Supplemental Material: Annu. Rev. Neurosci. 2021. 44:517-546
https://doi.org/10.1146/annurev-neuro-102320-085825

Annual Review of Neuroscience

How Cortical Circuits Implement Cortical Computations: Mouse Visual Cortex as a Model

Cristopher M. Niell and Massimo Scanziani

Supplemental Appendix

(VERY) BRIEF OVERVIEW OF THE ANATOMICAL ORGANIZATION OF MOUSE VISUAL CORTEX

What is mouse V1 made of, and how does it connect? The amount of available data on cell types, including morphology, electrophysiological properties, molecular identity, local and long range connectivity pattern exceeds that of any other area of mammalian cortex. This list of parts and their wiring provides the basis for understanding the cellular mechanisms of cortical computations and constraining models. Below we briefly discuss the large-scale organization of mouse V1 and the general principles of circuit connectivity at the level of cell types and layers. This will provide a context for the specific microcircuitry and cellular connectivity pattern discussed in the main text and the specific computations they implement. We also refer the reader to recent reviews focused on this topic (Harris & Mrsic-Flogel 2013, Harris & Shepherd 2015, Tremblay et al. 2016).

Large-scale Organization

Mouse V1 is roughly 1 mm thick, covers an area of ~2.5mm on the posterior dorsal surface of the brain (**Figure 1A, main text)** and contains $2.5x10^5$ neurons in each hemisphere. The area of mouse V1 is nearly 3 orders of magnitude smaller than macaque; notably, though, the area of V1 across species scales according to visual acuity (Srinivasan et al. 2015). Thus, the small area of mouse V1 does not necessarily represent reduced computational capacity relative to effective pixels in the visual input. Furthermore, primate V1 is only two times thicker, suggesting that the local circuitry in mouse may be closer in complexity than suggested by the total difference in area. As in all other mammalian species, mouse V1 has a retinotopic map, in that neighboring points across its surface correspond to neighboring locations in visual space.

Mouse V1 is also subdivided into six cytoarchitectonically distinct layers, though its lamination and sub-lamination is not as distinct as in cats or primates. This difference may represent fewer distinct parallel pathways carrying different types of information from the retina. Alternatively, neurons in different pathways may simply be intermingled anatomically in the mouse, rather than segregated into sub-laminae as in the primate. As in other species, the intrinsic connectivity of mouse V1 is primarily a vertical organization, as neurons extend their axons and dendrites across layers, with more limited horizontal connectivity (typically <200-300um) consistent with the presence of a topographic map in register across layers.

Cell Types and Circuit Organization

Cortical neurons fall into two broad classes - excitatory and inhibitory. Within each of these two broad classes there is a large morphological, electrophysiological, and molecular diversity. A tremendous advance over the past decade has been the ability to perform large-scale quantitative surveys, and in particular to characterize the same neurons with multiple approaches to determine how these classes align. According to recent surveys there are approximately 42 distinct molecular subtypes (Tasic et al. 2016) and at least 46 distinct "morpho-electric" types (Gouwens et al. 2019) of excitatory and inhibitory neurons in mouse V1. While this detailed information is enabling the emergence of a "standard model" for the census of cell types in mouse visual cortex, the matching of molecularly distinct types to known morphological and electrophysiological categories and how they connect within the local cortical circuit is still not clear. Nevertheless, these categorizations represent "parts lists" of the cortex and thus provide a basis for exploring the contribution of each part in computation.

Excitatory circuitry

Excitatory neurons communicate by contributing to spiking activity in downstream neurons, and thus, by synapsing among each other, they provide the basis for the flow of activity through the cortical circuit. While cortical excitatory neurons can be categorized according to distinct molecular, morphological and electro-physiologically categories (Tasic et al. 2016), these distinct types of cortical excitatory neurons are largely organized by layers (L) and by where they project. A simplified version of the canonical excitatory pathway through cortex (**Figure 1B, main text)** begins with visually evoked activity from the dorsal lateral geniculate nucleus (dLGN) of thalamus

entering V1 in L4, distributed to L2/3 and then down to layers 5 and 6. In fact, however all layers receive dLGN input, and there is a significant projection from L4 to L5, bypassing L2/3. Below we provide a brief general description of the excitatory neurons of V1, following the order of the classical canonical circuit organization.

