Specifically, many layer 5 neurons project to the superior colliculus and pulvinar, and many layer 6 neurons target the LGN (Gutierrez and Cusick, 1997; Lock et al., 2003; Ichida et al., 2014).

Neuronal circuits receive inputs and transform them in some way. Given the laminar circuit described for V1, what exactly sustains spiking activity in visual cortex? Studies in anesthetized macaque monkeys showed that pharmacological inactivation of the LGN virtually obliterates visual responses in V1 (Schmid et al., 2010; Schmid and Maier, 2015). In other words, V1 neurons' spiking depends almost entirely on LGN input.

The parvocellular (P), magnocellular (M) and koniocellular (K) neurons of the LGN terminate in different layers of V1 (Yoshioka et al., 1994) (**Fig. 3**). Axons from neurons in the M and P layers of the LGN preferentially target sublayers of layer 4C, while K neurons predominantly project to layers 1, 3 and 4A (Hubel and Wiesel, 1972; Callaway, 2005; Casagrande, 1994). Interestingly, layer 3 and 4 (especially layer 4A) in apes and humans differs significantly from that of other primates (Kaas and Collins, 2001; Preuss and Coleman, 2002; Garcia-Marin et al., 2013; Balaram et al., 2014). Thus, even within primates there are significant differences in the neuronal wiring of V1.

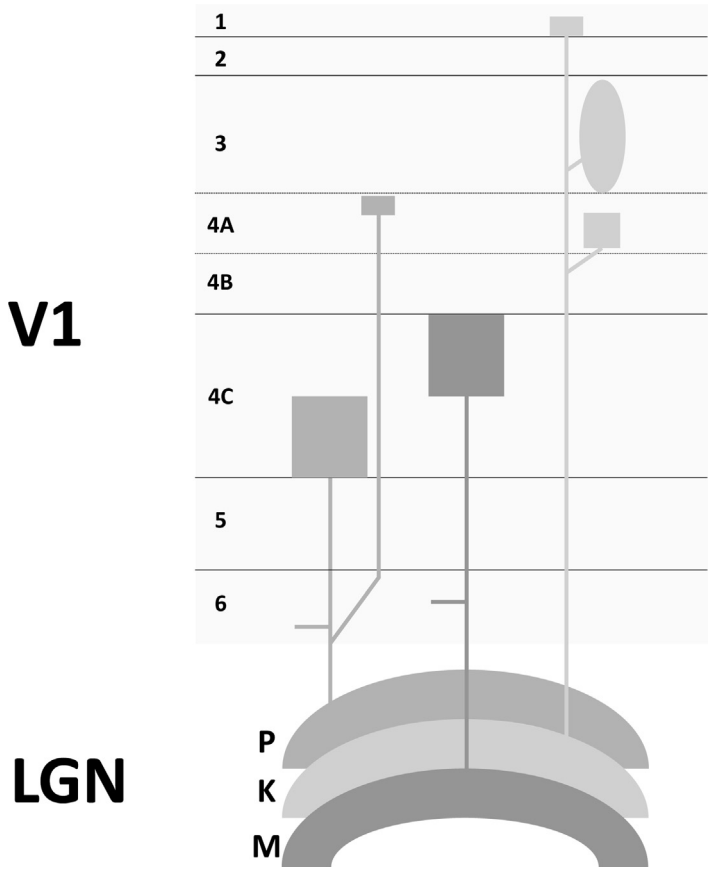

Figure 3 Simplified schematic of the main primary visual pathway afferents to V1 layers. Note that backprojections (feedback) from V is not shown. The lowermost part of the cartoon represents the three main types of layers (parvocellular, P; koniocellular, K and magnocellular, M) of the lateral geniculate nucleus of the thalamus (LGN). Note that macaque LGN actually contains several alternations of these types of layers (specifically, 2 M layers and 4 P layers that are interspaced by K layers). The vertical lines show the main axonal projections that originate in each of these types of LGN layers, using the same shades of gray, respectively. The uppermost part of the cartoon shows the layers of V1 using Brodmann's scheme (see **Fig. 1**). Boxes indicate the main projection targets and horizontal lines axonal branches, respectively. Note that both P and M layers mainly project to layer 4C of V1, albeit to spatially distinct sublayers. Neurons from these LGN layers also provide inputs to layer 6 of V1 via axon collaterals. The K neurons of LGN, which separate individual M and P layers, predominantly project to layers above 4C, and particularly target regions of V1 that are cytochrome oxidase (CO)-rich. These regions have been termed "blobs" due to their characteristic appearance in CO stains, and are indicated here by an oval shape. After Casagrande and Marion (2011), modified.

In addition to the LGN, area V1 receives input from many other parts of the brain. As discussed above, these inputs can exert powerful modulatory influences over V1 neurons. For example, there are nuclei in the brainstem and the basal forebrain that send serotonergic, noradrenergic and cholinergic projections to V1 (Adams et al., 2000; Zinke et al., 2006; Disney et al., 2007, 2012; Soma et al., 2012; Pinto et al., 2013; Shimegi et al., 2016; Sugihara et al., 2016; Herrero et al., 2017; Seillier et al., 2017; Krueger and Disney, 2019). Other subcortical inputs to V1 stem from the intralaminar nucleus of the thalamus, the amygdala and the pulvinar (Kennedy and Bullier, 1985; Lysakowski et al., 1988; Amaral et al., 2003). The claustrum also projects specifically to layer 4C in a retinotopic fashion (Amaral et al., 2003). Moreover, V1 receives massive feedback from all areas it projects to, including visual areas V2, V3, V3A, V4 and MT. V1 also receives input from a few higher-order visual areas in the temporal and parietal lobes that do not receive V1 input themselves (Felleman and Van Essen, 1991). All of these cortico-cortical connections are retinotopic, and project to all layers of V1, except for layer 4C (Perkel et al., 1986). More recent work suggests that V1 also receives input from non-visual cortical areas, such as in the frontal lobe (Markov et al., 2014).

