What can mice tell us about how vision works?

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Understanding the neural basis of visual perception is a long-standing fundamental goal of neuroscience. Historically, most vision studies were carried out on humans, macaques and cats. Over the past 5 years, however, a growing number of researchers have begun using mice to parse the mechanisms underlying visual processing; the rationale is that, despite having relatively poor acuity, mice are unmatched in terms of the variety and sophistication of tools available to label, monitor and manipulate specific cell types and circuits. In this review, we discuss recent advances in understanding the mouse visual system at the anatomical, receptive field and perceptual level, focusing on the opportunities and constraints those features provide toward the goal of understanding how vision works.

Studying vision in mice: the blind leading the blind?

Understanding how the brain gives rise to the experience of sight is an important and fundamental question that has garnered much attention over the years [1]. The long-standing emphasis stems from the fact that many mammals, including humans, rely on vision as their primary sense to evaluate their surroundings and guide their behavior. For more than a century, animal studies of visual system structure and function relied primarily on cats and non-human primates, such as macaques. The rationale for using those species is clear: they have large eyes, high visual acuity and their central visual pathways display many of the same features found in humans, such as well-segregated parallel pathways in the visual thalamus, and ocular dominance and orientation columns in the visual cortex [2]. Macaques also have a fovea and three cone photopigments, so they can be used to probe the neural basis of high acuity trichromatic color vision [3]. Moreover, macaques can be trained to engage in psychophysical tasks where they 'report' to the researcher what they observe [4].

Given the clear advantages of the macaque model, why would anyone opt to study vision in the mouse? After all, mice view the world at extremely low resolution [5], with the equivalent of 20/2000 vision. Moreover, the eyes and visual pathways of mice are one to two orders of magnitude smaller than in cats or primates [6], which creates substantial challenges for performing targeted recordings, and for tracing and lesioning specific neural pathways using conventional approaches.

The obvious, often-stated reason for using mice is 'genetics'. More precisely, mice allow unparalleled opportunities to study defined categories of cells and circuits. As discussed in Box 1, modern genetic tools provide the opportunity to see the structure of a defined visual cell type, map its connections, record its activity in response to visual stimulation and then selectively silence or activate that cell type in a reversible manner [7,8]. In theory, this arsenal of tools should allow one causally to link defined categories of visually driven cells with different aspects of vision and, in doing so, unify anatomy, physiology and perception.

There are also practical reasons for using mice. First, the past 5 years have seen a shift toward the widespread availability of transgenic mice, such as Cre-expressor lines, as well as molecular tools for *in vivo* circuit labeling and manipulation (e.g. viral transfection agents). Large-scale mouse consortiums and well-organized online catalogs currently enable any lab in the world to use molecular genetics to address important questions about brain circuitry and function. A second reason is that the smaller overall size of the mouse nervous system can be used to gather data over a large spatial scale; for instance, the total area of the mouse primary and extrastriate visual cortex spans only several millimeters across the cortical surface [9], potentially allowing the entire system to be visualized simultaneously. A third, and less obvious (but nonetheless influential) reason why many labs are now using mice to study vision is that mice are safer, simpler and less expensive to maintain than are cats or primates.

Despite all of these advantages, the goal is to understand how vision works, not to make life easy. Therefore, it is essential to know what the mouse visual system comprises and is capable of, and to consider carefully how that shapes the questions one can expect to answer about visual processing using this species.

The hardware and software of the mouse visual system

Recent years have shown a surge in the number of studies aimed at parsing the basic structure and function of mouse central visual pathways. Although that effort is far from complete, these studies generally support the argument that the mouse visual system is much more sophisticated than previously thought. Furthermore, it is proving to be a valuable model for addressing several fundamental questions about visual processing. Here, we review what is currently known about the architecture of mouse visual

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Box 1. Genetic tools for circuit analysis in the mouse visual system

Mice allow unparalleled opportunities to label, monitor and manipulate defined cell types and neural circuits. Combinatorial systems for gene expression, such as Cre–lox and the tetO–tTA systems, form the basis of many of the genetic tools thus far developed. In the Cre–lox system, Cre recombinase is expressed in the cells of interest, generally by a transgenic line with a cell-type specific promoter. Second, reporter and/or effector genes can be turned on specifically in the cells that express Cre, using appropriate regulatory sequences based on lox recombination sites. These reporter and/or effector genes can include: (i) fluorescent proteins to visualize specific neuron classes [94]; (ii) trans-synaptic tracers [95,96] to label connected cells; and (iii) optogenetic [97] or pharmacogenetic [98] tools to manipulate neuronal activity. Reporter and/or effector genes can be expressed either in transgenic lines or via local injection of appropriate viruses into brain regions of interest.

