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A mouse model of higher visual cortical function

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Abstract

During sensory experience, the retina transmits a diverse array of signals to the brain, which must be parsed to generate meaningful percepts that can guide decisions and actions. Decades of anatomical and physiological studies in primates and carnivores have revealed a complex parallel and hierarchical organization by which distinct visual features are distributed to, and processed by, different brain regions. However, these studies have been limited in their ability to dissect the circuit mechanisms involved in the transformation of sensory inputs into complex cortical representations and action patterns. Multiple groups have therefore pushed to explore the organization and function of higher visual areas in the mouse. Here we review the anatomical and physiological findings of these recent explorations in mouse visual cortex. These studies find that sensory input is processed in a diverse set of higher areas that are each interconnected with specific limbic and motor systems. This hierarchical and parallel organization is consistent with the multiple streams that have been found in the higher visual areas of primates. We therefore propose that the mouse visual system is a useful model to explore the circuits underlying the transformation of sensory inputs into goal-directed perceptions and actions.

Introduction

Two major goals of systems neuroscience are to understand how sensory inputs are processed to form percepts and how these percepts are integrated to guide decisions and actions. Studies of primary visual cortex (V1) have revealed some basic principles through which sensory inputs are processed to represent simple features in the external world[1–3]. However, much of the processing that is correlated with the perception of more complex features, as well as decisions and actions, seems to include areas outside of primary sensory cortex. For instance, while neurons in V1 are very effective at extracting simple features of stimuli such as the direction of motion of a drifting grating, they are not effective at extracting higher-order features. This is apparent when looking at responses of primate V1

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neurons to overlapping drifting gratings moving in orthogonal directions. When presented with this stimulus, the population of neurons in V1 respond selectively to the two directions of the component gratings; however, many neurons in higher visual areas such as the middle temporal (MT) area are selective for the summed direction of the two gratings, which is the pattern of motion that is actually perceived[4]. In addition, the activity of neurons in these higher areas is more likely to be correlated with the perceptual choices[5,6] and behavioral states of the animal[7–9]. By bringing the genetic and experimental tools of the mouse to bear on these higher areas, we hope to uncover some of the mechanisms that underlie the transformation of the component features of the visual scene into the rich perceptions of objects and patterns that are used to guide decisions and actions[10].

But is the functional organization of mouse visual cortex a good model for studying the operations of higher visual areas? In particular, an important principle for the organization of the visual system in primates has been the division of processing into separate hierarchical streams. In primates, there are two distinct anatomical and functional streams: the ventral and dorsal pathways that process specific features of a visual stimulus related to “what” and “where” it is, respectively[11]. An alternative formulation divides the two streams into “perception” and “action” pathways; this model has improved explanatory power for behavioral deficits associated with selective lesions and is consistent with the differential connectivity of the ventral and dorsal streams with limbic and motor targets, respectively[12,13]. While this sensorimotor perspective on vision is compelling, it remains speculative and the number and independence of visual streams remain a matter of debate[14–16]. Nonetheless, if we are to make progress in understanding the transformations that take place in the visual system by using the mouse as a model system, it is important to determine whether a similar hierarchical and parallel organization is present.

Mouse primary visual cortex

As in all mammals, visual input in the mouse is sent from the retina through the lateral geniculate nucleus (LGN) of the thalamus to V1. V1 neurons transform the center-surround LGN receptive fields into elongated receptive fields that are sharply tuned to multiple simple features including orientation, direction, and temporal and spatial frequency[17–24]. However, unlike in carnivores and primates, there is no apparent functional architecture for these features in mouse V1, where neighboring neurons display highly diverse receptive fields[19,25,•26].

One feature that is correlated among nearby neurons in mouse V1 is retinotopic preference. The presence of a retinotopic map in mouse V1 can be visualized with a variety of imaging approaches [19,•22,•23,27–30], and can be used to determine the boundaries of V1. By defining the boundaries of V1 and the other primary sensory areas, it is apparent that there is considerable cortical territory beyond V1, comprising the higher visual areas, that is comparatively unexplored (Figure 1A).

What lies beyond primary visual cortex

Historically, studies of the organization of higher visual areas in the rodent were dependent on cytoarchitectonics[31], electrophysiological recordings[32], or single tracer

injections[33,34]. Each approach gave a partial snapshot of the organization of the visual cortex, leading to a variety of hypotheses about the number and identity of higher visual areas[33,35,36].

A major turning point for the field came in 2007 when Wang and Burkhalter generated a comprehensive map of the visual cortex by making triple tracer injections into V1[37]. By using tangential sections to view all of the higher areas simultaneously, these triple anterograde injections revealed a constellation of nine distinct target visual areas surrounding V1. The multiple injections, strategically placed at different sites in V1, also revealed the retinotopic organization of these projections. Electrophysiology and imaging experiments replicated the anatomical maps and confirmed that these projections conferred a retinotopic organization to the target areas[•22,•23,28,37], suggesting that each area could comprise a complete representation of visual space (Figure 1B). The specific progression of the retinotopic map in each area can also be used as a fingerprint to confirm its identity and distinguish it from its neighbors. Moreover, the organization of these retinotopic mirror maps suggested homology with higher areas in primates; for example, the lateromedial (LM) area, like V2 in the primate, shares the vertical meridian with V1[38].