Why does the brain afford all of these numerous inputs to V1? One important function of these non-geniculate inputs to V1 might be to up- and down-regulate the output of V1 neurons to higher visual areas (Juan and Walsh, 2003). Some of the empirical evidence for that idea is derived from fMRI neuroimaging studies in which volunteers were asked to imagine visual stimuli at certain positions of the visual field. Even though there were no actual stimuli present, V1 was active at matching retinotopic positions of the visual field (Chen et al., 1998; Klein et al., 2000; Albers et al., 2013) (but see (D'Esposito et al., 1997; Mellet et al., 1998; Knauff et al., 2000)). In other words, top-down afferences from other parts of the brain seem sufficient to elicit V1 activity in the absence of visual stimulation. Similarly, fMRI studies demonstrated V1 activation in congenitally blind patients when they were reading Braille (Burton et al., 2002, 2004; Likova et al., 2016). In sum, while visually elicited V1 responses require activation of the LGN, non-LGN inputs thus seem to have the capacity for a strong impact on V1 activity and might also impact neuronal plasticity during development.

As noted above, neurons in all V1 layers, except layer 4C, send axons to other parts of the brain such as area V2 (Sincich et al., 2007) and other cortical and subcortical targets. Layer 6 of V1 contains a large fraction of cells that provide direct feedback connections to the LGN as well as axon collaterals to neurons in the thalamic reticular nucleus (TRN), which in turn inhibits LGN neurons (Wilson et al., 1995; Sillito and Jones, 2002; Bragg et al., 2017). These feedback connections are precise both in maintaining retinotopy, as well as in preserving the distinction between the M and P pathways (i.e., M and P cells in the LGN receive feedback from different groups of layer 6 neurons) (Ichida and Casagrande, 2002; Briggs and Usrey, 2007). While the LGN sends sparse input to some extrastriate visual cortical areas, such as MT (Sincich et al., 2004), these connections are remarkably sparse, and the respective feedback is likely accordingly minimal. V1's layer 6 thus serves a unique role in regulating the thalamic relay of the LGN and since this layer also receives direct LGN input via branching axon collaterals, feedback to the LGN can be remarkably rapid (Briggs and Usrey, 2007). Many layer 5 neurons send projections to the superficial layers of the superior colliculus and other midbrain areas such as the pretectum and nuclei in the pons that are involved in the motor commands leading to eye movements (Benevento et al., 1977; Lock et al., 2003). Perhaps as a consequence of this circuitry, electric stimulation of deep layer V1 neurons can evoke saccadic eye movements under certain conditions (Tehovnik et al., 2002). V1 layer 5 neurons also project to the pulvinar, where they provide major driving input (Moore et al., 2019).

Pulvinar neurons form a loop with V1, but also project reciprocally to many other visual areas, which suggests that the thalamic pulvinar could act as a "hub" of visual signals that is involved in perceptual and attentional selection (Saalmann and Kastner, 2009; Saalmann et al., 2012; Arcaro et al., 2015; Schmid and Maier, 2015; Saalmann and Kastner, 2015).

The output of the supragranular layers 1–3 is distinct from the that of the infragranular neurons mentioned above. Neurons in the supragranular layers 1–3 form connections with extrastriate visual areas (V2, V3, V3A, V4 and MT) as well as areas in the inferotemporal and parietal lobes (Perkel et al., 1986; Shipp and Zeki, 1989; Rockland and Virga, 1990; Budd, 1998). It is debated whether these outputs can be separated into a discrete set of physiologically and functionally distinct pathways, such as the M and P pathways of the LGN (Yabuta and Callaway, 1998; Sincich and Horton, 2002, 2005; Federer et al., 2009). Some researchers have suggested that the M, P and K pathways remain functionally separated throughout and beyond V1. More specifically, it has been suggested that the detailed, high spatial frequency information provided by P neurons in the LGN may be of greater relevance to and thus selectively feeding into the ventral visual areas concerned with visual object processing (i.e., the *what stream*). In contrast, the greater motion sensitivity of LGN M cells has been hypothesized to selectively feed the more dorsal visual areas concerned with processing spatial information and action planning (i.e., the *where/how stream*) (Vidyasagar, 2001; Laycock et al., 2008; Brown, 2009). However, there are several anatomical studies suggesting that these two pathways cannot easily be disentangled on the cortical level (Nassi and Callaway, 2006; Ninomiya et al., 2011; Yarch et al., 2019).

All of these observations combined suggest that considerable integration takes place in V1 before output is sent to other areas. The majority of V1 outputs target neighboring area visual area (V2). Cytochrome-oxidase (CO) stains show blotchy areas of high concentration in V1 layers 3A and 3B that have been termed *cytochrome oxidase blobs* due to their polka-dot like appearance. The regions between these blobs are called *interblobs*. The projections from V1 to V2 seem to be distinct with respect to these CO stains. Area V2 shows a different, more zebra-like pattern using the same staining technique, with thick and thin *CO bands* interleaved by pale bands. Neurons in V1 CO blobs target neurons in V2 thin bands, while neurons in the interblobs regions send projections to neurons within the thick and pale bands of V2 (Burkhalter and Bernardo, 1989; DeYoe et al., 1994; Xiao and Felleman, 2004).