The modular Cre system means that once a mouse line expressing Cre in a cell-type of interest is available, then anatomical identifica-tion, targeted recording, circuit tracing, and disruption of neuronal activity can all be achieved by either crossing the Cre mouse line to the appropriate effector mouse line or by injecting the appropriate Cre-dependent virus. Furthermore, because the Cre line clearly defines a cell population, rare neuronal subtypes that would otherwise be difficult to target can be systematically studied. Moreover, such results can be directly compared between labs without the ambiguity of traditional neuronal classification schemes. Although it remains to be seen how well such genetically defined populations align with physiological functional classes in the thalamus and cortex, such an approach has already proven to be effective in identifying specific subpopulations of DSGCs in the retina (eg. [33,36,37]; Figure I). Genetic ablation of melanopsin ipRGCs in the mouse has also recently been performed [99] and has proven valuable in addressing their specific contributions to visual processing.
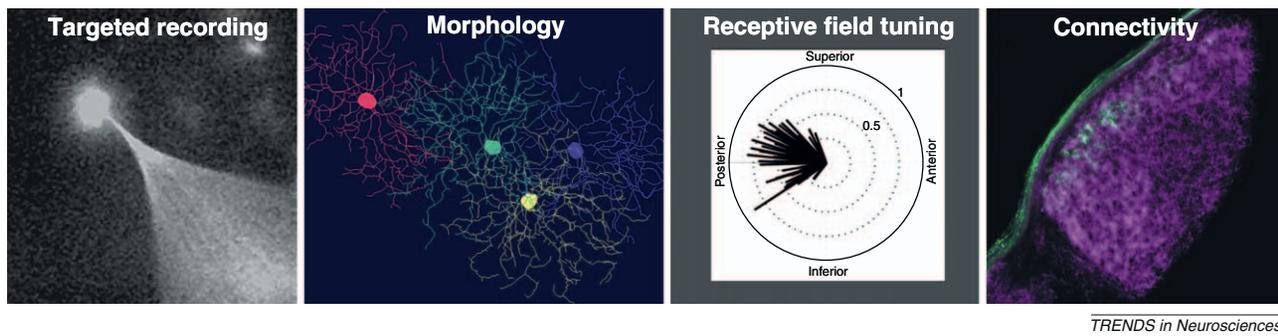
Figure I. Cellular and physiological characterization of genetically identified retinal ganglion cell (RGC) subtypes in mice. Populations of On–Off direction-selective RGCs (DSGCs) can be genetically identified using transgenic mouse lines that express fluorescent markers (such as GFP) under the control of specific promoters. The GFP-expressing cells can be targeted for electrophysiological recordings and/or filling with dye. When one or several of the GFP-expressing cells are filled with dye, their morphology and geometric relationship to one another can then be assessed. Their receptive field tuning to specific light stimuli [in this case stimuli moving along different axes of the retina: superior (up), inferior (down), anterior (toward nasal retina) or posterior (toward temporal retina)] can also be determined. The cells shown here are all tuned for posterior motion. These parameters can then be matched to the axonal connectivity of the GFP-expressing cells. The example shown here depicts GFP-expressing axons from posterior tuned On–Off DSGCs within the visual thalamus. All RGC axons are labeled in magenta. Image of targeted recording provided by Mihai Manu and Steven Baccus; remaining panels reproduced, with permission, from [36].

circuits and the types of information processing they per-form, using the long-standing categories of retina, retino-geniculo-striate and retino-collicular pathways as a gener-al framework for thinking about the mechanisms that shape visual perception and behavior. Although there is a tradition of using the mouse visual system for studies of neural development and plasticity [10,11], here we focus on the potential of the mouse as a model for probing visual processing *per se*.

Retina

The photoreceptor mosaic places a fundamental limit on visual information

Just as the charged-coupled device (CCD) in a digital camera converts incoming photons into electrical signals, the retinal photoreceptor mosaic generates neural signals that represent the image reaching the eye. Thus, whereas the attributes of the pixels in a digital camera (i.e. the number of pixels, color coding properties, etc.) determine the quality of the photos a camera takes, the attributes of retinal photoreceptors constrain every aspect of what the brain learns about the visual scene.

The mouse retina is rod dominated [12] and thereby specialized for vision under low light (scotopic) conditions. Approximately 3% of mouse photoreceptors are cones and these express one or a combination of two photopigments:

one sensitive to short wavelengths of light [centered at 360 nm (ultraviolet; UV)] and one sensitive to medium wavelengths of light [centered at 511 nm (green)] [13]. These are distinct from the third photopigment, melanopsin [14], which is expressed by a subset of retinal ganglion cells (discussed below). Because mice lack the long wavelength 'red' cone photopigment found in many primates, mice (similar to cats) are dichromats and cannot discriminate red from green hues. The distribution of rods across the mouse retina is relatively uniform, whereas the cones exhibit marked regional variation; UV-dominant cones, some of which coexpress medium wavelength sensitive opsins (M-opsins), are enriched in the ventral retina [15,16].

Owing to the overall difference in the size of their eyes, the total number of photoreceptors (rods and cones) in mouse retina is dwarfed in comparison to primates. Per unit area of retina, however, the mouse retina has more photoreceptors than does that of the macaque [12,17,18]. Why then is primate vision so much sharper than mouse vision? First, because the eye of a mouse is much smaller than that of a primate, there are fewer photoreceptors spanning a given area of the visual scene. Second, in primates, 99% of cones reside in the fovea, a specialized region that occupies approximately 1% of the retinal area [19]. The fovea is used for high-contrast, high-acuity tasks, such as reading or detecting small objects at a distance. By

contrast, peripheral vision is low acuity and allows one to detect either large objects at a distance or small objects at closer range, especially objects that are moving. The mouse does not have a fovea and, therefore, its entire retina is similar to the peripheral retina of primate; indeed, cone density in the mouse retina (per mm^2) is similar to that found in the primate eye at approximately 3 mm away from the fovea [12]. Thus, an understanding of the mouse photoreceptor mosaic demonstrates that it is highly efficient at sampling the visual scene, given the constraints of a small eye. Furthermore, it indicates that the mouse might be a promising model for studies of low-acuity, peripheral vision, in addition to studies of rod-dependent night vision.

In theory, mice could be used to study certain aspects of trichromatic foveal vision, but that would require, at a minimum, transgenic manipulations of the mouse photoreceptor mosaic. Interestingly, a third long wavelength sensitive photopigment (i.e. a red cone photopigment) was recently genetically inserted into mice [20]. Remarkably, that single manipulation proved sufficient to enable red-green colors to be discriminated by the transgenic mice. Such a finding underscores the extent to which the photoreceptors are the major bottleneck for visual perception. Moreover, it indicates that the rest of the mouse visual system is equipped to process sophisticated combinations of visual information, even though that information is not normally extracted from the world.

