CHAPTER

25

Visual System

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The mouse is a small nocturnal mammal, and many of the features of its visual system, such as the large size of the lens, are shared with other nocturnal mammals. The somatosensory and olfactory systems of mice are relatively large, and the visual and auditory systems are less impressive by comparison. However, the development of gene targeting has made the mouse visual system an increasingly important area of study. A comprehensive analysis of the anatomy and physiology of the mouse visual system has recently been published (Chalupa and Williams, 2008), and we recommend that researchers dealing with any aspect of the mouse visual system make use of this valuable textbook. The present chapter will summarize the major anatomical features of the mouse visual system. It is aimed at a reader who is commencing research in this area, and who needs an overview of the structure and connections of the mouse visual system. The present chapter owes a great deal to the description of the anatomy of the mouse visual system by Leamey et al. (2008), which appears in the Chalupa and Williams textbook.

THE EYE AND RETINA

The mouse has a relatively small eye; it measures 3.4 mm from anterior surface of the cornea to anterior surface of the choroid (Remtulla and Hallett, 1985). The combined length of the cornea and lens is equal to 60% of the total length of the eye (Fig. 25.1). The relatively large size of the lens is a characteristic of many small nocturnal animals.

The basic structure of the mouse retina is the same as that of other mammals, with three main layers of neuronal cell bodies – the retinal ganglion cell (RGC) layer, the inner nuclear layer (bipolar cells and amacrine cells), and the outer nuclear layer (which contains the nuclei of the photoreceptor cells). The ganglion cell layer and the inner nuclear layer are separated by the inner plexiform layer (IPL), and the outer nuclear layer and inner nuclear layer are separated by the outer plexiform layer (OPL). The axons of ganglion cells (optic nerve layer) lie on the retinal surface of the ganglion cell layer. The photoreceptor (rod and cone) processes that contain

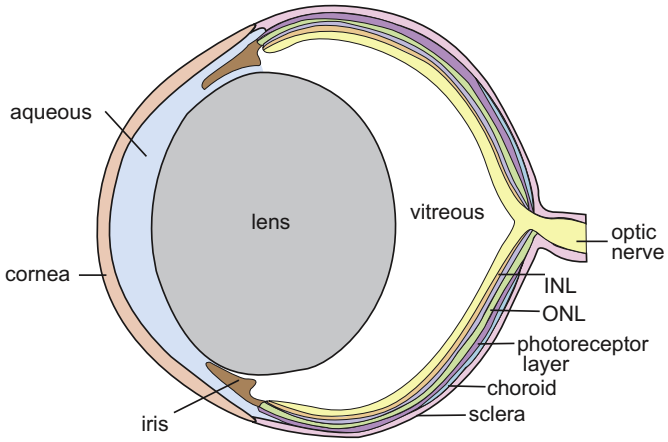

FIGURE 25.1 A diagram of the mouse eye, showing the relatively large lens. (ONL=outer nuclear layer of the retina; INL=inner nuclear layer of the retina.

visual pigments lie between the outer nuclear layer and the pigment epithelium layer.

PHOTORECEPTOR LAYER

As in other nocturnal animals, rods greatly outnumber cones in the photoreceptor layer. In the mouse the ratio of rods to cones is about 30 to 1 (Carter-Dawson and LaVail, 1979). Jeon et al. (1998) found that there are 6.4 million rods and 180,000 cones in the retina of the C57 black mouse. The 6.4 million rods project to about 200,000 rod bipolar cells, whereas the 180,000 cones project to about 400,000 cone bipolar cells (Strettoi and Volpini, 2002). This proportional relationship between rods and cones and bipolar cells is typical of nocturnal mammals. Whereas the rod-to-rod bipolar pathway is essentially a simple convergence process, the cone bipolar system forms a complex network of transverse and vertical pathways in the retina.

The peak of spectral sensitivity of rod photoreceptor opsin is at 497–500 nm (Fan et al., 2005). The spectral sensitivity of cones is related to their position in the retina. The cones of the dorsal retina are primarily sensitive to ultraviolet light, with a peak sensitivity at 360 nm. On the other hand, the cones of the ventral retina are primarily responsive to medium wavelength light, with a peak sensitivity at 508 nm (Nikonov et al., 2006; Szel et al., 1992; 1993).

HORIZONTAL CELLS

Horizontal cells are found at the border between the outer plexiform layer and the inner nuclear layer. As their name suggests, these cells are elongated in the horizontal plane, and their processes spread horizontally across the retina. Many mammals have three classes of horizontal cells, but in the mouse only one type is found (Peichl et al., 1998). The morphology of horizontal cells shows considerable variation between different strains of mice (Raven et al., 2005). Together with bipolar cells, horizontal cells play a role in lateral inhibition, which increases contrast and so enhances the detectability of objects of interest.

