The Network for Intracortical Communication in Mouse Visual Cortex

Andreas Burkhalter

Abstract New techniques for identifying cell types, tracing their synaptic partners, imaging and manipulating their activity in behaving organisms have made mice a widely used model for linking brain circuits to behavior. Most behaviors are tied to vision: identifying objects, guiding movements of body parts, navigating through the environment, and even social interactions. Reason enough to focus on the mouse visual cortex. To find our way around in the occipital cortex, we needed a map. We took a classic approach and traced in the same animal the outputs from multiple retinotopic sites of primary visual cortex (V1) and compared the relative location of projections in the extrastriate cortex. We found nine extrastriate maps and showed by single unit recordings that each of the connectional maps contained visually responsive neurons whose receptive fields were mapped in orderly fashion and completely covered the visual field. Remarkably, a tiny region of one sixth of a dime contained a two- to three-times larger number of areas than the highly developed somatosensory and auditory cortices. By tracing the connections, we found that each of the ten visual areas projected to 25–35 cortical targets and interconnected virtually all of the areas reciprocally with one another. Although the binary graph density of the connection matrix was nearly complete, the connection strengths between areas within the ventral and dorsal cortex differed, indicating that the information from V1 flowed into distinct but interconnected streams. Unit recordings and calcium imaging studies showed that the ventral and dorsal streams processed different spatiotemporal information, which aligned with known properties of streams in primates. Analyses of the laminar patterns of interareal projections showed that areas were organized at multiple levels, suggesting that each stream represented a processing hierarchy.

A. Burkhalter (✉)
Department of Neuroscience, Washington University School of Medicine, St. Louis, MO 63110, USA
e-mail: burkhala@pcg.wustl.edu

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Introduction

Over the past decades, neuroscience research has shown that sensory inputs are processed at multiple locations distributed across the brain. These regions do not encode specific mental faculties but are responsible for specific unitary operations (Kandel and Hudspeth 2013). Cognition arises in a network of serial and parallel pathways between functionally discrete units, each responsible for elements—but not all aspects—of a given function. Although the tenet of functional localization holds that neural processing is modular, the structure of the underlying network and the rules of interareal communication are not well understood. Thanks to the development of powerful new tools for recording, labeling and genetically manipulating brain circuits, the mouse visual system has emerged as a tractable system in which these questions can be addressed with unprecedented precision (Luo et al. 2008; Huberman and Niell 2011; Oh et al. 2014; Zingg et al. 2014).

Mice are most active at night and rely heavily on their whiskers for recognizing objects and their ears and noses for hearing and social communication (Holy and Guo 2005; Jadhav and Feldman 2010; Stowers et al. 2013). When starved for food, mice are diurnal and use dichromatic vision for guiding their actions in the field (Jacobs et al. 2004; Daan et al. 2011; Baden et al. 2013). Through their small eyes with afoveate retinas, the world looks blurred and lacks the rich detail experienced by humans, whose vision is 100 times sharper. At close range, however, the acuity of 0.5 cycles/deg is sufficient to resolve landmark features that can be used for referencing locomotion-dependent path integration signals during spatial navigation (Prusky et al. 2000; Prusky and Douglas 2005; Chen et al. 2013). In fact, experiments on visual object recognition have shown that rats, and presumably mice, can use invariant shape information to identify landmarks from a variety of different viewing angles (Alemi-Neissi et al. 2013). These studies demonstrate that mice process multiple complex visual cues and associate them with motor actions. Many of these computations are performed in interconnected cortical and subcortical networks, bringing up the questions of what the architecture of these networks is and how do functionally distinct areas communicate with each other.

