Exploring the Next Frontier of Mouse Vision

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Two studies in this issue of Neuron apply in vivo functional imaging techniques to map out and record from mouse extrastriate visual cortex. They find that distinct areas show hallmarks of processing for different types of visual input and provide a promising path forward to investigate how complex image analysis is performed in the mouse visual system.

An incredible amount of computation goes on between light hitting the eye and our interpretation of what we see around us. This process starts at the photoreceptors, where photons are transduced into neural activity that travels through a series of brain regions, each extracting increasingly refined features, such as the selectivity of primary visual cortex (V1) for edges at specific orientations. These computations reach their culmination in the collection of visual cortical areas beyond V1, known collectively as “extrastriate” cortex, where neurons encode high-order visual features such as objects, faces, motion, and foreground/background separation (Orban, 2008).

In primates, the multiple extrastriate regions are often interpreted as creating a hierarchy with two main pathways: the ventrally located “what is it?” stream and the dorsally located “where is it?” stream (Figure 1A). (Felleman and Van Essen, 1991; Ungerleider and Mishkin, 1982). Neurons in ventral/“what” areas can have specific responses to particular objects, such as a face, in a manner that is invariant to position or viewing angle. In contrast, neurons in the dorsal/“where” areas process motion and represent location of objects or textures, irrespective of their identity. These pathways have also been defined in terms of a perception/action dichotomy—e.g., recognizing an object versus reaching toward it (Goodale and Milner, 1992). Although the two stream model is certainly a simplification, it is clear that extrastriate cortex utilizes specialized pathways to integrate the low-level features encoded in V1 and parse out different aspects of the visual scene (Nassi and Callaway, 2009). Since many of these tasks, such as face recognition and image segmentation, are still challenging for computer algorithms, there is great interest in investigating how the brain implements these high-level computations.

Recently, the mouse has emerged as a powerful model system for studying vision. A primary drive behind this is the development of a wide array of genetic tools to both analyze connectivity and control activity in neural circuits (Luo et al., 2008), along with the experimental accessibility for recording and manipulation relative to human and nonhuman primates. On the other hand, the fact that the mouse is a nocturnal species with relatively low acuity raises the possibility that its visual system could be missing important aspects of vision studied in primates. However, a number of recent studies, from the retina up to V1, have demonstrated that most, though not all, basic properties of visual function are present in the mouse (Huberman and Niell, 2011). These observations open the door to using the new genetic tools available in mouse to address fundamental questions about how neural circuits process visual information.

Until now, primary visual cortex has been the farthest station along the visual pathway to be intensively studied in the mouse at the level of individual neurons. In this issue of Neuron, two groups report initial forays into mouse extrastriate cortex (Andermann et al., 2011; Marshel et al., 2011), armed with novel optical methods that allow them to identify and record from the various cortical areas. The two studies are complementary in many ways. Marshel et al. provide a detailed functional map of the layout of nine extrastriate areas in the anesthetized mouse and show that among a subset of six of these, each region has a unique signature of spatiotemporal tuning. On the other hand, Andermann et al. studied awake mice and concentrated more closely on two particular regions suggested to be part of the dorsal stream, finding that each is differently specialized for motion processing.

A tantalizing glimpse of this uncharted territory beyond V1 had previously been provided by mapping and anatomical studies from Andreas Burkhalter and colleagues (Wang and Burkhalter, 2007; Wang et al., 2011). These studies demonstrated that the region around V1 contains a number of cortical areas each encompassing its own mapped representation of visual space (Figure 1B), much as seen in monkeys and humans. Furthermore, the connectivity of these regions suggested a homology with the dorsal and ventral pathways in the primate cortex. In contrast to primates, where visual cortex spans centimeters, the entirety of extrastriate cortex in the mouse spans less than five millimeters, with some areas only a few hundred microns across. While this creates some challenge in targeting the regions for recordings, it also raises the exciting possibility of simultaneously recording from a substantial fraction of the cells performing a high-level visual function, such as invariant object recognition.

In navigating this territory, both groups used an elegant combination of large-field imaging to identify cortical areas on a broad scale, followed by zooming in to record the individual visual response properties of populations of neurons within a region (Figure 2). Visual cortical areas can be defined by the presence of a distinct representation of visual space, known as a retinotopic map. Both groups...
Two-photon calcium imaging allows the mapping of extrastriate visual areas, as proposed by Burkhalter and colleagues (Wang and Burkhalter, 2007), thereby allowing them to probe the mouse's entire visual stimulus presentation system that was able to measure complete retinotopic maps in even the smallest areas with far greater precision than before. This mapping confirmed the layout shown in Figure 1A, with emphasis on putative gateway areas LM and AL. Adapted with permission from Wang and Burkhalter (2007).