THE INNER NUCLEAR LAYER – BIPOLAR AND AMACRINE CELLS

Each rod bipolar cell in the mouse receives input from about 30 rod photoreceptors (Strettoi and Volpini, 2002). The majority of rod bipolar cells project to AII amacrine cells, which in turn project to ganglion cells. Some rods send their signal via gap junctions with cone photoreceptors and so connect with the retinal cone pathway (Tsukamoto et al., 2001). The cone bipolar cells are divided into ON and OFF groups, which allows them to signal small changes in luminance. The ON and OFF cone bipolar cells differ in the expression of glutamate receptors on dendrites in the inner plexiform layer (Sun and Kaloniatis, 2006). Detailed morphological study has revealed five different types of OFF cone bipolar cells and four different types of ON cone bipolar cells in the mouse, whereas there is only one type of rod bipolar cell (Ghosh et al., 2004).

Amacrine cells are interneurons whose cell bodies are located in the inner part of the inner nuclear layer. Input to amacrine cells comes from bipolar cells, and the amacrine cells in turn project to RGCs. Amacrine cells vary widely according to their position in the IPL, the neurotransmitters they release, and their dendritic architecture, and more than 30 different types have been identified. Most amacrine cells are inhibitory – either GABAergic or glycinergic. It is difficult to identify amacrine cells on morphological grounds alone, and this has made it difficult to estimate the total number of amacrine cells (Strattoi and Masland, 1996).

RETINAL GANGLION CELL LAYER

The number of ganglion cells in the mouse has been estimated at 45,000 to 65,000 (Drager and Olsen, 1980; Jeon et al., 1998). Drager and Olsen (1981) found that the peak RGC density was 8,000 cells/mm^2. The area of peak RGC density in the retina is known as the area centralis; the RGC density here is 3.5 times greater than at the periphery of the retina (Drager and Olsen, 1980). The area of peak RGC density overlies the area of peak rod density (100,000 per mm^2) and the peak cone density (16,000/mm^2) (Jeon et al., 1998).

The upper limit of visual acuity in the mouse has been estimated to be 1.3 cycles/degree on the basis of the peak RGC density and the retinal magnification factor (Hallett, 1987). This is similar to the figure of 0.4–0.5 cycles/degree obtained from behavioral studies (Schmucker et al., 2005).

From an anatomical point of view it has proven difficult to identify different classes of RGCs in the mouse that might be equivalent to those that have been described in the cat and monkey (Coombs and Chalupa, 2008). Complex labeling and morphometric techniques are being increasingly used in studies of mouse RGC types (Coombs et al., 2006).

RGCs can be divided on functional grounds into two main types – those which convey only general information on luminance and those which contribute to the formation of an image (Provencio et al., 1998). The image-related group projects to the DLG and SC, whereas the luminance group projects to areas of the brain involved in circadian rhythm control and pupillary reflexes (Hattar et al., 2006).

Stone and Pinto (1992) showed that the majority of mouse RGCs have large receptive fields (2–10 degrees in diameter). These authors found that some mouse RGCs were similar to cat X cells, whereas others were similar to cat Y cells, but a more recent study (Carcieri et al., 2003) failed to find a clear separation into different functional types.

In the mouse there are about 700 intrinsically photosensitive ganglion cells (ipRGCs). These RGCs contain melanopsin and appear to be important in the regulation of circadian rhythms and pupillary reflexes (Hattar et al., 2002). The ipRGCs project to the suprachiasmatic nucleus, the pregeniculate nucleus (formerly ventral lateral geniculate), the intergeniculate leaflet, preoptic region, the hypothalamic subparaventricular zone, the superior colliculus, the nucleus of optic tract, the perisupraoptic nucleus, the medial amygdala, the lateral habenula, the posterior limitans nucleus, the periaqueductal grey, and the margins of the dorsal lateral geniculate (Hattar et al., 2003, 2006).

The majority of mouse RGCs project to the contralateral side of the brain, and these axons cross in the optic chiasm. A relatively small number project to the ipsilateral side. The proportion of ipsilaterally projecting RCGs is 2–3% (Drager and Olsen, 1980), compared to 0.6% in rabbits. In mice the eyes are positioned more frontally than in rabbits, and the binocular field of view is about 30 to 40 degrees (Drager, 1978; Drager and Olsen, 1980).

In other mammals the ipsilaterally projecting RGCs are located in the dorsal and ventral parts of the temporal retina. In the mouse, this ipsilaterally projecting area is mostly in the ventral part of the temporal retina. This area is called the ventrotemporal crescent (VTC) (Drager, 1978). The VTC contains both ipsilaterally and contralaterally projecting RGCs, with ipsilaterally projecting RGCs in the minority (15%).