Thalamocortical Projections to Mouse Visual Cortex

The visual cortex receives thalamic input from the lateral geniculate (LGN) and the lateral posterior (LP) nuclei. LGN inputs to V1 terminate most densely in layers 3 and 4, and more sparsely in layer 1 and at the layer 5/6 border (Dräger 1974; Antonini et al. 1999). In addition, sparse projections from the LGN terminate in the lateral extrastriate areas but avoid medial extrastriate cortex (Antonini et al. 1999). V1 also receives thalamocortical inputs from LP, which terminate in layers 1 and 5. LP inputs to surrounding extrastriate cortex terminate in layers 1, 3, 4 and 6 (Hughes 1977; Herkenham 1980). Although the extrastriate target areas of

these connections were not positively identified, the results show that thalamocortical inputs from thalamic relays are deployed to V1 as well as to surrounding extrastriate cortex (Sanderson et al. 1991). With this thalamocortical input in place, it is not surprising that expression of the activity-dependent immediate early gene, *Arc*, shows that much of the thalamorecipient cortex is driven by visual input (Burkhalter et al. 2013).

Cortical Cartography

Inspired by the emerging field of genetics of the mouse brain (Sidman et al. 1965), Caviness (1975) rang in the modern era of mouse cartography. Refining the surface-based maps of lissencepahlic mouse cortex constructed by the classic 'cytoarchitects' (Woolsey 1967), Caviness introduced the flatmap format that displayed the cortex in a single map that preserved the natural topology of parcels (Van Essen 2013). In this map, 26 neocortical parcels were identified and, for the first time, clearly showed the shape and extent of V1, including the surrounding extrastriate areas 18a and 18b. A more detailed surface-based map based on the Allen Reference Atlas identified 34 cytoarchitectonic parcels (Dong 2008; Ng et al. 2010), which is similar to the 37 parcels identified in a widely used slice-based atlas by Franklin and Paxinos (2007). Using a variety of histochemical and immunological markers in tangential sections of physically flattened cortex, we were able to identify only 23 parcels, but many with much greater confidence than possible with the classic Nissl stain (Wang et al. 2011, 2012). Notably, our parcellation scheme falls short in the auditory, posterior parietal and visual cortices, which are at the very locations in which we found multiple topographic maps (Wang and Burkhalter 2007). Thus, it appears that some of the areas annotated in the atlases are inspired by our area map, but in reality their borders are too subtle to be identified with confidence by cytoarchitectonic criteria.

Areal Organization of Visual Cortex

Early topographic mapping studies using microelectrodes showed that extrastriate cortex surrounding V1 contains multiple orderly maps of the visual field (Dräger 1975; Wagor et al. 1980). The conclusion from the layout of the visuotopic maps was that V1 is adjoined on the lateral side by area V2, which is flanked by V3. On the medial side, V1 is adjoined by two additional maps, a rostral area Vm-r and a caudal area Vm-c (Wagor et al. 1980). This primate-inspired areal layout was soon challenged by the discovery that V1 projection targets vastly outnumbered the reported visuotopic areas (Olavarria and Montero 1989). In the eyes of some investigators, the mismatch argued against an organization in which V1 was surrounded by a string of areas and favored a scheme in which the projection

patches represented inputs to distinct modules within a single area (Kaas et al. 1989). With rodents rapidly taking center stage in neuroscience, the time was ripe to revisit the issue. By labeling the connections of two to three distinct visuotopic locations of V1 with different tracers in the same animal, making side-by-side comparisons of projections in extrastriate cortex and mapping receptive fields, we produced maps of rat and mouse visual cortex (Coogan and Burkhalter 1993; Wang and Burkhalter 2007; Fig. 1). In both species we found maps that strongly argued against the primate-inspired scheme proposed by Wagor et al. (1980), in which a single large area surrounded lateral and rostral V1. Instead,