Retinal ganglion cells encode diverse and often sophisticated features of the visual world

After photoreceptors convert light into electrical impulses, that information is filtered by the three major classes of retinal interneuron: the horizontal, bipolar and amacrine cells, each of which includes 1–40 types (1–2 horizontal; 10–15 bipolar; and 40 amacrine cell types) [21]. All of the major retinal interneuron types found in primates are also present in the mouse. These interneurons filter and transmit visual information to the retinal ganglion cells (RGCs), which in turn, project to greater than 20 central brain regions. Thus, all the information about the visual world that the brain receives is encoded in the spiking activity of RGCs.

The classic textbook description of RGCs consists of three major types, all with center-surround organization [1] In carnivores, these subtypes are commonly known as X (or beta), Y (or alpha) and W (gamma) RGCs; in monkeys, they are called midget, parasol and koniocellular RGCs, respectively [2,22]. In reality, the number of RGC types (often referred to as subtypes) is far more complex, with more than 20 RGC subtypes having been described across species [23]. Also, the information encoded by an individual RGC subtype is often much more sophisticated than just center surround; for example, salamander and rabbit RGCs have been shown to code for specific directions of motion, edges and object versus background motion [24–26]. In addition, a surprising discovery during the past decade is the existence of RGCs that express the photopigment melanopsin. This enables them to transduce photons directly, independently of photoreceptors [14,27]. These intrinsically photosensitive RGCs (ipRGCs) have been found in many species, including mice, macaques and humans [27–29].

Recently, several groups used sophisticated anatomical and genetic techniques to label and record from defined subtypes of mouse RGCs. The main conclusion of these studies is that mouse RGCs are highly diverse, encompassing at least 22 anatomically distinct subtypes [30] (Figure 1). In addition to having three subtypes of alpha Y-like RGCs and four to five subtypes of melanopsin ipRGCs, the mouse retina harbors eight or more different subtypes of direction-selective RGCs (DSGCs) [31–37]. DSGCs are particularly numerous in mouse retina, and current estimates indicate they comprise at least half of the total number of RGCs [12,33]. Furthermore, one study observed that some mouse RGCs are sensitive to approaching or 'looming' stimuli [38], suggesting that other complex feature-detecting RGCs will be found in the near future.

In considering whether the mouse is a generalizable model for studying vision, an important issue to resolve is how the 22 RGC subtypes found in the mouse correspond to the 20 subtypes in the primate. The recent identification of RGC subtype-specific genes and immunohistochemical markers in the mouse [31–37] will allow this question to be further addressed in primates, including humans. Indeed, studies of mouse ipRGCs helped generate tools that were applied to probe for, and confirm the existence of, the same cells in primate retina [29,32,39]. It will be interesting to see whether such tools also help reveal the presence of DSGCs in primates. In the meantime, it remains to be determined whether the preponderance of DSGCs in the mouse retina makes it more attractive, or less ideal, as a model of primate vision.

Mouse visual thalamus is positioned to relay complex information to the cortex

Mammalian RGCs project to more than 20 subcortical targets [40], including the dorsal lateral geniculate nucleus (dLGN) of the thalamus, which sends information to the cortex, and several other regions that mediate behaviors ranging from reflexive eye movements to pupil dilation. Of the 24 subcortical visual areas, by far the most experimental attention has focused on the dLGN, because of its role in processing and relaying visual information to the cortex for conscious visual perception (Figure 1). However, to date, there has been only one dedicated quantitative survey of dLGN receptive fields in the mouse [41]. This study confirmed the presence of neurons with classical On and Off center-surround receptive fields, transient and sustained responses, and sizes similar to those measured in mouse RGCs. Neurons in the mouse dLGN also have both burst and tonic modes of firing [42,43]. Thus, aside from an apparent lack of 'frequency-doubling' Y-like cells, the physiological accounts of mouse dLGN neurons indicate that they have the same basic properties as the dLGN of cats or primates.