Functional organization of the higher visual areas

The identification of this map of the higher visual areas has paved the way for exploration of functional properties of neurons in these areas. Most experiments thus far have probed neurons in the higher visual areas with the same simple drifting gratings that effectively drive neurons in V1. While these stimuli may not be ideal for driving the higher visual areas, they have the advantage of allowing direct comparison with the properties of V1 neurons and precise measurement of tuning features that have classically distinguished the dorsal and ventral pathways such as spatial and temporal frequency. Each of the higher visual areas has distinct preferences for these features[•22–•24,29]. For instance, neurons in anterolateral area (AL) are preferentially driven by stimuli at high temporal and low spatial frequencies while neurons in posteromedial area (PM) are driven by stimuli at low temporal and high spatial frequencies. In fact, each area has specific preferences that comprise a subset of the range present in V1, suggesting that each is specialized to perform a distinct role in processing of the visual scene[•22,•23]. Along with this increase in specialization, receptive fields in mouse V1 also increase in size as one travels up the visual hierarchy[37].

How might these hierarchical transformations in receptive fields occur? One suggestion comes from the functional characterization of the axonal projections from V1 to the higher visual areas. This study found that the function of the population of neurons projecting to each area was matched to the function of its target area[••26]. These projections likely contribute to the increase in specialization seen in the higher visual areas; however, other subcortical sources of input, and/or local computations, may also shape the generation of these receptive fields. The convergence of spatially distributed V1 neurons preferring the same spatial and temporal frequencies onto each area may contribute to the observed increase in receptive field size. In addition, this enlargement may be due to area-specific differences in local circuits that define the inhibitory surround[39].

The existence of functional streams

The connections between the higher visual areas and their downstream targets can also give clues to the functional organization of the network. From the first in a series of tracer studies[••40], LM for instance was found to send projections to putative ventral visual areas, such as laterointermediate (LI) and postrhinal (POR) and posterior (P), as well as to putative dorsal visual areas, such as AL, PM and anteromedial (AM). Thus, LM may be involved in both processing streams, similar to V2 in carnivores and primates[14]. However, like ventral areas, LM also sends projections to limbic areas such as the lateral entorhinal cortex and the amygdala, in addition to the superficial, sensory-related layers of the superior colliculus, suggesting that it is mainly part of the ventral stream[••40–42]. In contrast, AL has strong connections with the prefrontal and motor cortex, and the deeper, motor-related layers of the superior colliculus as well as putative dorsal stream areas such as rostromedial (RL) and anterior (A)[••40–42].

In a technical and theoretical tour de force, these findings were confirmed and extended by Wang, Sporns and Burkhalter, who exhaustively labeled each of the 10 visual cortical areas and performed a quantitative network analysis of their projection targets [••43]. In all, 30 cortical targets were identified, in addition to the ten visual areas, each of which could be assigned to the dorsal or ventral streams according to their relative contribution to motor and limbic processing, respectively. All ten visual cortical areas sent projections to the other nine, but quantitative analysis of the connection strengths showed that they could be segregated into two groups that were more densely connected within group than across groups (Figure 1C).

Even more strikingly, the two groups of retinotopically organized visual cortical areas (with the exception of V1) could be strongly segregated by their connections to 30 nonvisual areas. LM, LI, P and POR projected to the ventral stream; AL, PM, RL, AM and A to the dorsal stream. The ventral targets included hippocampus, olfactory cortex, insular gustatory/visceral cortex, the parahippocampal areas, and the auditory areas. The dorsal targets included retrosplenial cortex, the somatosensory and motor areas, and the prefrontal areas. Thus, although the mouse visual cortical areas are fewer in number, smaller, and less hierarchically organized than those in the primate, their interconnections and projections follow rules that clearly demonstrate homologous dorsal and ventral streams.

Moreover, when approached from a functional perspective, the areas fall into categories consistent with an “action guidance/object recognition” dichotomy. For instance, most neurons in AL prefer fast speeds such as those that might be encountered from optic flow during locomotion while area A may be important for visual input related to self-motion as it is necessary for decision-making during navigation[44]. The preferences of neurons in PM for slow speeds and the peripheral field of view are appropriate for tracking and orienting towards slowly moving objects. Indeed, psychophysical data and lesion studies suggest a role for PM in optomotor learning[45,46]. Thus, despite having distinct preferences for visual stimuli, areas AL and PM are both well-suited to the action-oriented dorsal stream [•22,••43]. Conversely, consistent with their role in the ventral stream, lesions to LM and

POR in rodents disrupt the identification and assignment of affective value to objects[47–49].