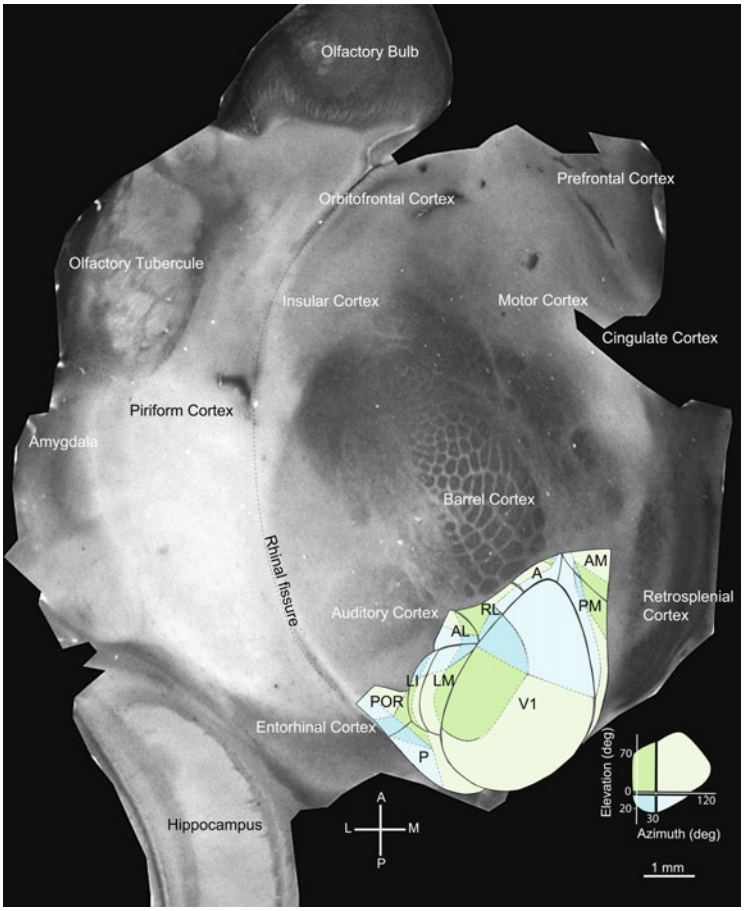

Fig. 1 Area map of mouse visual cortex. Tangential section through flatmounted left cortical hemisphere stained with an antibody against the muscarinic type 2 acetylcholine receptor. The different colors indicate different quadrants of the right visual field. Abbreviations: *A* anterior area, *AL* anterolateral area, *AM* anteromedial area, *LI* laterointermediate area, *LM* lateromedial area, *V1* primary visual cortex, *P* posterior area, *PM* posteromedial area, *POR* postrhinal area, *RL* rostrolateral area, *A* Anterior, *L* lateral, *M* medial, *P* posterior

the results showed an organization in which V1 was surrounded by a string of small areas that each contained a complete map of the visual field. This finding suggested that ancestral cortex had a complex organization and that select areas identified in primates might be homologous to primordial extrastriate areas in rodents (Rosa and Krubitzer 1999). One of these may be the lateromedial area (LM), which is the only area that shares the vertical meridian with V1 and, for that reason, resembles V2 in primates (Allman and Kaas 1971). But, unlike V2, which has a split horizontal meridian representation, the map in LM is topologically equivalent to the visual field. In fact, this is true for every visuotopic map we have identified, which all show that the margins of the visual field are mapped along the areal borders. To minimize the length of the connections between areas, matching topographic locations in different maps are aligned across shared borders. One of the lessons from these studies is that extrastriate cortex surrounding V1 contains a larger number of areas than annotated in widely used atlases (Franklin and Paxinos 2007; Dong 2008) and employed as references for the mesoscale connectome (Oh et al. 2014; Zingg et al. 2014). It is important to note that, except for the V1 border, which is readily detected in Nissl-stained sections, the cytoarchitecture of the surrounding extrastriate cortex is remarkably uniform. The single exception is the LM/anterolateral area (AL) border, which can be identified by Nissl staining but only when the eyes are keyed to the cytoarchitectonic transition, highlighted by the expression of the muscarinic type 2 acetylcholine receptor (Wang et al. 2011). However, perhaps the most surprising result is that the mouse visual cortex, which is one third the size of barrel cortex, contains at least ten areas, seven more than the somatosensory cortex. One interpretation of the unexpected multitude of visuotopic maps is that vision for perception and for guiding motor actions arises from a larger number of unitary operations than somatosensation and that these elementary processes are represented in different visual areas.