Laminar Differentiation of Spontaneous Activity

To what extent does spontaneous (ongoing) neural activity vary as a function of cortical layer and what does this tell us about the network organization of V1? One way to assess this is by looking at spontaneous activity. In 1995, Snodderly and Gur examined this question by measuring the ongoing spiking rate of neurons in different layers of V1 in the awake macaque (Snodderly and Gur, 1995). They found a striking difference in the spontaneous neural spiking rates measured from different layers of animals sitting in complete darkness. Neurons in layers that receive direct input from the principal layers of the lateral geniculate nucleus (cortical layers 4C, 6, and 4A) showed high spontaneous firing. By contrast, neurons in other layers (cortical layers 2/3, 4B and 5) were nearly silent. Subsequent neurophysiological investigations revealed a similar laminar distribution of mass action (i.e., slow varying extracellular voltages, likely related to synaptic activation) (Maier et al., 2010). The absence of spiking in layers 2/3 and 4B is curious since most V1 corticocortical projections originate in these layers, with layers 2/3 giving rise to the majority of ascending connections and layer 4B giving rise to the majority of interhemispheric connections (Kennedy et al., 1986). Spiking activity mediated along corticocortical fibers is the principal means of large-scale corticocortical communication and would therefore seem a likely candidate to support correlated network activity in the cerebral cortex. Taken together, these results suggest that individual V1 layers contribute differently to measures of resting state activity. A finding demonstrating layer-specific fMRI coupling between anatomically connected cortical areas in humans supports this possibility (Polimeni et al., 2011).

As the reader can discern from the above, studying the cortical (laminar) microcircuit has become increasingly popular and important in recent years. We expect this trend to continue thanks due to rapid advances in electrode technology that allow for sampling hundreds to thousands of neurons across layers simultaneously (Jun et al., 2017; Steinmetz et al., 2018; MuskNeuralink, 2019).

Summary

Our understanding of the biological processes that underlie brain function is limited by current technology. While powerful, the main techniques that have dominated systems neuroscience during the past several decades have led us to study the brain mainly at the microscopic level—such as the study of the activity of single neurons—or the macroscopic level—such as the study of large scale activity across the cortex. Recently, researchers have adopted more refined neuroimaging techniques and begun to use technology that allows for the recordings of hundreds or even thousands of neurons at a time. With this changing tide, we are witnessing an emphasis of the mesoscopic, network-level of neuronal function. Now, we are now able to track the flow of activity within large networks of anatomically connected neurons. Moreover, thanks to modern tools, we can now discern the functionally, morphologically and biochemically distinct properties of cells that actively take part in that process. And we now benefit from new statistical (machine learning) tools that link cellular processes to the computations and information processing that shape perception and behavior. Our current knowledge of the primate visual cortex will serve as a solid foundation with which to use this modern technology.

References

Fitzpatrick, D., Lund, J.S., Schmechel, D.E., Towles, A.C., 1987. Distribution of GABAergic neurons and axon terminals in the macaque striate cortex. J. Comp. Neurol. 264, 73–91.
Adams, M.M., Hof, P.R., Gattass, R., Webster, M.J., Ungerleider, L.G., 2000. Visual cortical projections and chemoarchitecture of macaque monkey pulvinar. J. Comp. Neurol. 419, 377–393.
Adesnik, H., 2018. Cell type-specific optogenetic dissection of brain rhythms. Trends Neurosci. 41, 122–124.
Albers, A.M., Kok, P., Toni, I., Dijkerman, H.C., de Lange, F.P., 2013. Shared representations for working memory and mental imagery in early visual cortex. Curr. Biol. 23, 1427–1431.
Amaral, D.G., Behniea, H., Kelly, J.L., 2003. Topographic organization of projections from the amygdala to the visual cortex in the macaque monkey. Neuroscience 118, 1099–1120.
Anderson, J.C., Martin, K.A.C., 2009. The synaptic connections between cortical areas V1 and V2 in macaque monkey. J. Neurosci. 29, 11283–11293.
Angelucci, A., Bullier, J., 2003. Reaching beyond the classical receptive field of V1 neurons: horizontal or feedback axons? J. Physiol. Paris 97, 141–154.
Araque, A., Parpura, V., Sanzgiri, R.P., Haydon, P.G., 1999. Tripartite synapses: glia, the unacknowledged partner. Trends Neurosci. 22, 208–215.
Arcaro, M.J., Pinsk, M.A., Kastner, S., 2015. The anatomical and functional organization of the human visual pulvinar. J. Neurosci. 35, 9848–9871.
Bakkum, B.W., 2015. The line of Gennari–sometimes history gets it right. J. Hist. Neurosci. 24 (1), 95–101.
Balaram, P., Kaas, J.H., 2014. Towards a unified scheme of cortical lamination for primary visual cortex across primates: insights from NeuN and VGLUT2 immunoreactivity. Front. Neuroanat. 8, 81.
Balaram, P., Young, N.A., Kaas, J.H., 2014. Histological features of layers and sublayers in cortical visual areas V1 and V2 of chimpanzees, macaque monkeys, and humans. Eye Brain 2014, 5–18.
Bannister, A.P., 2005. Inter- and intra-laminar connections of pyramidal cells in the neocortex. Neurosci Res 2, 95–103.
Bastos, A.M., Usrey, W.M., Adams, R.A., Mangun, G.R., Fries, P., Friston, K.J., 2012. Canonical microcircuits for predictive coding. Neuron 76, 695–711.
Benevento, L.A., Rezak, M., Santos-Anderson, 1977. An autoradiographic study of the projections of the pretectum in the rhesus monkey (*Macaca mulatta*): evidence for sensorimotor links to the thalamus and oculomotor nuclei. Brain Res. 127, 197–218.
Beul, S.F., Hilgetag, C.C., 2015. Towards a "canonical" agranular cortical microcircuit. Front Neuroanat 8, 165.
Billings-Gagliardi, S., Chan-Palay, V., Palay, S.L., 1974. A review of lamination in area 17 of the visual cortex *Macaca mulatta*, 3, 619–629.
Binzegger, T., Douglas, R.J., Martin, K.A.C., 2004. A quantitative map of the circuit of cat primary visual cortex. J. Neurosci. 24, 8441–8453.
Blasdel, G.G., Lund, J.S., 1983. Termination of afferent axons in macaque striate cortex. J. Neurosci 7, 1389–1413.
Bragg, E.M., Fairless, E.A., Liu, S., Briggs, F., 2017. Morphology of visual sector thalamic reticular neurons in the macaque monkey suggests retinotopically specialized, parallel stream-mixed input to the lateral geniculate nucleus. J. Comp. Neurol. 525, 1273–1290.
Briggs, F., Usrey, W.M., 2007. A fast, reciprocal pathway between the lateral geniculate nucleus and visual cortex in the macaque monkey, 27, 5431–5436.
Brodmann, K., 1909. Vergleichende Lokalisationslehre der Grosshirnrinde.
Brown, J.M., 2009. Visual streams and shifting attention. Prog. Brain Res. 176, 47–63.
Budd, J.M., 1998. Extrastriate feedback to primary visual cortex in primates: a quantitative analysis of connectivity. Proc. Biol. Sci. 265, 1037–1044.
Burkhalter, A., Bernardo, K.L., 1989. Organization of corticocortical connections in human visual cortex. Proc. Natl. Acad. Sci. U. S. A. 86, 1071–1075.
Burton, H., Snyder, A.Z., Conturo, T.E., Akbudak, E., Ollinger, J.M., Raichle, M.E., 2002. Adaptive changes in early and late blind: a fMRI study of Braille reading. J. Neurophysiol. 87, 589–607.
Burton, H., Sinclair, R.J., McLaren, D.G., 2004. Cortical activity to vibrotactile stimulation: an fMRI study in blind and sighted individuals. Hum. Brain Mapp. 23, 210–228.
Callaway, E.M., 1998. Local circuits in primary visual cortex of the macaque monkey. Annu. Rev. Neurosci. 21, 47–74.
Callaway, E.M., 2005. Structure and function of parallel pathways in the primate early visual system. J. Physiol. 566, 13–19.
Caputi, A., Melzer, S., Michael, M., Monyer, H., 2013. The long and short of GABAergic neurons. Curr. Opin. Neurobiol. 23, 179–186.
Casagrande, V.A., 1994. A third parallel visual pathway to primate area V1. Trends Neurosci. 17, 305–310.
Casagrande, V., Marion, R.T., 2011. Processing in the Primary Visual Cortex.
Chen, W., Kato, T., Zhu, X.H., Ogawa, S., Tank, D.W., Ugurbil, K., 1998. Human primary visual cortex and lateral geniculate nucleus activation during visual imagery. Neuroreport 9, 3669–3674.
Chen, K., Azeez, A., Chen, D.Y., Biswal, B.B., 2020. Resting-state functional connectivity: signal origins and analytic methods. Neuroimaging Clin. N. Am 30, 15–23.
Choi, J.Y., Cui, Y., Kim, B.G., 2015. Interaction between hypertension and cerebral hypoperfusion in the development of cognitive dysfunction and white matter pathology in rats. Neuroscience 303, 115–125.
Cox, M.A., Dougherty, K., Westerberg, J.A., Schall, M.S., Maier, A., 2019. Temporal dynamics of binocular integration in primary visual cortex. J. Vis. 19, 13.
D'Esposito, M., Detre, J.A., Aguirre, G.K., Stallcup, M., Alsop, D.C., Tippet, L.J., Farah, M.J., 1997. A functional MRI study of mental image generation. Neuropsychologia 35, 725–730.
Das, A., Gilbert, C.D., 1995. Long-range horizontal connections and their role in cortical reorganization revealed by optical recording of cat primary visual cortex, 375, 780–784.
DeFelipe, J., Alonso-Nanclares, L., Arellano, J.I., 2002. Microstructure of the neocortex: comparative aspects. J. Neurocytol. 31, 299–316.
DeYoe, E.A., Felleman, D.J., Van Essen, D.C., McClendon, E., 1994. Multiple processing streams in occipitotemporal visual cortex, 371, 151–154.
Disney, A.A., Aoki, C., Hawken, M.J., 2007. Gain modulation by nicotine in macaque v1. Neuron 56, 701–713.