So far, however, spatiotemporal analyses of receptive fields have found as many differences within each stream -- for instance the speed preferences between AL and PM[22,23] -- as between streams[23]. Compared to the striking differences found between dorsal and ventral receptive fields found in the primate[14], studies of receptive fields in the higher visual areas of the mouse are still in their infancy, having concentrated on simple spatiotemporal stimuli. Although new techniques can accelerate the study of many aspects of mouse vision, investigating the functional differences between areas will require the design of appropriate visual stimuli and development of visually guided tasks for the rodent.

Limitations of anatomical approaches

Efforts to classify the overall density of synaptic connections of projections from one area to another remain a dominant approach for investigating the interconnectivity and potential function of streams in primates, carnivores and rodents[37,43,50]. However, these diagrams of net strength of input to a given area may not accurately predict the function of neurons in the target area. This is because the physiology and functional preferences of a projection neuron cannot be directly inferred from the anatomy. First, the strength of projections to an area depends not only on the number of synapses but on the strength of each synapse. For instance, glutamatergic projections can activate a variety of ionotropic and metabotropic receptors that have differing effects on the postsynaptic neurons[51]. In addition, the glutamatergic projections from V1 recruit local inhibitory neurons within the higher visual areas[52]; the balance of excitation and inhibition will therefore depend on a variety of factors that may differ across areas. Some subset of these projections could be net inhibitory and thus mediate competition between streams.

More importantly, the function of a projection does not necessarily constitute a random sampling of the functional properties in the source area[26]. Thus, without determining the functional content of a projection, we cannot predict its activity during vision. For instance, while the density of the projection from V1 to LM is higher than the projections to AL or PM, this does not mean that the impact of V1 on LM is stronger for all types of visual stimuli. Instead, the density of the projection may reflect the diversity of information being transmitted (e.g. high diversity projection to LM and low diversity to AL and PM (Figure 1D)). Thus, in order to disentangle the function of these cortical sensory pathways, future experiments will need to determine both the sensory information that is carried by each anatomical projection as well as its physiological impact on its target area during vision. The mouse visual system, bolstered by a growing set of genetic tools and the interareal roadmap delineated thus far, should help make these experiments possible.

Conclusion

Initial explorations of the mouse visual cortex suggest that it does have a parallel and hierarchical organization similar to primates and carnivores. There are clearly important differences, and direct homologies between areas are difficult to find. One clear difference is

that mice have fewer and comparatively primitive higher visual areas. The ventral stream appears particularly impoverished[53]; perhaps mice with more enriched environments, or those that are required to do visual discrimination tasks for their livelihood, might have more developed ventral areas.

Alternatively, the areal cortical organization of the mouse brain might simply be constrained by its small size[54,55]. Another consequence of the small size of the mouse brain is that some of the higher visual areas abut other primary sensory areas such as auditory (A1) and somatosensory (S1) cortex[37]. In fact, RL and A have robust projections to S1 while LI, P and POR project to A1[43,56]. Conversely, the higher visual areas receive sensory input from these other modalities as well[57](N. Jikomes and MA, *personal communication*), supporting multisensory integration at a comparatively early stage in cortical processing. One possibility is that these sensory systems are simply feeding into affective and motor pathways, decreasing the redundancy of the network[58,59].

The compactness of the mouse visual system also means that sensory processing, decision-making and motor outputs must occur within only a few synapses from each other. Interestingly, those output areas, such as the colliculus, motor cortex, prefrontal cortex, and amygdala, are the same output structures as in the primate. Thus, the compact nature of the mouse visual cortex could actually be an advantage, allowing the study of a simplified sensorimotor loop that retains its homology to the primate system. Thus, studying the networks of higher visual areas in mice should give us a better idea of the cellular and circuit mechanisms that underlie the generation of perceptions, decisions and actions.

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Highlights

We review recent anatomical and physiological findings about mouse visual cortex.

Vision is processed in multiple cortical areas

Visual cortical areas are interconnected with specific limbic and motor areas.

The mouse visual system is a useful model for exploring networks of cortical areas

Figure 1. Anatomical and functional organization of mouse visual cortex

A. Fluorescent images from a mouse expressing td-Tomato in parvalbumin positive interneurons (*PV-cre:Ai9* mice) from a flatmount *ex vivo* section (left) or through an *in vivo* chronic cranial window (right). Td-Tomato expression highlights primary sensory areas (V1- primary visual cortex; S1- primary somatosensory cortex; A1- primary auditory cortex). **B.** Anterograde labeling of V1 projection neurons via fluorescently conjugated dextran injections reveal retinotopically organized arborizations within the higher visual areas. Adapted with permission from Wang and Burkhalter, 2007. **C.** Connectivity matrix between V1 and nine higher visual areas. Thickness of lines represents the average reciprocal connectivity between areas as measured by the density of axonal projections. Areas are divided into two functional modules: ventral (m1, red) and dorsal (m2, blue). Adapted with permission from Wang, Sporns and Burkhalter, 2012. **D.** Projections from the same region within V1 to the higher visual areas carry distinct visual information; namely, projections to AL prefer stimuli moving at fast (red) speeds while those to PM prefer slow (blue) speeds. LM receives comparatively diverse input from V1; this could explain the increased anatomical density of this projection.