Layer 4 is the primary (though not only) target of dLGN input to V1 (Ji et al. 2016). L4 excitatory neurons (Scala et al. 2019) receive relatively little input from other layers of cortex, and therefore any transformation in the representation of the visual stimulus from dLGN to cortical L4 represents computation performed within L4. L4 excitatory neurons provide their primary output locally, within V1, to other L4 neurons (Seeman et al. 2018) as well as to L2/3 and L5 neurons (Olivas et al. 2012), though they also send long range projections to other cortical targets (Harris et al. 2019). Thus, L4 neurons serve largely as an input to the rest of the cortical circuit.

Layer 2/3 excitatory neurons receive dLGN input, although to a lesser extent than L4 (Ji et al. 2016). Instead, the primary local excitatory inputs are feedforward connections originating from L4 (Olivas et al. 2012) and recurrent connections within L2/3 (Seeman et al. 2018). In addition, L2/3 are reciprocally connected with L5 excitatory neurons (Jiang et al. 2015, Olivas et al. 2012). L2/3 are also a major source of feedforward output to other visual and non-visual cortical areas (Harris et al. 2019, Kim et al. 2020).

Layer 5 excitatory neurons receive strong feedforward input from L4 and L2/3 (Jiang et al. 2015, Olivas et al. 2012), as well from the dLGN (Ji et al. 2016). L5 neurons also excite each other through local recurrent connections (Seeman et al. 2018). Neurons in L5 also form major output pathways out of V1. They can be divided into two distinct groups depending on whether these output projections target cortical or subcortical structures (Kim et al. 2015, 2020; Lur et al. 2016). Furthermore, L5 neurons that project to subcortical structures form distinct subgroups depending on the specific subcortical targets they project to (e.g. the superior colliculus, the basal ganglia, the higher visual thalamus (pulvinar)) (Kim et al. 2015, Liang et al. 2015, Lur et al. 2016).

Layer 6 is generally associated with feedback to thalamus (Alitto & Usrey 2003), but in fact contains two broad excitatory cell classes that differ strikingly in their morphology and connectivity - neurons that project to thalamus and neurons that project to other cortical targets, both within V1 and distally (Harris et al. 2019, Kim et al. 2014, Vélez-Fort et al. 2014).

Finally, Layer 1 consists primarily of neuronal processes, both the apical tufts of local cortical neurons and long-range axonal inputs from other areas (Ibrahim et al. 2020). It therefore

represents more of a switchboard for connectivity than a processing layer. However, it does contain a sparse population of inhibitory neurons (Schuman et al. 2019) that encode a range of visual and non-visual signals consistent with long-range inputs (Ibrahim et al. 2016).

Inhibitory circuitry

To understand how inhibitory neurons impact cortical computation, we need to determine how they are integrated into the cortical circuit, that is, who excites them, who inhibits them, and who they inhibit. Given their great molecular, morphological and electrophysiological diversity (Markram et al. 2004, Tremblay et al. 2016), this may seem a daunting task. However, in the mouse, the large spectrum of inhibitory neurons can be subdivided into three primary classes (Rudy et al. 2011), based on expression of molecular markers parvalbumin (PV), somatostatin (SOM), and the ionotropic serotonin receptor (5-HTR3A) (**Figure 1C, main text)**. Even such a broad subdivision has been extremely helpful in revealing the general connectivity pattern and broad functional distinctions of inhibitory neurons in V1. Below we summarize the properties and circuit organization of these three categories of inhibitory neurons**.** Each of these categories has a distinct circuit motif that can be engaged for different computations, which we discuss in the main text.

PV neurons are excited by ascending afferent inputs as well as by local recurrent inputs (e.g. PV neurons in L4 are excited by dLGN afferents and by L4 excitatory neurons) (Ji et al. 2016, Jiang et al. 2015); they inhibit excitatory neurons by forming synapses on their soma, proximal dendrites and axon initial segment. As such, they are well poised to control the output of excitatory neurons. PV neurons also inhibit one another. PV neurons have narrow action potentials and, thus, are often referred to as ”fast spiking” (McCormick et al. 1985). This electrophysiological signature allows one to identify them even with extracellular recording in vivo. They mainly fall into two morphological classes, basket and chandelier cells.