To generate a more complete map of the extrastriate areas, Marshel et al. performed this initial mapping using intrinsic signal imaging, measuring either changes in intrinsic signal imaging, measuring either changes in reflectance due to the hemodynamic response or changes in autofluorescence due to metabolism, both dependent on neural activity. This allows responses to be mapped much like fMRI, but at much higher spatial resolution, and had previously been used to identify four visual area around V1 (Kalatrick and Stryker, 2003).

To generate a more complete map of the extrastriate areas, Marshel et al. followed this initial intrinsic signal imaging with a second mapping using fluorescence calcium imaging. In their method, several localized injections were used to load the cortex with the fluorescent calcium indicator OGB-1 (Stosiek et al., 2003), which increases its fluorescence with the calcium influx that accompanies action potentials. Using low-magnification two-photon imaging, along with a visual stimulus presentation system that allowed them to probe the mouse’s entire field of view in spherical coordinates, they were able to measure complete retinotopic maps in even the smallest areas with far greater precision than before. This mapping confirmed the layout proposed by Burkhalter and colleagues (Wang and Burkhalter, 2007), thereby resolving uncertainty over the definition and organization of the extrastriate areas.

Based upon this identification, Marshel et al. targeted each region for further study at single-cell resolution (Figure 2). Two-photon calcium imaging allows the study of a number of cells simultaneously in a field of view, by delivering visual stimuli and extracting the fluorescence trace from individual neurons to deduce their functional properties (Ohki et al., 2005). They presented drifting sinusoidal gratings in order to measure a number of basic response parameters, including orientation and direction selectivity, and spatial and temporal frequency tuning. A careful statistical analysis of these responses demonstrated that the repertoire of tuning properties in each area provides a unique signature that can be used to distinguish them from one another. This makes it unlikely that some of these areas are duplications, or that they simply represent multiple visual maps within a single area. But within this diversity there were also some intriguing similarities. Nearly all extrastriate areas seemed to increase orientation selectivity relative to V1, as well as responding to higher temporal frequencies. There was also one subset of areas responded to lower spatial frequencies but with increased direction selectivity, suggesting motion processing as expected for the dorsal stream.

The report from Andermann et al., rather than surveying a large number of extrastriate areas, focuses in on comparing two potential dorsal regions relative to V1. They also took advantage of a GFP-based genetically encoded calcium indicator, GCaMP3 (Tian et al., 2009). By using a virus to express GCaMP3 in cortex, they were able to image over multiple sessions in awake, rather than anesthetized, mice. Although GCaMP3 is not as sensitive to single action potentials (Tian et al., 2009), this technique should prove extremely powerful in the future, particularly with the continual improvements in genetically encoded calcium indicators and the potential for studying individual neurons longitudinally.

After a coarse mapping to find the relevant locations, Andermann et al. largely concentrated on two areas (Figure 1B)—AL, which was proposed to be the “gateway” into the dorsal stream (Wang et al., 2011), and PM, which also receives a strong direct input from V1 and was also a candidate dorsal region, although this assignment is less clear. Using similar drifting sinusoidal gratings to Marshall et al., they found a striking dichotomy between these two areas: AL was responsive to low spatial frequencies and high temporal frequencies—large features moving fast—while PM was responsive to high spatial frequencies and low temporal frequencies—fine detail moving slowly. The first property is suggestive of optic flow, the movement of objects and landmarks across the visual field as one moves through the environment, and the authors note that the very high speeds these neurons responded to could correspond to the stimuli seen by a running mouse. The responses of the second area, PM, are more indicative of an object recognition area, except that their analysis revealed a further specialization for motion processing: as spatial frequency was varied, the preferred temporal frequency changed in a manner to keep the preferred speed constant. This form of speed tuning was relatively uncommon in V1, suggesting that it is a new feature being
In the cortical areas that were studied by both groups, there were some significant inconsistencies. Marshel et al. found that both orientation selectivity and direction selectivity increased in most extrastriate areas relative to V1, while Andermann et al. found little change in orientation selectivity and in fact a decrease in direction selectivity, outside of V1. Andermann et al. also found much higher temporal frequency preferences, including V1. Some of these probably represent true divergence between the anesthetized versus awake cortex, although they could also be experimental differences resulting from the specific stimulus sets used to probe selectivity, different sensitivities of the calcium indicators which could distort tuning curves, or differences in the populations of neurons being sampled in each area.