Disney, A.A., Aoki, C., Hawken, M.J., 2012. Cholinergic suppression of visual responses in primate V1 is mediated by GABAergic inhibition. J. Neurophysiol. 108, 1907–1923.
Dougherty, K., Cox, M.A., Westerberg, J.A., Maier, A., 2019. Binocular modulation of monocular V1 neurons. Curr. Biol. 29, 381–391.e4.
Douglas, R.J., Martin, K.A.C., Whitteridge, D., 1989. A canonical microcircuit for neocortex. Neural Comput. 1, 480–488.
Douglas, R.J., Martin, K.A., 2004. Neuronal circuits of the neocortex. Annu. Rev. Neurosci. 27, 419–451.
Federer, F., Ichida, J.M., Jeffs, J., Schiessl, I., McLoughlin, N., Angelucci, A., 2009. Four projection streams from primate V1 to the cytochrome oxidase stripes of V2. J. Neurosci. 29, 15455–15471.
Felleman, D.J., Van Essen, D.C., 1991. Distributed hierarchical processing in the primate cerebral cortex. Cereb. Cortex 1, 1–47.
Flores, G., Flores-Gómez, G.D., de Jesús Gomez-Villalobos, M., 2016. Neuronal changes after chronic high blood pressure in animal models and its implication for vascular dementia. Synapse 70, 198–205.
Garcia-Marin, V., Ahmed, T.H., Afzal, Y.C., Hawken, M.J., 2013. Distribution of vesicular glutamate transporter 2 (VGluT2) in the primary visual cortex of the macaque and human. J. Comp. Neurol. 521, 130–151.
Gilbert, C.D., 1983. Microcircuitry of the visual cortex. Annu. Rev. Neurosci. 6, 217–247.
Glover, J.C., 2009. "The developmental and functional logic of neuronal circuits": commentary on the Kavli Prize in Neuroscience. Neuroscience 163 (4), 977–984.
Godlove, D.C., Maier, A., Woodman, G.F., Schall, J.D., 2014. Microcircuitry of agranular frontal cortex: testing the generality of the canonical cortical microcircuit. J. Neurosci. 34, 5355–5369.
Grinvald, A., Frostig, R.D., Siegel, R.M., Bartfeld, E., 1991. High-resolution optical imaging of functional brain architecture in the awake monkey. Proc. Natl. Acad. Sci. U. S. A. 88, 11559–11563.
Gur, M., Kagan, I., Snodderly, D.M., 2005. Orientation and direction selectivity of neurons in V1 of alert monkeys: functional relationships and laminar distributions. Cerebr. Cortex 15, 1207–1221.
Gutierrez, C., Cusick, C.G., 1997. Area V1 in macaque monkeys projects to multiple histochemically defined subdivisions of the inferior pulvinar complex. Brain Res. 765, 349–356.
Harris, K.D., Mrsic-Flogel, T.D., 2013. Cortical connectivity and sensory coding. Nature 503, 51–58.
Haug, H., 1987. Brain sizes, surfaces, and neuronal sizes of the cortex cerebri: a stereological investigation of man and his variability and a comparison with some mammals (primates, whales, marsupials, insectivores, and one elephant). Am. J. Anat. 180, 126–142.
He, B.J., Zempel, J.M., Snyder, A.Z., Raichle, M.E., 2010. The temporal structures and functional significance of scale-free brain activity. Neuron 66, 353–369.
Herculano-Houzel, S., Collins, C.E., Wong, P., Kaas, J.H., Lent, R., 2008. The basic nonuniformity of the cerebral cortex. Proc. Natl. Acad. Sci. U. S. A. 105, 12593–12598.
Herrero, J.L., Gieselmann, M.A., Thiele, A., 2017. Muscarinic and nicotinic contribution to contrast sensitivity of macaque area V1 neurons. Front. Neural Circ. 11, 106.
Horton, J.C., Adams, D.L., 2005. The cortical column: a structure without a function. Phil. Trans. Roy. Soc. Lond. B 360, 837–862.
Horton, J.C., Hocking, D.R., 1997. Timing of the critical period for plasticity of ocular dominance columns in macaque striate cortex. J. Neurosci. 17, 3684–3709.
Hubel, D.H., Wiesel, T.N., 1968. Receptive fields and functional architecture of monkey striate cortex. J. Physiol. 195, 215–243.
Hubel, D.H., Wiesel, T.N., 1972. Laminar and columnar distribution of geniculo-cortical fibers in the macaque monkey, 146, 421–450.
Hubel, D.H., Wiesel, T.N., 1974. Uniformity of monkey striate cortex: a parallel relationship between field size, scatter, and magnification factor. J. Comp. Neurol. 158, 295–305.
Hubel, D.H., Wiesel, T.N., 1977. Ferrier lecture. Functional architecture of macaque monkey visual cortex, 198, 1–59.
Hubel, D.H., Wiesel, T.N., 1998. Early exploration of the visual cortex, 20, 401–412.
Ichida, J.M., Casagrande, V.A., 2002. Organization of the feedback pathway from striate cortex (V1) to the lateral geniculate nucleus (LGN) in the owl monkey (*Aotus trivirgatus*). J. Comp. Neurol. 454, 272–283.
Ichida, J.M., Mavity-Hudson, J.A., Casagrande, V.A., 2014. Distinct patterns of corticogeniculate feedback to different layers of the lateral geniculate nucleus. Eye Brain 2014, 57–73.