SOM neurons are excited by local inputs and much less by ascending afferents (e.g. SOM neurons in L4 are not excited by dLGN afferents (Ji et al. 2016) and SOM neurons in L2/3 are excited by L2/3 but not L4 neurons (Adesnik et al. 2012)); They provide inhibition to all other cell types, both excitatory and inhibitory, but, in contrast to PV neurons, don’t inhibit one another (Jiang et al. 2015, Karnani et al. 2016, Pfeffer et al. 2013). Thus, they serve as “master regulators” of inhibition across the local population. Because their synapses target the dendrites of excitatory

neurons, they provide inhibition at the input stage. A large fraction of SOM inhibitory neurons fall into a morphological class known as Martinotti cell.

Among 5-HT3A neurons, the best studied sub-class are the vasoactive intestinal peptide-expressing (VIP) neurons due to existence of a VIP-cre transgenic line (Taniguchi et al. 2011). In contrast to PV and SOM neurons, VIP neurons specifically target other inhibitory neurons, while mostly avoiding excitatory neurons (Ayzenshtat et al. 2016, Jiang et al. 2015, Pfeffer et al. 2013). By inhibiting inhibitory neurons VIP neurons are thus a key element of the canonical "disinhibitory" circuit in cortex. These neurons receive local input as well as long-range cortical input and neuromodulatory input. VIP neurons correspond morphologically to double bouquet cells. The remaining non-VIP expressing 5-HTR3A neurons are mainly neurogliaform cells, which provide broad inhibition, but very little is known about how they impact V1 processing.

dLGN input

The dLGN of thalamus provides the direct pathway for ascending information from the retina to V1. This input has exquisite laminar and cell-type specificity. dLGN afferents excite V1 neurons across all layers, yet neurons located in L4 receive the strongest excitation, consistent with the fact that the highest density of dLGN axonal arbors resides in this layer (Ji et al. 2016) **(Figure 1B, main text)**. In addition to their laminar preference, dLGN afferents are also highly selective relative to the cortical neuron types they impinge on: excitatory neurons and PV neurons are their main cellular targets, while VIP and SOM neurons, the two other main classes of cortical inhibitory neurons receive little or no excitation from the dLGN (Ji et al. 2016) **(Figure 1D, main text)**. Furthermore, PV neurons receive stronger excitation from dLGN afferents as compared to excitatory neurons (Ji et al. 2016).

Literature cited

Adesnik H, Bruns W, Taniguchi H, Huang ZJ, Scanziani M. 2012. A neural circuit for spatial summation in visual cortex. *Nature*. 490(7419):226–31

Alitto HJ, Usrey WM. 2003. Corticothalamic feedback and sensory processing. *Curr. Opin. Neurobiol.* 13(4):440–45

Ayzenshtat I, Karnani MM, Jackson J, Yuste R. 2016. Cortical Control of Spatial Resolution by VIP+ Interneurons. *J. Neurosci.* 36(45):11498–509

Gouwens NW, Sorensen SA, Berg J, Lee C, Jarsky T, et al. 2019. Classification of electrophysiological and morphological neuron types in the mouse visual cortex. *Nat. Neurosci.* 22(7):1182–95

Harris JA, Mihalas S, Hirokawa KE, Whitesell JD, Choi H, et al. 2019. Hierarchical organization of cortical and thalamic connectivity. *Nature*. 575(7781):195–202

Harris KD, Mrsic-Flogel TD. 2013. Cortical connectivity and sensory coding. *Nature*. 503(7474):51–58

Harris KD, Shepherd GMG. 2015. The neocortical circuit: themes and variations. *Nat. Neurosci.* 18(2):170–81

Ibrahim LA, Mesik L, Ji X-Y, Fang Q, Li H-F, et al. 2016. Cross-Modality Sharpening of Visual Cortical Processing through Layer-1-Mediated Inhibition and Disinhibition. *Neuron*. 89(5):1031–45

Ibrahim LA, Schuman B, Bandler R, Rudy B, Fishell G. 2020. Mining the jewels of the cortex's crowning mystery. *Curr. Opin. Neurobiol.* 63:154–61

Jiang X, Shen S, Cadwell CR, Berens P, Sinz F, et al. 2015. Principles of connectivity among morphologically defined cell types in adult neocortex. *Science*. 350(6264):aac9462

Ji X-Y, Zingg B, Mesik L, Xiao Z, Zhang LI, Tao HW. 2016. Thalamocortical Innervation Pattern in Mouse Auditory and Visual Cortex: Laminar and Cell-Type Specificity. *Cereb. Cortex*. 26(6):2612–25