Recent genetic–anatomical tracing studies revealed that the mouse dLGN might be even more sophisticated than previously thought. These studies demonstrated that both alpha (Y-like) RGCs as well as different subtypes of On–Off DSGCs project to the dLGN [31–37]. Moreover, the different functional categories of RGCs connect to dLGN neurons in a series of parallel spatially distinct layers, and appear to include dedicated 'direction-selective' territories
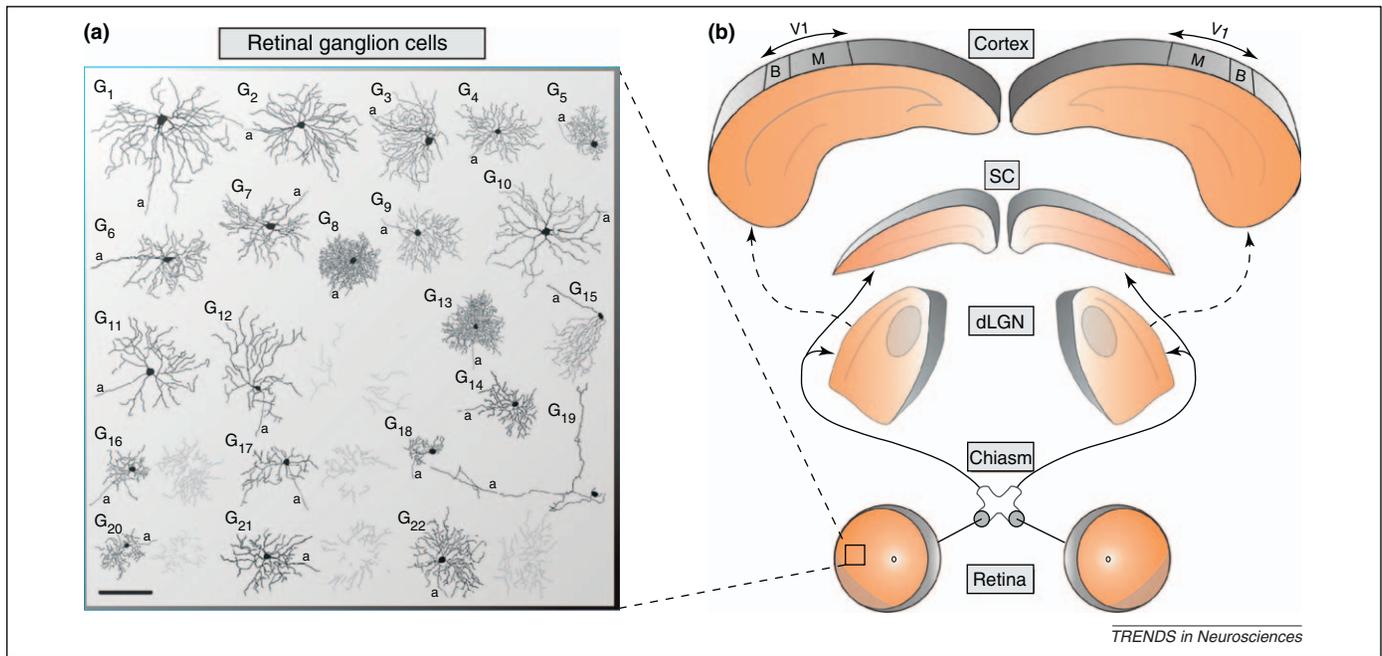
Figure 1. Basic architecture of mouse retinal ganglion cells (RGCs) and visual pathways. **(a)** Mouse RGCs include 22 anatomically distinct subtypes, termed 'G1–G22' [30]. Representative examples of reconstructions of RGCs in each category (based on dye injections) are shown. Dark lines depict the somas and dendritic arbors of each cell. Lighter gray lines indicate dendritic arbors in deeper layers of the inner retina. Each patch of retina includes some, or all, of these 22 subtypes and all of these extend axons into the brain. **(b)** Schematic diagram of the mouse visual pathways described here, showing direct retinal projections (solid arrows) to the dorsal lateral geniculate nucleus (dLGN) and to the superior colliculus (SC) as well as geniculo-cortical pathways from the dLGN to visual cortex (dashed arrows). For simplicity, most of the 20-plus subcortical visual targets are not shown. Shaded portions of the retinas indicate the location of RGCs whose axons do not cross at the optic chiasm and instead project ipsilaterally. Ovals in the dLGN correspond to the termination zones of the ipsilateral-projecting RGC axons. The binocular ('B') and monocular ('M') fields in the V1 area of the cortex are shown. The lighter lines in the dLGN and SC represent the approximate boundaries where axons of different functional categories of RGCs terminate [31–37]. Reproduced, with permission, from [30] (a).

[31–37]. Given the known role of the dLGN in relaying visual information to the cortex (Figure 1), an intriguing question is how the specialized tuning of RGCs and dLGN neurons influences receptive fields in the cortex.

With DSGCs, and perhaps other complex feature-encoding RGCs projecting to the dLGN, why have only linear center-surround dLGN neurons been reported in the mouse thus far [41]? One possibility is that mouse dLGN receptive fields were assessed using white-noise reverse correlation-based mapping; one third of the dLGN cells recorded in this study could not be analyzed with this procedure and, thus, could not be characterized [41]. Another possible reason is that many On–Off DSGCs have relatively thin, slow conductive axons and they project to a narrow (approximately 200 µm wide) layer adjacent to the optic tract [33]. It is unlikely that dLGN cells restricted to that layer would be recorded unless one was specifically looking for them. In light of the recent findings of DSGC and other complex inputs projecting to the mouse dLGN, it will be important to revisit the issue of response properties and cell types in the mouse dLGN, and to relate them to the laminar location of recording.

The notion of dLGN neurons tuned for visual features more sophisticated than center surround is not just an oddity of the mouse. Direction-selective receptive fields have also been described in the rabbit dLGN [44], and both orientation- and direction-selective neurons are present in the cat dLGN [45]. Interestingly, many of the 20-plus RGC subtypes described in the primate retina appear to project directly to the dLGN [46], suggesting that primate dLGN neurons also might be tuned for, not only center surround, but also complex features of the visual world.

Primary visual cortex: a canonical circuit for extracting image features?

The visual cortex of the mouse bears many similarities to that of other species, with the typical six-layered structure, retinotopic organization, and a variety of excitatory and inhibitory neuronal subtypes. The classical hallmark of primary visual cortex (V1), as described by Hubel and Wiesel [47], is that cells respond most strongly to edges or bars of light at a particular orientation, a property known as 'orientation selectivity'. Consistent with the conserved aspects of visual representation in the retina and LGN, the mouse cortex demonstrates orientation selectivity [48–50]. Indeed, the degree of orientation selectivity in mouse, in terms of the range of orientations that a given cell will respond to [50], is similar to that seen in the cat or monkey, despite the fact that visual acuity varies by almost two orders of magnitude across these species [51] (Figure 2a). The fact that the degree of orientation selectivity is relatively invariant from mouse to primate suggests this is a fundamental aspect of the cortical computation [51].