James, B., Darnet, L., Moya-Díaz, J., Seibel, S.-H., Lagnado, L., 2019. An amplitude code transmits information at a visual synapse. Nat. Neurosci. 22, 1140–1147.
Juan, C.-H., Walsh, V., 2003. Feedback to V1: a reverse hierarchy in vision, 150, 259–263.
Jun, J.J., Steinmetz, N.A., Siegle, J.H., Denman, D.J., Bauza, M., Barbarits, B., Lee, A.K., Anastassiou, C.A., Andrei, A., Aydın, Ç., Barbic, M., Blanche, T.J., Bonin, V., Couto, J., Dutta, B., Gratiy, S.L., Gutnisky, D.A., Häusser, M., Karsh, B., Ledochowitsch, P., Lopez, C.M., Mitelut, C., Musa, S., Okun, M., Pachitariu, M., Putzeys, J., Rich, P.D., Rossant, C., Sun, W.-L., Svoboda, K., Carandini, M., Harris, K.D., Koch, C., O'Keefe, J., Harris, T.D., 2017. Fully integrated silicon probes for high-density recording of neural activity. Nature 551, 232–236.
Kaas, J.H., 1992. Do humans see what monkeys see? Trends Neurosci. 15, 1–3.
Kaas, J.H., Collins, C.E., 2001. The organization of sensory cortex. Curr. Opin. Neurobiol. 11, 498–504.
Kaskan, P.M., Lu, H.D., Dillenburger, B.C., Roe, A.W., Kaas, J.H., 2007. Intrinsic-signal optical imaging reveals cryptic ocular dominance columns in primary visual cortex of New World owl monkeys. Front. Neurosci. 1, 67–75.
Kenet, T., Bibitchkov, D., Tsodyks, M., Grinvald, A., Arieli, A., 2003. Spontaneously emerging cortical representations of visual attributes. Nature 425, 954–956.
Kennedy, H., Bullier, J., 1985. A double-labeling investigation of the afferent connectivity to cortical areas V1 and V2 of the macaque monkey. J. Neurosci. 5, 2815–2830.
Kennedy, H., Dehay, C., Bullier, J., 1986. Organization of the callosal connections of visual areas V1 and V2 in the macaque monkey. J. Comp. Neurol. 247, 398–415.
Klein, I., Paradis, A.L., Poline, J.B., Kosslyn, S.M., Le Bihan, D., 2000. Transient activity in the human calcarine cortex during visual-mental imagery: an event-related fMRI study. J. Cognit. Neurosci. 12 (Suppl. 2), 15–23.
Knauff, M., Kassubek, J., Mulack, T., Greenlee, M.W., 2000. Cortical activation evoked by visual mental imagery as measured by fMRI. Neuroreport 11, 3957–3962.
Krueger, J., Disney, A.A., 2019. Structure and function of dual-source cholinergic modulation in early vision. J. Comp. Neurol. 527, 738–750.
Larson-Prior, L.J., Power, J.D., Vincent, J.L., Nolan, T.S., Coalson, R.S., Zempel, J., Snyder, A.Z., Schlaggar, B.L., Raichle, M.E., Petersen, S.E., 2011. Modulation of the brain's functional network architecture in the transition from wake to sleep. Prog. Brain Res. 193, 277–294.
Laycock, R., Crewther, D.P., Crewther, S.G., 2008. The advantage in being magnocellular: a few more remarks on attention and the magnocellular system. Neurosci. Biobehav. Rev. 32, 1409–1415.
Lennie, P., Movshon, J.A., 2005. Coding of color and form in the geniculostriate visual pathway (invited review). J. Opt. Soc. Am. A Opt. Image Sci. Vis. 22, 2013–2033.
Liang, H., Gong, X., Chen, M., Yan, Y., Li, W., Gilbert, C.D., 2017. Interactions between feedback and lateral connections in the primary visual cortex. Proc. Natl. Acad. Sci. U. S. A. 114, 8637–8642.
Likova, L.T., Tyler, C.W., Cacciamani, L., Mineff, K., Nicholas, S., 2016. The cortical network for Braille writing in the blind. IS&T Int. Symp. Electron. Imaging 2016, 1–6.
Lock, T.M., Baizer, J.S., Bender, D.B., 2003. Distribution of corticotectal cells in macaque. Exp. Brain Res. 151, 455–470.
Lübke, J., Feldmeyer, D., 2007. Excitatory signal flow and connectivity in a cortical column: focus on barrel cortex. Brain Struct. Funct. 1, 3–17.
Lund, J.S., Yoshioka, T., Levitt, J.B., 1993. Comparison of intrinsic connectivity in different areas of macaque monkey cerebral cortex. Cereb. Cortex 3, 148–162.
Lysakowski, A., Standage, G.P., Benevento, L.A., 1988. An investigation of collateral projections of the dorsal lateral geniculate nucleus and other subcortical structures to cortical areas V1 and V4 in the macaque monkey: a double label retrograde tracer study. Exp. Brain Res. 69, 651–661.
Maier, A., 2013. Neuroscience: the cortical layering of visual processing. Curr. Biol. 23, R959–R961.
Maier, A., Adams, G.K., Aura, C., Leopold, D.A., 2010. Distinct superficial and deep laminar domains of activity in the visual cortex during rest and stimulation. Front. Syst. Neurosci. 4.
Marín-Padilla, M., 1998. Cajal–Retzius cells and the development of the neocortex. Trends Neurosci. 21, 64–71.
Maunsell, J.H., van Essen, D.C., 1983. The connections of the middle temporal visual area (MT) and their relationship to a cortical hierarchy in the macaque monkey. J. Neurosci. 12, 2563–2586.