In fact, while Marshel et al. could evoke detectable responses from about half the neurons in V1, though dropping as low as 16% in one extrastriate area, Andermann et al. measured responses in only about 10% of neurons across areas. Because the relatively low fraction of cells activated in both studies could be biased to specific subsets of neurons, it is difficult to compare the results or to extrapolate the data to be representative of the entire population in any area.

What do these studies together tell us about the functional organization of mouse extrastriate cortex in terms of processing pathways? The dorsal areas studied by each group are quite consistent with the predictions for motion processing. However, because the tuning properties of AL and PM were largely nonoverlapping, it seems unlikely that AL could be providing the major input into PM, as would be predicted for a single dorsal pathway with AL as the gateway (Wang et al., 2011). Furthermore, based on anatomy, mouse V1 neurons project directly to most of the extrastriate visual areas (Wang and Burkhalter, 2007), rather than the multiple sequential stages as in primate cortex. Thus, it may be that in mouse the dorsal stream splits into independent branches sooner than the extended hierarchical organization of primates.

Results on putative ventral stream areas were less conclusive. Both groups studied LM, the proposed gateway to the ventral stream (Wang et al., 2011), but either found it similar to V1 or more like the dorsal areas. The other putative ventral region studied by Marshel et al. (LI) showed high spatial frequency preference, but no other specialization for processing shape or form. It is clear that further studies of these areas will be needed to make any definitive statement about their homology to the primate ventral areas.

The two reports clearly demonstrate that the various extrastriate areas are differentiated from each other, suggesting specialization for certain computations. The task ahead now is to determine exactly what these computations are for each area—what are the novel features being extracted from the visual scene? While the sinusoidal gratings used in both studies are an excellent starting point to characterize the diversity across areas, and provide constraints on the types of computation being implemented, future studies can now begin investigating each area individually with specific stimuli, and ideally behaviors, to determine the precise visual processing they are performing.

Will there be a mouse equivalent of primate extrastriate areas such as MT or IT, in line with the conserved aspects of visual processing seen previously? Or will the commonalities break down in extrastriate cortex? It is possible that either the mouse will lack the sophisticated invariant forms of processing supported by high acuity in primates, or that the higher visual areas might simply be specialized for different tasks that are more appropriate for the mouse’s
A Role for Phasic Dopamine Neuron Firing in Habit Learning

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In this issue of Neuron, Wang et al. (2011) show that mice with dopamine neuron-specific NMDAR1 deletion have attenuated phasic dopamine neuron firing and a deficit in habit learning. These findings indicate that brain regions sensitive to phasic dopamine signals may underlie habit learning.

Dopamine (DA) neurons of the midbrain usually fire spontaneously at low rates, a firing mode that is called “tonic.” Occasionally, DA neurons fire extra spikes in brief episodes referred to as “phasic” or “burst” firing. Phasic firing is caused by events of motivational significance, such as unexpected primary rewards, and stimuli that predict reward over successive stages of a learning task (Ljungberg et al., 1992). Although DA neurons are sometimes activated by aversive stimuli, the majority of DA neurons are inhibited by these stimuli (Ungless et al., 2004). In theoretical work, DA neuron firing activity has been modeled as a reward prediction error signal, for example, in the temporal difference (TD) learning framework (Montague et al., 1996). In TD learning, the dopamine neuron firing activity plays the role of a teaching signal, improving subsequent predictions by strengthening the appropriate synapses. However, although such work offers attractive explanations for observed DA cell activity, which correlates with the predictions of the models, it is important to go beyond correlation and experimentally investigate the causal role of phasic bursts of DA neurons in animal learning.

Previous studies have shown that excitatory drive required for burst firing of DA neurons is mediated by NMDA receptors (Tepper and Lee, 2007). In order to investigate the role of NMDAR-mediated phasic DA activity in behavioral learning, Wang et al. (2011) generated dopamine-neuron-specific NMDAR1 knockout (DAT-NR1-KO) mice. Wang et al. (2011) show that compared with control DA neurons, phasic firing activity was, as expected, greatly reduced in DA neurons of DAT-NR1-KO mice. On the other hand, no difference between controls and DAT-NR1-KO mice was observed in the tonic firing rate. Thus, by using these mice it should be possible to assess which behavioral functions require the phasic firing of dopamine neurons.

Even in the simplest tasks, we expect that reduced phasic firing of DA neurons would have a profound effect, because dopamine is central in many aspects of learning and behavior. For example, in TD models, DA neurons encode a reward-prediction error. If that is correct, then reduction of the phasic bursts in DA neurons might be expected to disrupt, or at least slow down, learning of conditioned responses. Contrary to this...