A recent quantitative electrophysiological survey of response properties across the layers of mouse V1 confirmed that nearly all of the hallmarks of cortical visual processing are present [50], including spatial frequency tuning, direction selectivity, linear and nonlinear responses (corresponding to Hubel and Wiesel's simple and complex cells, respectively), as well as contrast gain control and contrast-invariant tuning. Indeed, even the spatial substructure of individual receptive fields is similar from mouse to monkey (Figure 2b), once the relative size of those receptive fields has been compensated, as
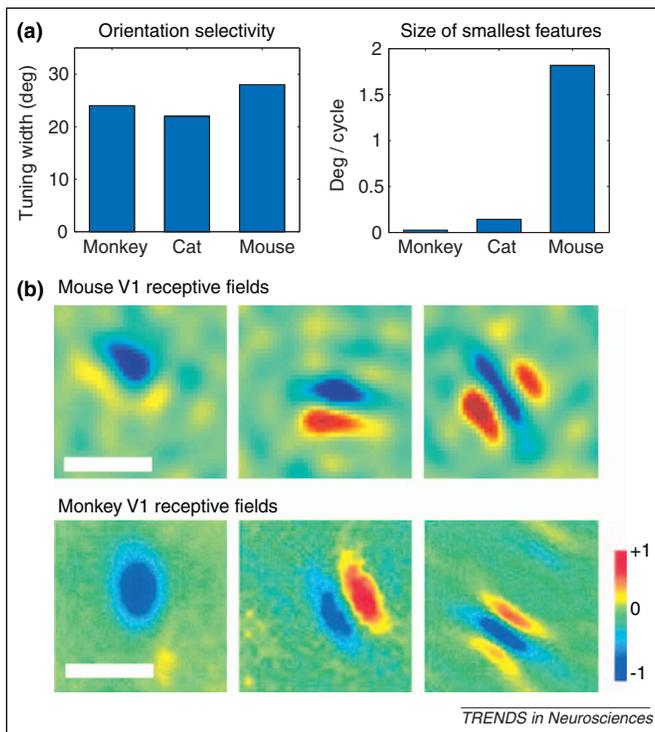
Figure 2. Similarity of cortical response properties across species despite differences in spatial resolution. **(a)** The degree of orientation selectivity is comparable across species (i), despite the fact that their behavioral acuity (the smallest feature they can detect) varies by nearly two orders of magnitude (ii). Mouse data from [50,92], remainder from [51]. **(b)** Three example simple cell receptive fields in V1, from mouse (i) and monkey (ii), showing a similar range of spatial structure. The scale bar for mouse is 20 degrees, whereas that for monkey is approximately 1 degree. Red and blue correspond to On and Off subregions, respectively. The similarity in structures demonstrates that cortical neurons in both species respond to similar visual features, but of different size. Mouse data from [50]; monkey data from [93]. In both studies, receptive fields were measured by reverse correlation methods in anesthetized animals.

quantitative scale-free analysis has shown [50]. Together, these findings suggest that the mouse cortex is indeed performing similar computations as in other species, just at lower spatial resolution.

By contrast, although mouse V1 has a clear topographic map of visual space, other types of large-scale organization are absent. In particular, many higher species show an ordered map of orientation [52], which varies across the cortical surface in a stereotypical pattern of 'pinwheels' [53]. The lack of such an orientation map might have been one reason why many researchers suspected that mice would have decreased orientation selectivity, because some theoretical models hypothesize that this large-scale orientation map would play a role in the tuning of individual cells [54]. However, orientation maps appear to be absent in all rodents, even those with relatively higher acuity, such as rats [55,56] and squirrels [57], despite equivalent orientation tuning of individual cortical cells (Figure 2b). Thus, orientation maps are dispensable for generating sharp orientation tuning in individual cells. Although such maps might not play a direct role in cortical function [58], they might be important for wiring efficiency [59]. Further studies determining which aspects of visual cortical processing are shared across species, and which are not, can thus help elucidate the essential principles of both the visual system [51] and cortical function generally [60].

Among cortical neurons, the most striking morphological diversity lies in the class of inhibitory neurons. A range of intricate morphologies has been observed, leading to terms that include chandelier, basket and double bouquet cells [61]. The highly specialized structures have led to many proposals for correspondingly specialized function in cortical processing [62]. However, testing such proposals has been challenging, owing to the difficulty in matching up morphological, molecular markers and electrophysiological properties, and then using these properties to identify neurons in an active circuit.

Recently, a combination of *in vivo* recording techniques together with molecular tools to enable the identification of specific inhibitory subtypes led to a flurry of studies addressing the difference in visual response properties between inhibitory and excitatory neurons in mouse V1. These studies used a variety of approaches to identify recorded cell types, including two-photon imaging of Cre lines with either Cre-dependent viral expression [63] or fluorescent reporter lines [64], two-photon imaging followed by retrospective immunohistochemistry [65], and two-photon targeted cell-attached recordings [66]. Although there are some discrepancies, the general conclusion is that a large class of inhibitory neurons, the parvalbumin expressing fast-spiking neurons, shows much less selectivity than the corresponding excitatory neurons. This significant population of untuned cells is a feature observed in the mouse but one that is possibly not present in other species, although recent studies in cats and monkeys have shown more diversity in orientation selectivity than previously appreciated [67,68].

Furthermore, in one of the aforementioned studies [66], a separate subset of inhibitory neurons, which express somatostatin and are generally dendrite-targeting Martinotti cells, was targeted. This class of cells did show orientation selectivity and tended to fire at a delay relative to the parvalbumin subclass of interneurons. Therefore, these two populations could be subserving very different functions; in one case delivering inhibition representing the sum of local activity to the soma (which would be ideal for gain control), and, in the other case, delivering tuned, but slightly delayed, inhibition to the dendrites (which would be ideal for gating of excitatory inputs).

Thus, genetic tools are beginning to allow the identification and targeted recording of defined neuronal subtypes in the cortex, leading to much more specific hypotheses about their roles in processing visual information and in governing cortical dynamics. It is now just a short step to test these hypotheses causally, by using genetic tools to not only label and record from specific cortical cell types, but also to regulate their activity, and monitor the impact that has on cortical function and visual perception.