Markov, N.T., Ercsey-Ravasz, M.M., Ribeiro Gomes, A.R., Lamy, C., Magrou, L., Vezoli, J., Misery, P., Falchier, A., Quilodran, R., Gariel, M.A., Sallet, J., Gamanut, R., Huissoud, C., Clavagnier, S., Giroud, P., Sappey-Marinier, D., Barone, P., Dehay, C., Toroczkai, Z., Knoblauch, K., Van Essen, D.C., Kennedy, H., 2014. A weighted and directed interareal connectivity matrix for macaque cerebral cortex. Cereb. Cortex. 24, 17–36.
Mellet, E., Petit, L., Mazoyer, B., Denis, M., Tzourio, N., 1998. Reopening the mental imagery debate: lessons from functional anatomy. Neuroimage 8, 129–139.
Mennes, M., Kelly, C., Zuo, X.-N., Di Martino, A., Biswal, B.B., Castellanos, F.X., Milham, M.P., 2010. Inter-individual differences in resting-state functional connectivity predict task-induced BOLD activity. Neuroimage 50, 1690–1701.
Mikula, S., Trotts, I., Stone, J.M., Jones, E.G., 2007. Internet-enabled high-resolution brain mapping and virtual microscopy. Neuroimage 35, 9–15.
Mitzdorf, U., 1985. Current source-density method and application in cat cerebral cortex: investigation of evoked potentials and EEG phenomena. Physiol. Rev. 65, 37–100.
Moore, B., Li, K., Kaas, J.H., Liao, C.-C., Boal, A.M., Mavity-Hudson, J., Casagrande, V., 2019. Cortical projections to the two retinotopic maps of primate pulvinar are distinct. J. Comp. Neurol. 527, 577–588.
Mountcastle, V.B., 1997. The columnar organization of the neocortex, 120, 701–722.
Muckli, L., Petro, L.S., 2013. Network interactions: non-geniculate input to V1. Curr. Opin. Neurobiol. 23, 195–201.
Musk, E., Neuralink, 2019. An integrated brain-machine interface platform with thousands of channels. J. Med. Internet Res. 21, e16194.
Nassi, J.J., Callaway, E.M., 2006. Multiple circuits relaying primate parallel visual pathways to the middle temporal area. J. Neurosci. 26, 12789–12798.
Nelson, S.B., 2002. Cortical microcircuits. Neuron 36, 19–27.
Ninomiya, T., Sawamura, H., Inoue, K.-I., Takada, M., 2011. Differential architecture of multisynaptic geniculo-cortical pathways to V4 and MT. Cerebr. Cortex 21, 2797–2808.
Nowak, L.G., Munk, M.H., Girard, P., Bullier, J., 1995. Visual latencies in areas V1 and V2 of the macaque monkey. Vis. Neurosci. 12, 371–384.
Perkel, D.J., Bullier, J., Kennedy, H., 1986. Topography of the afferent connectivity of area 17 in the macaque monkey: a double-labelling study. J. Comp. Neurol. 253, 374–402.
Piccolino, M., 1998. Animal electricity and the birth of electrophysiology: the legacy of Luigi Galvani. Brain Res. Bull. 46 (5), 381–407.
Pinto, L., Goard, M.J., Estandian, D., Xu, M., Kwan, A.C., Lee, S.-H., Harrison, T.C., Feng, G., Dan, Y., 2013. Fast modulation of visual perception by basal forebrain cholinergic neurons. Nat. Neurosci. 16, 1857–1863.
Polimeni, J.R., Fujimoto, K., Keil, B., Greve, D.N., Fisch, B., Wald, L.L., 2011. Resting-state correlation between depths within columns of voxels radial to the cortical surface. Proc. Int. Soc. Magn. Reson. Med. 19, 636.
Preuss, T.M., Coleman, G.Q., 2002. Human-specific organization of primary visual cortex: alternating compartments of dense Cat-301 and calbindin immunoreactivity in layer 4A. Cerebr. Cortex 12, 671–691.
Quin, C.E., 1994. The soul and the pneuma in the function of the nervous system after Galen. J. R. Soc. Med. 87, 393–395.
Raichle, M.E., 2015. The brain's default mode network. Annu. Rev. Neurosci. 38, 433–447.
Rakic, P., 2003. Developmental and evolutionary adaptations of cortical radial glia. Cerebr. Cortex 13, 541–549.
Rakic, P., 2008. Confusing cortical columns. Proc. Natl. Acad. Sci. U. S. A. 105, 12099–12100.
Ringach, D.L., Shapley, R.M., Hawken, M.J., 2002. Orientation selectivity in macaque V1: diversity and laminar dependence. J. Neurosci. 22, 5639–5651.
Rocca, J., 1997. Galen and the ventricular system. J. Hist. Neurosci. 6 (3), 227–239.
Rockel, A.J., Hiorns, R.W., Powell, T.P.S., 1980. The basic uniformity in structure of the neocortex. Brain 103, 221–244.
Rockland, K.S., 1998. Complex microstructures of sensory cortical connections. Curr. Opin. Neurobiol. 8, 545–551.
Rockland, K.S., Drash, G.W., 1996. Collateralized divergent feedback connections that target multiple cortical areas. J. Comp. Neurol. 373, 529–548.
Rockland, K.S., Pandya, D.N., 1979. Laminar origins and terminations of cortical connections of the occipital lobe in the rhesus monkey. Brain Res. 179, 3–20.
Rockland, K.S., Virga, A., 1989. Terminal arbors of individual "feedback" axons projecting from area V2 to V1 in the macaque monkey: a study using immunohistochemistry of anterogradely transported *Phaseolus vulgaris*-leucoagglutinin. J. Comp. Neurol. 285, 54–72.