Interareal Connections

To study the interareal network of visual cortex, we injected the anterograde tracer biotinylated dextran amine (BDA) into ten areas, which we identified by their location relative to callosal landmarks (Wang et al. 2012). Projections to 40 targets were identified based on a combination of cytoarchitectonics and the expression of various molecular markers. The projection strength of each pathway was determined by the optical density of labeled axon branches and terminals in the target zone relative to the total output. Earlier studies have shown that optical density is tightly correlated with bouton density (Wang et al. 2011). The results of the 10×40 connectivity matrix show 307 of 390 possible linkages (79 %), which accounts for a 13 % higher graph density than in the macaque cortex (Markov et al. 2013). The connection density within the visual cortex proper is even higher, showing that virtually all of the ten visuotopically organized areas are interconnected reciprocally with one another (Wang et al. 2012). The connection strengths span at least

three orders of magnitude, showing a long-tailed distribution with small numbers of strong and a large numbers of weak connections. Although the connection strength in mouse cortex varies over a narrower range than in macaque (Markov et al. 2011), the lognormal distribution found in both species indicates that the fundamental principles of cortical connectivity are evolutionarily conserved.

In primates, visual information is processed in dorsal and ventral cortical streams specialized for 'where' an object is located or for guiding actions and 'what' an object is (Ungerleider and Mishkin 1982; Goodale and Milner 1992). If such streams exist in mice, how do they arise from a network with seemingly low binary specificity? One way this might be achieved is by routing the flow of information through pathways with different connection strengths. Consistent with this notion, we found that each source area of visual cortex had a unique profile of connection strengths. We assessed between-area similarities and found that the projection strengths among dorsal and ventral networks were distinct. The dorsal network consisted of areas AL, rostrolateral area (RL), anteromedial area (AM), posteromedial area (PM) and anterior area (A), whereas V1, LM, lateointermediate area (LI), postrhinal area (POR) and posterior area (P) were grouped in the ventral network (Wang et al. 2012). Although streams were revealed in the graph of cortex-wide connections, we wondered whether they were present in the 10×10 connectivity graph of visuotopically organized areas. The graph of projection strengths clearly grouped areas into dorsal (i.e., AL, RL, AM, PM, A) and ventral (i.e., V1, LM, LI, POR, P) communities in which connections within modules were twice as strong as those between modules. Within modules, the shortest pathways were always direct. By contrast, the shortest pathways between modules were often indirect, which means that the combined strength of the indirect path was stronger that the direct path. Thus, for communication between modules, the most effective path may be indirect. Interestingly, not a single short path linking the two modules travels through V1, indicating that, similar to cat and monkey (Sporns et al. 2007), V1 is not a network hub for interareal communication. Instead, judged by the number of connections, this role belongs to area LM. Although lower in the hierarchy than monkey V4, which has a similar status in the network, LM may play a critical role in integrative processing of visual information.

Cortical Hierarchy

The idea that hierarchical relationships between areas of mouse visual cortex can be derived from the laminar organization of connections goes back to analyses of primate cerebral cortex (Felleman and Van Essen 1991; Markov et al. 2014). In monkey, it was noticed that many reciprocal connections consisted of feedforward projections terminating in layer 4 and feedback projections terminating outside of layer 4. Such asymmetrical linkages are present between most reciprocally connected pairs of cortical areas. In rat and mouse, reciprocal interareal connections share many of the features found in primate (Coogan and Burkhalter 1990, 1993;

Dong et al. 2004a). However, unlike in primates, feedforward axonal projections from V1 are not restricted to layer 4. Instead, the projections terminate in a column across all layers. Importantly, however, feedforward connections always include layer 4. In contrast, feedback projections from surrounding extrastriate cortex to layer 4 of V1 are extremely sparse and preferentially terminate in layers 1, 2, 3, 5 and 6. Thus, the asymmetry in the innervation strength of layer 4 is the hallmark feature of reciprocal interareal connections. While these are striking similarities to feedforward and feedback connections in monkey, it is important to note that the columnar pattern of feedforward connections in rodents differs from that in monkey, which is restricted to layer 4. In fact, rodent feedforward connections resemble more closely the lateral connections in monkey (Felleman and Van Essen 1991). A likely reason for this difference is that feedforward connections in rodents originate from layers 2–6 (Coogan and Burkhalter 1988), whereas, in monkey, layers 2 and 3 are the main sources of these connections (Felleman and Van Essen 1991). From a developmental perspective, Dehay and Kennedy (2007) have argued that layers 2 and 3 in primates are different from layers 2 and 3 in mice, which lack the computational components of primate cortex. Abandoning input from deep layers in feedforward connections and increasingly relying on inputs from layers 2 and 3 may be a structural manifestation of the superior sophistication in interareal communication in primates.