Mouse extrastriate cortex has multiple tiers for higher level visual processing

The primary visual cortex sends its output to a hierarchical series of extrastriate visual areas [69], which in cat, primate and human have been show to represent a variety of higher order visual features, including motion, depth perception, image segmentation and object recognition [70]. An organizing principle of these areas is the notion of a

ventral stream carrying information about object identity (the 'what' pathway), and a dorsal stream, carrying information about object location (the 'where' pathway) [71]. However, beyond this rough flowchart, much less is known about how the particular visual features are computed by the neural circuitry within and between these regions.

Anatomical [9] and other mapping studies [72,73] have revealed the presence of several extrastriate visual areas in mouse cortex, with up to nine receiving direct input from V1. Furthermore, their patterns of connectivity are consistent with a dorsal and ventral stream, as in other species [74]. However, very little is known about the functional properties of these areas in mouse. Several studies using extracellular recording [75] (Gao, E. *et al.*, Society for Neuroscience Abstract no. 641.6, 2006) and two-photon imaging (Garrett, M. *et al.*, Society for Neuroscience Abstract no. 483.20, 2010) have begun to demonstrate different tuning properties in various regions of mouse visual cortex; however, it is not yet clear what the different functional roles of these regions might be. In particular, it would be intriguing to probe these regions with stimuli or behavioral tasks that might be appropriate for assessing roles in the 'what' versus 'where' pathways, and to use new circuit analysis techniques to determine how these areas perform the image processing that results in high-level visual representations.

Superior colliculus: a midbrain center for visually driven behavior

The superior colliculus (SC) is a midbrain structure that receives direct retinal input to its superficial layers (Figure 1), as well as integrating other sensory modalities across its full depth [76]. In non-mammalian vertebrates, such as fishes, frogs and birds, the SC is known as the optic tectum, and is the primary center for visual processing. Neurons in the optic tectum include a broad and sophisticated repertoire of visual responses, such as direction selectivity and looming detectors [77]. In mammals, neurons in the superficial (visual) layers of the SC primarily respond to small, moving spots, either light or dark, within a relatively broad region of visual space, and direction-selective SC neurons have also been described. Activity in the deep layers of the SC results in eye and/or head movements toward the corresponding region of visual space [78].

A recent electrophysiological study of the mouse SC confirms that most receptive fields are similar to those of other mammals [79], but larger owing to the lower resolution of the retina of the mouse. This study also found direction- and even orientation-selective SC cells. Interestingly, orientation selectivity was not dependent on input from the cortex, suggesting that it is either inherited directly from orientation-selective RGCs or computed separately in the SC; for instance, by summing inputs from DSGCs with opposite directions of preferred motion.

The presence of these diverse visual responses in the SC might be because of the intermediate position of the mouse in the evolutionary hierarchy, with SC and cortex playing a shared role in visual processing. Indeed, mice can still perform simple target detection tasks even after lesions of the visual cortex [5], suggesting that some of the functions ascribed to the visual cortex in cats and primates are collicular mediated in mice. By contrast, the role of the SC in parsing the visual scene and directing visually guided behaviors might be underestimated in higher species, where the majority of focus has been on the role of the SC in saccadic eye movements [80]. As the mouse takes on an ever-more prominent role as a model for visual processing, it will be critical to address whether much of what is assumed to be cortically mediated in other species is actually carried out by the SC in mice, and to consider the potentially broader role of the SC across species [80].

Visual psychophysics: linking circuits to perception

Perhaps the most promising aspect of studying vision in the mouse is the prospect of linking molecular and cellular aspects of neural circuit function with actual visual perception. In particular, one can begin to address the question of how the various parts of the visual system described above, with their specific cell types and connectivity, confer the ability to detect and identify stimuli in the visual world, as measured quantitatively with psychophysics. Traditionally, it was thought that visual psychophysics could only be performed with primates. However, the increased focus on in the mouse visual system has led to a growing number of psychophysical and behavioral assays that are allowing more detailed characterization of mouse visual function. These assays range from basic reflexive behaviors to relatively complex visual discrimination tasks. The following overview is not meant to be exhaustive, but rather illustrates the range of different behavioral assays available, as well as the factors to be taken into consideration in choosing a behavioral task to test a particular visual function in the mouse (see also [81] for an earlier review).

The optomotor response provides a rapid measure of visual function without training