Rockland, K.S., Virga, A., 1990. Organization of individual cortical axons projecting from area V1 (area 17) to V2 (area 18) in the macaque monkey. Vis. Neurosci. 4, 11–28.
Roe, A.W., Ts'o, D.Y., 1999. Specificity of color connectivity between primate V1 and V2. J. Neurophysiol. 82, 2719–2730.
Saalmann, Y.B., Kastner, S., 2009. Gain control in the visual thalamus during perception and cognition. Curr. Opin. Neurobiol. 19, 408–414.
Saalmann, Y.B., Kastner, S., 2015. The cognitive thalamus. Front. Syst. Neurosci. 9, 39.
Saalmann, Y.B., Pinsk, M.A., Wang, L., Li, X., Kastner, S., 2012. The pulvinar regulates information transmission between cortical areas based on attention demands. Science 337, 753–756.
Salin, P.A., Bullier, J., 1995. Corticocortical connections in the visual system: structure and function. Physiol. Rev. 75, 107–154.
Schmid, M.C., Maier, A., 2015. To see or not to see - thalamo-cortical networks during blindsight and perceptual suppression. Prog. Neurobiol. 126, 36–48.
Schmid, M.C., Mrowka, S.W., Turchi, J., Saunders, R.C., Wilke, M., Peters, A.J., Ye, F.Q., Leopold, D.A., 2010. Blindsight depends on the lateral geniculate nucleus. Brain 466, 373–377.
Seillier, L., Lorenz, C., Kawaguchi, K., Ott, T., Nieder, A., Pourriahi, P., Nienborg, H., 2017. Serotonin decreases the gain of visual responses in awake macaque V1. J. Neurosci. 37, 11390–11405.
Self, M.W., van Kerkoerle, T., Supèr, H., Roelfsema, P.R., 2013. Distinct roles of the cortical layers of area V1 in figure-ground segregation. Curr. Biol. 23, 2121–2129.
Sherman, S.M., 2001. Thalamic relay functions. Prog. Brain Res. 134, 51–69.
Sherman, S.M., Guillery, R.W., 2002. The role of the thalamus in the flow of information to the cortex. Philos. Trans. R Soc. Lond. B Biol. Sci. 357, 1695–1708.
Sherman, S.M., Guillery, R.W., 1996. Functional organization of thalamocortical relays. J. Neurophysiol. 3, 1367–1395.
Sherman, S.M., 2017. Functioning of circuits connecting thalamus and cortex. Compr. Physiol. 7, 713–739.
Sherman, S.M., 2005. Thalamic relays and cortical functioning. Prog. Brain Res. 149, 107–126.
Shimegi, S., Kimura, A., Sato, A., Aoyama, C., Mizuyama, R., Tsunoda, K., Ueda, F., Araki, S., Goya, R., Sato, H., 2016. Cholinergic and serotonergic modulation of visual information processing in monkey V1. J. Physiol. Paris 110, 44–51.
Shipp, S., 2005. The importance of being agranular: a comparative account of visual and motor cortex, 360, 797–814.
Shipp, S., Zeki, S., 1989. The organization of connections between areas V5 and V1 in macaque monkey visual cortex. Eur. J. Neurosci. 1, 309–332.
Silberberg, G., Gupta, A., Markram, H., 2002. Stereotypy in neocortical microcircuits, 25, 227–230.
Sillito, A.M., Jones, H.E., 2002. Corticothalamic interactions in the transfer of visual information. Philos. Trans. R. Soc. Lond. B Biol. Sci. 357, 1739–1752.
Sincich, L.C., Horton, J.C., 2002. Divided by cytochrome oxidase: a map of the projections from V1 to V2 in macaques. Science 295, 1734–1737.
Sincich, L.C., Horton, J.C., 2005. The circuitry of V1 and V2: integration of color, form, and motion. Annu. Rev. Neurosci. 28, 303–326.
Sincich, L.C., Park, K.F., Wohlgemuth, M.J., Horton, J.C., 2004. Bypassing V1: a direct geniculate input to area MT. Nat. Neurosci. 7, 1123–1128.
Sincich, L.C., Jocson, C.M., Horton, J.C., 2007. Neurons in V1 patch columns project to V2 thin stripes. Cerebr. Cortex 17, 935–941.
Singer, W., Aldenhoff, J.B., 1987. A current source density analysis of field potentials evoked in slices of visual cortex. Exp. Brain Res. 69, 213–219.
Slovin, H., Arieli, A., Hildesheim, R., Grinvald, A., 2002. Long-term voltage-sensitive dye imaging reveals cortical dynamics in behaving monkeys. J. Neurophysiol. 88, 3421–3438.
Snodderly, D.M., Gur, M., 1995. Organization of striate cortex of alert, trained monkeys (*Macaca fascicularis*): ongoing activity, stimulus selectivity, and widths of receptive field activating regions. J. Neurophysiol. 74, 2100–2125.
Soma, S., Shimegi, S., Osaki, H., Sato, H., 2012. Cholinergic modulation of response gain in the primary visual cortex of the macaque. J. Neurophysiol. 107, 283–291.
Steinmetz, N.A., Koch, C., Harris, K.D., Carandini, M., 2018. Challenges and opportunities for large-scale electrophysiology with Neuropixels probes. Curr. Opin. Neurobiol. 50, 92–100.
Sugihara, H., Chen, N., Sur, M., 2016. Cell-specific modulation of plasticity and cortical state by cholinergic inputs to the visual cortex. J. Physiol. Paris 110, 37–43.