Karnani MM, Jackson J, Ayzenshtat I, Tucciarone J, Manoocheri K, et al. 2016. Cooperative Subnetworks of Molecularly Similar Interneurons in Mouse Neocortex. *Neuron*. 90(1):86–100

Kim EJ, Juavinett AL, Kyubwa EM, Jacobs MW, Callaway EM. 2015. Three Types of Cortical Layer 5 Neurons That Differ in Brain-wide Connectivity and Function. *Neuron*. 88(6):1253–

67

Kim EJ, Zhang Z, Huang L, Ito-Cole T, Jacobs MW, et al. 2020. Extraction of Distinct Neuronal Cell Types from within a Genetically Continuous Population. *Neuron*. 107(2):274–82.e6

Kim J, Matney CJ, Blankenship A, Hestrin S, Brown SP. 2014. Layer 6 corticothalamic neurons activate a cortical output layer, layer 5a. *J. Neurosci.* 34(29):9656–64

Liang F, Xiong XR, Zingg B, Ji X-Y, Zhang LI, Tao HW. 2015. Sensory Cortical Control of a Visually Induced Arrest Behavior via Corticotectal Projections

Lur G, Vinck MA, Tang L, Cardin JA, Higley MJ. 2016. Projection-Specific Visual Feature Encoding by Layer 5 Cortical Subnetworks. *Cell Rep.* 14(11):2538–45

Markram H, Toledo-Rodriguez M, Wang Y, Gupta A, Silberberg G, Wu C. 2004. Interneurons of the neocortical inhibitory system. *Nat. Rev. Neurosci.* 5(10):793–807

McCormick DA, Connors BW, Lighthall JW, Prince DA. 1985. Comparative electrophysiology of pyramidal and sparsely spiny stellate neurons of the neocortex. *J. Neurophysiol.* 54(4):782–806

Olivas ND, Quintanar-Zilinskas V, Nenadic Z, Xu X. 2012. Laminar circuit organization and response modulation in mouse visual cortex. *Front. Neural Circuits*. 6:70

Pfeffer CK, Xue M, He M, Huang ZJ, Scanziani M. 2013. Inhibition of inhibition in visual cortex: the logic of connections between molecularly distinct interneurons. *Nat. Neurosci.* 16(8):1068–76

Rudy B, Fishell G, Lee S, Hjerling-Leffler J. 2011. Three groups of interneurons account for nearly 100% of neocortical GABAergic neurons. *Dev. Neurobiol.* 71(1):45–61

Scala F, Kobak D, Shan S, Bernaerts Y, Laturnus S, et al. 2019. Layer 4 of mouse neocortex differs in cell types and circuit organization between sensory areas. *Nat. Commun.* 10(1):4174

Schuman B, Machold RP, Hashikawa Y, Fuzik J, Fishell GJ, Rudy B. 2019. Four Unique Interneuron Populations Reside in Neocortical Layer 1. *J. Neurosci.* 39(1):125–39

Seeman SC, Campagnola L, Davoudian PA, Hoggarth A, Hage TA, et al. 2018. Sparse recurrent excitatory connectivity in the microcircuit of the adult mouse and human cortex. *Elife*. 7:

Srinivasan S, Carlo CN, Stevens CF. 2015. Predicting visual acuity from the structure of visual cortex. *Proc. Natl. Acad. Sci. U. S. A.* 112(25):7815–20

Taniguchi H, He M, Wu P, Kim S, Paik R, et al. 2011. A Resource of Cre Driver Lines for Genetic Targeting of GABAergic Neurons in Cerebral Cortex

Tasic B, Menon V, Nguyen TN, Kim TK, Jarsky T, et al. 2016. Adult mouse cortical cell taxonomy revealed by single cell transcriptomics. *Nat. Neurosci.* 19(2):335–46

Tremblay R, Lee S, Rudy B. 2016. GABAergic Interneurons in the Neocortex: From Cellular Properties to Circuits. *Neuron*. 91(2):260–92

Vélez-Fort M, Rousseau CV, Niedworok CJ, Wickersham IR, Rancz EA, et al. 2014. The Stimulus Selectivity and Connectivity of Layer Six Principal Cells Reveals Cortical Microcircuits Underlying Visual Processing. *Neuron*. 84(1):238