The optomotor response is a reflexive behavior whereby an animal will move its eyes or head to follow a moving visual field. This reflex behavior (also known as optokinetic tracking), which serves to stabilize the image of the visual world on the retina, has been exploited in the mouse as a way to assess visual thresholds quantitatively [82]. A computer-controlled stimulus and head-tracking system provides a semi-automated measure of the range of spatial frequencies and contrast that an animal can track (Figure 3a). This method provides a sensitive measure of visual thresholds without the need for behavioral training, which can be useful as a rapid screen for deficits in the eye. However, this reflex is probably controlled by subcortical mechanisms involving pretectal, collicular and brainstem nuclei and is unlikely to require the cortex for its expression. In fact, the spatial frequency thresholds measured for the optomotor reflex are slightly lower than for cortical-dependent tasks. [5]. The basic neural pathways thought to generate the optomotor response have been described [83], but rigorous tests of the involvement of specific pathways or cell types have not yet been performed to determine the circuit mechanisms that generate and modulate the optomotor response.
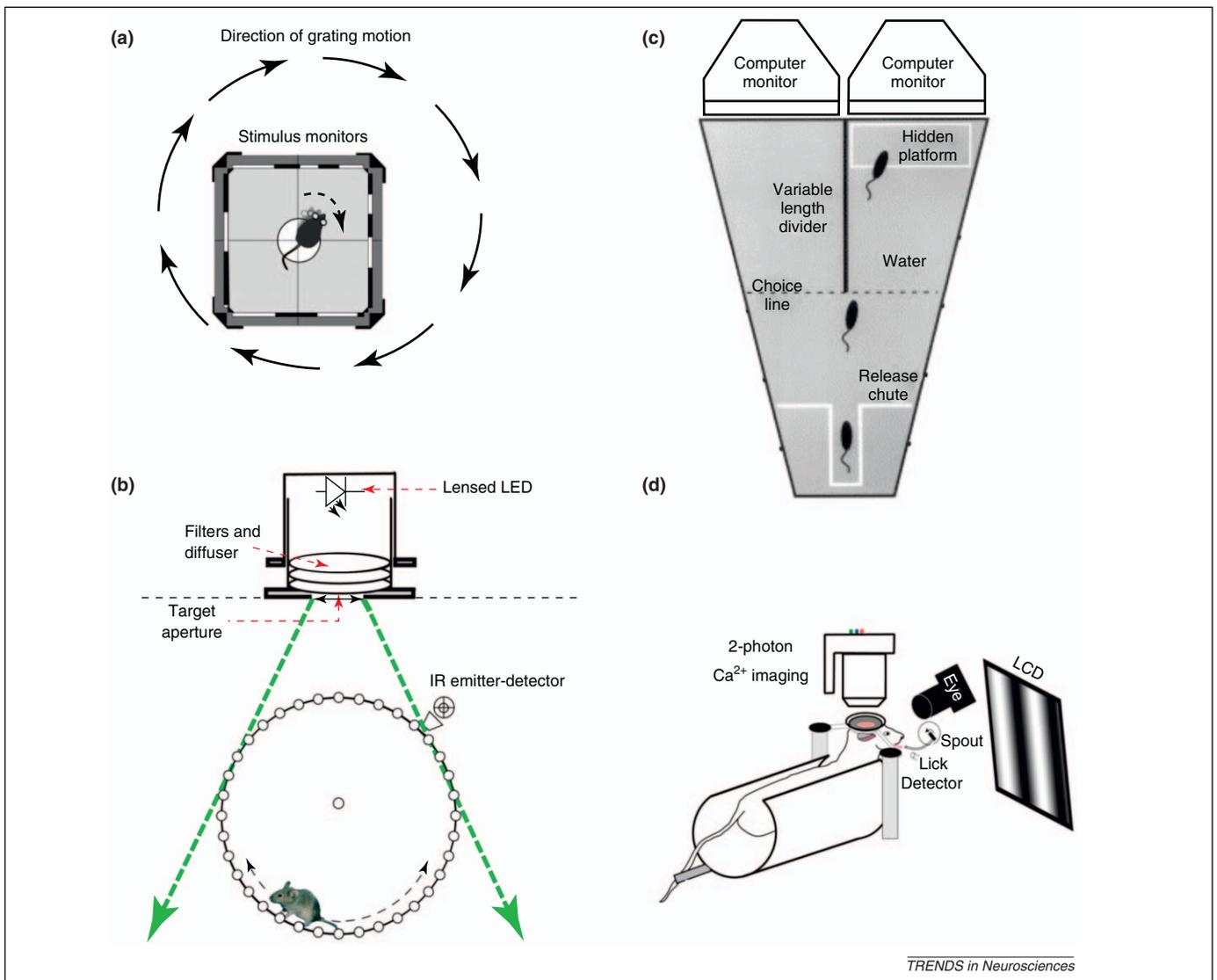
Figure 3. Behavioral paradigms for assessing mouse visual function. **(a)** Optomotor response as a measure for visual thresholds [82]. The mouse reflexively tracks moving gratings that are presented on computer screens surrounding the enclosure. The spatial frequency of the gratings is varied to determine the smallest features that the mouse will track. **(b)** Running task for the measurement of photoreceptor thresholds [84]. A filtered light-emitting diode (LED) is used to provide a defined luminance source. When the luminance changes, the mouse must stop running on the wheel to receive a reward (e.g. water or food). The motion of the animal is automatically recorded by an infrared (IR) emitter-detector. The defined geometry allows precise measurements of photon fluxes at the eye. **(c)** Two-alternative forced choice swimming task [92]. The mouse is placed in a water-filled Y-maze, with a hidden platform on one end. A computer-controlled stimulus is presented on the side with the platform, and the mouse must detect the stimulus and swim toward the correct side to find the platform and be released from the water. **(d)** Go/no-go licking task, combined with two-photon imaging [90]. Head-fixed mice are trained to lick only when a grating of the correct orientation is presented on a monitor in front of them. Incorrect licking is punished by a 'time-out'. Concurrent two-photon imaging of calcium signals in the cortex allows for the measurement of neural correlates, and a camera detects eye movement. Reproduced, with permission, from [82] (a), [84] (b), [92] (c) and [90] (d).

Trained behavioral tasks reveal visual function: from photoreceptor sensitivity to orientation discrimination

The perceptual correlates of the biophysical properties of photoreceptors have recently been tested in a novel behavioral paradigm [84], wherein a mouse is trained to receive a water reward if it stops running when it detects a luminance stimulus (Figure 3b). By measuring detection thresholds in wild-type mice and two mouse lines lacking rod and cone signaling, respectively, this study was able to determine the perceptual sensitivity of both rod and cone pathways [84]. Remarkably, although the mouse retina is rod dominated, their cone sensitivities were found to be similar to those of humans [85]. Furthermore, the rod sensitivity is so powerful that the mice could detect and report as few as approximately 30 photons arriving at the eye [84]. In addition to providing a direct link between

photoreceptor function and the visual perception of a mouse, it should prove possible to adapt such a task, which takes advantage of the natural propensity of mice to run, to measure the detection of more complex (e.g. patterned) visual stimuli.