Tehovnik, E.J., Slocum, W.M., Schiller, P.H., 2002. Differential effects of laminar stimulation of V1 cortex on target selection by macaque monkeys. Eur. J. Neurosci. 16, 751–760.
Thomson, A.M., Bannister, A.P., 2003. Interlaminar connections in the neocortex. Cerebr. Cortex 13, 5–14.
Tootell, R.B., Switkes, E., Silverman, M.S., Hamilton, S.L., 1988. Functional anatomy of macaque striate cortex. II. Retinotopic organization. J. Neurosci. 8, 1531–1568.
Ts'o, D.Y., Frostig, R.D., Lieke, E.E., Grinvald, A., 1990. Functional organization of primate visual cortex revealed by high resolution optical imaging. Science 249, 417–420.
Tsodyks, M., Kenet, T., Grinvald, A., Arieli, A., 1999. Linking spontaneous activity of single cortical neurons and the underlying functional architecture. Science 286, 1943–1946.
van Kerkoerle, T., Self, M.W., Dagnino, B., Gariel-Mathis, M.-A., Poort, J., van der Togt, C., Roelfsema, P.R., 2014. Alpha and gamma oscillations characterize feedback and feedforward processing in monkey visual cortex. Proc. Natl. Acad. Sci. U. S. A. 111 (40), 14332–14341.
van Kerkoerle, T., Self, M.W., Roelfsema, P.R., 2017. Layer-specificity in the effects of attention and working memory on activity in primary visual cortex. Nat. Commun. 8, 13804.
Vidyasagar, T.R., 2001. From attentional gating in macaque primary visual cortex to dyslexia in humans. Prog. Brain Res. 134, 297–312.
Vnek, N., Ramsden, B.M., Hung, C.P., Goldman-Rakic, P.S., Roe, A.W., 1999. Optical imaging of functional domains in the cortex of the awake and behaving monkey. Proc. Natl. Acad. Sci. U. S. A. 96, 4057–4060.
Wandell, B.A., Dumoulin, S.O., Brewer, A.A., 2007. Visual field maps in human cortex. Neuron 56, 366–383.
Wilson, J.R., Hendrickson, A.E., Sherk, H., Tigges, J., 1995. Sources of subcortical afferents to the macaque's dorsal lateral geniculate nucleus. Anat. Rec. 242, 566–574.
Wood, K.C., Blackwell, J.M., Geffen, M.N., 2017. Cortical inhibitory interneurons control sensory processing. Curr. Opin. Neurobiol. 46, 200–207.
Xiao, Y., Felleman, D.J., 2004. Projections from primary visual cortex to cytochrome oxidase thin stripes and interstripes of macaque visual area 2. Proc. Natl. Acad. Sci. U. S. A. 101, 7147–7151.
Yabuta, N.H., Callaway, E.M., 1998. Functional streams and local connections of layer 4C neurons in primary visual cortex of the macaque monkey. J. Neurosci. 18, 9489–9499.
Yarch, J., Larsen, H., Chen, M., Angelucci, A., 2019. Morphological cell types projecting from V1 layer 4B to V2 thick and thin stripes. J. Neurosci. 39, 7501–7512.
Yew, B., Nation, D.A., Alzheimer's Disease Neuroimaging Initiative, 2017. Cerebrovascular resistance: effects on cognitive decline, cortical atrophy, and progression to dementia. Brain 140, 1987–2001.
Yoshioka, T., Levitt, J.B., Lund, J.S., 1994. Independence and merger of thalamocortical channels within macaque monkey primary visual cortex: anatomy of interlaminar projections. Vis. Neurosci. 11, 467–489.
Zinke, W., Roberts, M.J., Guo, K., McDonald, J.S., Robertson, R., Thiele, A., 2006. Cholinergic modulation of response properties and orientation tuning of neurons in primary visual cortex of anaesthetized Marmoset monkeys. Eur. J. Neurosci. 24, 314–328.