In primates, different hierarchical levels are associated with different stages of visual processing (Felleman and Van Essen 1991). One way stimulus complexity is expressed is by the convergence of input reflected in the size of receptive fields. Recordings in mouse visual cortex show that receptive fields in V1 are small (10 deg) and increase across different extrastriate visual areas to reach a size that covers most of the visual field (Wang and Burkhalter 2007). Indirect support for an areal hierarchy also comes from the pattern of subcortical connections. For example, only areas V1 and LM receive input from the main afferent LGN nucleus (Oh et al. 2014). Thalamocortical inputs to all other visual areas originate from the LP nucleus (Oh et al. 2014). In addition, projections from V1 to the superior colliculus terminate in the most superficial sensory layers, whereas the outputs from higher areas are sent to deeper visuomotor layers (Coogan and Burkhalter 1993; Wang and Burkhalter 2013).

Synaptic Organization of Feedforward and Feedback Connections

Signatures for a cortical hierarchy are also observed in the distinct synaptic connectivity of feedforward and feedback connections. Both types of interareal connections are made by excitatory, glutamatergic pyramidal cells (Johnson and Burkhalter 1994; Domenici et al. 1995; Dong et al. 2004b), whereas long-range projections of GABAergic neurons are negligible (McDonald and Burkhalter 1993;

but see Caputi et al. 2013). In rat and mouse, feedforward and feedback connections to higher (i.e., LM) and lower visual areas (i.e., V1) provide monosynaptic input to pyramidal cells and GABAergic neurons (Dong et al. 2004b). Among the targets in layers 2 and 3, we found a handful of somatostatin- and calretinin-expressing interneurons but the vast majority of GABAergic cells expressed parvalbumin (Gonchar and Burkhalter 1999, 2003). Thus, in the target region, responses of pyramidal cells to excitatory feedforward and feedback inputs are influenced by disynaptic feedforward inhibition from parvalbumin neurons. Although the laminar projection pattern of feedforward and feedback circuits are distinct (Dong et al. 2004a), structurally the circuits for feedforward inhibition are similar in both pathways (Gonchar and Burkhalter 1999). Physiologically, however, the responses of pyramidal cells to feedforward inputs are opposed by stronger inhibition than the responses to feedback inputs (Shao and Burkhalter 1996; Dong et al. 2004b). The reasons for the pathway-specific excitatory/inhibitory balance are that feedforward inputs to parvalbumin-expressing neurons are relatively stronger than to pyramidal cells whereas feedback inputs to both types of cells are similar (Yang et al. 2013). The stronger excitation of parvalbumin neurons is probably due to signaling via calcium-permeable GluR2-lacking AMPA receptors that elicit large quantal amplitude responses with fast kinetics (Hull et al. 2009). By contrast, feedforward inputs to pyramidal cells are mediated by slow, small-amplitude AMPA receptors (Hull et al. 2009). The result of the fast/large amplitude AMPA-mediated currents at feedforward inputs onto parvalbumin-expressing neurons is that feedforward inhibition is initiated reliably and in a precisely timed manner. In contrast, small amplitude and slower AMPA-mediated currents at feedback synapses facilitate integration of convergent inputs onto pyramidal neurons. The motif of feedforward inhibition not only balances excitation but influences circuit gain and dynamics (Kepecs and Fishell 2014). We can only speculate what effects diverse feedforward inhibition might have on the processing of visual signals in feedforward and feedback circuits. In the static mode, feedforward circuits are good for selecting correlated inputs. Computational modelling has shown that this enhances stimulus detection and improves the accuracy of stimulus representation, whereas, in the default mode, the feedback circuit may improve response probability to sensory input (Kremkow et al. 2010). However, when top-down attention is focused on a stimulus, the excitatory/inhibitory balance may change and improve the accuracy of stimulus detection (Wang et al. 2013).