Typical tests of spatial memory and navigation, such as the Morris water maze and Barnes maze, are inherently also tests of visual function, because the landmarks in these tests are generally distal visual cues [81]. In a recent technical tour de force, head-fixed mice were trained to navigate a virtual environment, wherein images were projected onto a screen while the mouse ran on a spherical treadmill [86]. The fact that mice can perform such tasks and create spatial representations in the brain based on the visual environment [87], clearly demonstrates that they use their vision for such navigation. However, quantification of visual function

is more difficult in these navigational tasks, because cues can vary with distance and viewing angle, and are not generally manipulated in a parameterized way, although the virtual-reality maze might provide a means to do so.

As a more quantitative test of pattern vision, a two-alternative forced choice task [5] has been used, where mice must swim toward an appropriate visual stimulus to escape the water (Figure 3c). By using computer-generated stimuli and a succession of trials, it is possible to measure properties such as acuity and contrast sensitivity thresholds, which confirm that mice can behaviorally report the presence of a stimulus with an acuity limited primarily by retinal sampling [5]. This technique has also been used to study differences in visual ability across mouse strains [88]. However, owing to the time-consuming nature of each trial, and the level of stress induced in the mice, only approximately 50 trials can be performed per day on such a test, limiting the number of parameters that can be tested. An alternative method, utilizing a touch-screen for the animal to indicate responses, and delivery of a food pellet as a reward, has had success in demonstrating that mice can perform complex shape discrimination [89], although with a similar constraint in the number of trials per day.

To take advantage of many of the new tools available, a head-fixed preparation would be preferable, to allow concurrent imaging or the delivery of light stimulation for optogenetic studies. Furthermore, it is desirable for the animals to be able to perform a large number of trials to obtain reliable characterization across a range of stimulus parameters. A go/no-go task for mice was recently reported [90], where the mice learned to lick only in response to the appropriate stimulus to receive a water reward (Figure 3d). Hundreds of trials of such a task could be performed per day. In addition to characterizing learning and visual performance, by measuring psychometric curves and detection thresholds on consecutive days of training, this study demonstrated that simultaneous measurement of neural responses could be performed repeatedly on subsequent days by two-photon imaging of a genetically encoded calcium indicator. However, a more extensive training period (several weeks) was required compared with reflexive or innate behaviors, and some animals failed to learn the task. Thus, there is currently a trade-off between ease of training and the type of information that can be obtained in behavioral paradigms.

A major advantage of psychophysical assays is that they provide a means to record from cells during a relevant behavioral task, as opposed to during passive viewing. This is an important point, given that visual processing depends on behavioral state [43,91]. Furthermore, in combination with genetic methods to map and selectively activate and/or inactivate defined cell types, they allow the possibility of linking cellular and network mechanisms with visually guided behavior and perception.

Concluding remarks

In summary, the studies presented here provide a compelling argument for the use of the mouse in studying visual processing. Although fueled by the rapid development of genetic tools for circuit analysis (Box 1), this approach is bolstered by the growing evidence that, despite the obvious

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Box 2. Challenges of studying vision in mouse

Despite the potential benefits of using the mouse as a model for visual studies, there are several caveats that must be kept in mind.

- Mouse strains can differ dramatically in terms of visual function and, in fact, many strains are partially or completely blind owing to inherited photoreceptor degeneration and albinism [88].
- Mice are non-foveal and, as a result, they might rely on head movements more than eye movements to view specific portions of visual space.
- Behavioral assays need to be adapted to tasks that mice can accomplish, both in terms of stimulus parameter range and the means of reporting responses.
- It is unclear to what extent visual perception in mice relies on the cortex and, in general, controls are needed to ensure that a particular task depends on the brain region being studied, even if it has been demonstrated in other species.
- Although it has been shown that mice can make simple discriminations, such as orientation and shape, it remains to be determined what types of higher order visual processing and cognitive decisions they can perform.
- Laboratory mice are often raised in what effectively are visually and behaviorally deprived environments, which have significant effects on visual system development [100].
- Some questions might simply not be addressable in mice. Obvious examples include face recognition and the cognitive visual functions underlying reading. However, it might turn out that even fundamental aspects of vision, such as stereopsis or spatially localized attention, are not tractable in the mouse.

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differences in visual behaviors and acuity in the mouse compared with primates, the similarities dramatically outnumber the differences.

Along with the promise of the mouse as a model system, however, come certain potential pitfalls (Box 2). In particular, it is necessary to pay careful attention to potential species differences if one hopes to draw general conclusions about visual system function from mouse studies. Another fundamental challenge will involve combining the powerful molecular-genetic tools with the quantitative measurements of vision science. Although these are very different fields, harnessing the strengths of both should allow unprecedented traction in questions that date back to the earliest investigations of how the visual system works (Box 3).

Box 3. Important questions in visual neuroscience

Although the genetic tools in mouse open up several new experimental paradigms, a big challenge is to apply them to broadly significant questions about how vision works. The following are some long-standing questions that might now be amenable to direct experimental investigation.

- What is the full repertoire of retinal response properties that conveys the visual image to the brain?
- How much of classical cortical response properties are in fact computed in the retina (e.g. direction selectivity)?
- Do specific interneuron subtypes regulate distinct aspects of cortical function, such as contrast gain control or attentional modulation?
- How do ensemble responses of visual neurons relate to perception and decision making?
- How are image scenes segmented by the visual system, to identify objects versus background?
- How does the visual system recognize objects despite changes in their position, size, illumination, and so on?
- How and where are visual memories stored?
- How do various disease processes compromise visual function, and what can be done to remedy the deficits?

Note added in proof

As this review went to press, Busse *et al.* [101] published a nose-poke based contrast detection task, wherein mice perform hundreds of trials to generate psychometric curves. The authors were able to model alternate strategies that affect the animal's behavior, which allowed reliable estimation of contrast sensitivity even in the presence of unreliable task performance.

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