Dorsal and Ventral Processing Streams

Motivated by the perplexing number of visual areas and their striking connectivity within hierarchically organized dorsal and ventral streams, it was natural to search for analogies to the distributed processing within ‘where’ and ‘what/action’ streams of primates (Ungerleider and Mishkin 1982; Goodale and Milner 1992). The proposal that rat cortex contains distinct streams that are specialized for visual

guidance and object recognition was made almost 25 years ago (Kolb 1990). Since then, numerous studies have shown that deficits in pattern discrimination were associated with lesions in lateral extrastriate visual cortex, whereas damage to cortex anterior and medial to V1 affected polysensory integration and spatial navigation (Kolb and Walkey 1987; Wong and Brown 2006; Torrealba and Valdes 2008; Zhang et al. 2010). But the lesioning techniques used in these studies did not afford the spatial resolution for linking the behavioral deficit unequivocally to specific areas, a problem that will likely be overcome by optogenetic approaches (Lien and Scanziani 2013). Recently, significant progress was made by two-photon imaging of calcium transients in upper layer neurons of multiple areas in mouse visual cortex (Andermann et al. 2011; Marshel et al. 2011; Roth et al. 2012). These recordings showed that tuning to high spatial frequency was more common in LI than in AL, RL and AM, which are more selective for high temporal frequency and the direction of motion. Although these findings are broadly consistent with the concept that ventral stream areas are specialized for image detail and dorsal stream areas preferentially respond to transient inputs (Van Essen and Gallant 1994), the results show inconsistencies. For example, neurons of the ventral stream area, LM, have low spatial acuity and are tuned to high temporal frequencies. It is possible that, similar to V2 of primates (Nassi and Callaway 2009), LM consists of functionally distinct compartments and the true response properties were masked by averaging across modules. Further, counter to the prediction, neurons in the dorsal stream area, PM, have high spatial acuity and prefer longer-lasting, slow moving objects. One way to explain these inconsistencies is that high spatial acuity and sensitivity to slow visual motion recorded in PM provides landmark information, which is used to calibrate distance and direction signals from locomotion used for path integration (Harvey et al. 2012; Saleem et al. 2013).

Although distinct streams are observed in the cortex, functionally distinct channels emerge from the retina, are present in the LGN and can be traced throughout the afferent visual pathway to V1 (Piscopo et al. 2013; Cruz-Matin et al. 2014; Dhande and Huberman 2014). In V1, neural responses represent a weighted combination of inputs from parallel afferent geniculocortical pathways and feedback inputs from higher cortical areas with distinct spatiotemporal properties (Gao et al. 2010). From V1, impulses are sent to different areal streams. The question then is whether the functional differences arise in V1 or are generated in the dorsal or ventral areas to which V1 sends its output. To address this question, Glickfeld et al. (2013) labeled striate cortical inputs from V1 with the calcium indicator GCaMP3.3 and imaged calcium transients in axon terminals projecting to LM, AL and PM. The results show that the visual preferences of each projection are different and matched those of neurons in the target area, suggesting that each area inherits the response properties from functionally specialized neurons in V1. The important conclusion of this work is that different V1 neurons transmit information tailored to its projection target. This organization is consistent with our observation that individual V1 neurons largely lack collateral projections and project to single area of extrastriate cortex (Wang and Burkhalter 2005). More recently, similar results have been reported in the connectivity between V1, LM and AL, supporting

the idea that interareal transmission relies on dedicated neuronal connections (Berezovskii et al. 2011). The overall conclusion of these studies is that the binary specificity of the network of interareal connection might be much greater than indicated by pathway tracing of connections with tracers that lack cellular specificity.

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