GLIAL CELLS IN THE RETINA

The largest glial cells in the retina are the Muller cells which extend from the ganglion cell layer to the junction of the photoereceptor inner segments and cell body (Haverkamp and Wassle, 2000). Muller cells have a variety of functions and have recently been suggested as playing a role in focusing light on the photoreceptors (Franze et al., 2007). In addition to the Muller cells, astrocytes are found in optic nerve fiber layer and microglial cells are found in the inner nuclear layer.

THE BLOOD SUPPLY TO THE MOUSE RETINA

The retina is supplied with blood by the retinal and choroidal circulations (Stone and Valter, 2008). Retinal arteries arise from the central artery of the retina, which in turn is a branch of the ophthalmic artery. The retinal arteries radiate away from the optic nerve head across the vitreous surface of the retina. The arterioles and capillaries arising from the retinal arteries supply the inner half of the retina. Venous drainage follows the retinal arteries back to the optic nerve head. The choroidal circulation forms a vascular bed that lies between the retina and the sclera; this layer is known as the tunica vasculosa of the eye. Adjacent to the retinal pigmented epithelium, there is a layer of fenestrated capillaries, known as the choriocapillaris. Oxygen diffuses from the choriocapillaris, across the retinal pigmented epithelium to supply the photoreceptors. A very high flow rate is required to deliver adequate oxygen to the photoreceptors. Because the choriocapillaris does not autoregulate, photoreceptors are vulnerable to high oxygen levels which if prolonged, may cause photoreceptor death (Stone and Valter, 2008; Walsh et al., 2004).

THE OPTIC NERVE

The optic nerve of the mouse is formed by the convergence of RGC axons at the optic nerve head. The region where the optic nerve fibres pierce the choroid and sclera is referred to as the lamina cribrosa. After the axons leave the eye they are at first unmyelinated, but become myelinated in the posterior part of the orbit (May, 2008). The number of axons forming the optic nerve varies greatly between mouse strains, ranging from 32,000 to 87,000 (Williams et al., 1996). Williams et al. (1996) found that the optic nerve of the much-studied

C57/BL6J strain contains about 55,000 axons, and the optic nerve of the Balb/cJ strain contains about 64,000 axons. The optic nerve fibers range in diameter from 0.3–4.2 micrometers with a peak around 0.8 micrometers (Strom and Williams, 1998). The optic nerve contains both astrocytes and oligodendrocytes. As in other mammals, oligodendrocytes are absent in the intraocular part of the nerve. Microglia are present in small numbers in the optic nerve (Wong et al., 1979).

THE OPTIC CHIASM AND OPTIC TRACT

The optic chiasm extends from the ventral surface of the caudal part of the preoptic area to the hypothalamus at the level of the caudal border of the suprachiasmatic nucleus (Watson and Paxinos, 2010). The optic chiasm lies immediately ventral to the suprachiasmatic nucleus and the third ventricle. The optic tract moves laterally and caudally to wrap around the hypothalamus and diencephalon. Rostrally, the lateral edge of the optic tract is surmounted by the supraoptic nucleus of the hypothalamus. Further caudally, the optic tract lies between the lateral hypothalamus and the cerebral peduncle medially, and the medial nucleus of the amygdala laterally. It sweeps dorsally to reach the pregeniculate nucleus and the DLG (Fig. 25.2). The supraoptic decussation is closely related to the optic chiasm. It lies at first ventral to the optic chiasm, and extends laterally on the dorsal surface of the optic tract. The fibers in the supraoptic decussation are not related to the visual system; they connect parts of the pallidum and hypothalamus.

THE CENTRAL PROJECTIONS OF THE RETINA

The mouse retina projects to hypothalamic, diencephalic, and midbrain nuclei (Gooley et al., 2003; Hattar et al., 2002; 2006; Leamey et al., 2008). In the hypothalamus, the axons of RGCs end mainly in the suprachiasmatic nucleus, but also in the subparaventricular zone and the anterior hypothalamic nucleus (Hattar et al., 2006). In the diencephalon, the axons terminate in prosomere 3 (the pregeniculate nucleus – formerly called the ventral lateral geniculate nucleus), prosomere 2 (the dorsal lateral geniculate nucleus, the intergeniculate leaflet, the lateral habenular nucleus, and part of the medial terminal nucleus), and prosomere 1 (the pretectal nuclei and the medial, lateral, and dorsal terminal nuclei). The largest retinal projection in the mouse is to the superior colliculus of the midbrain. In the rat, only about one third of RGCs project to the DLG, whereas all project to the superior colliculus (Dreher et al., 1985). It seems likely that a similar arrangement is present in the mouse.

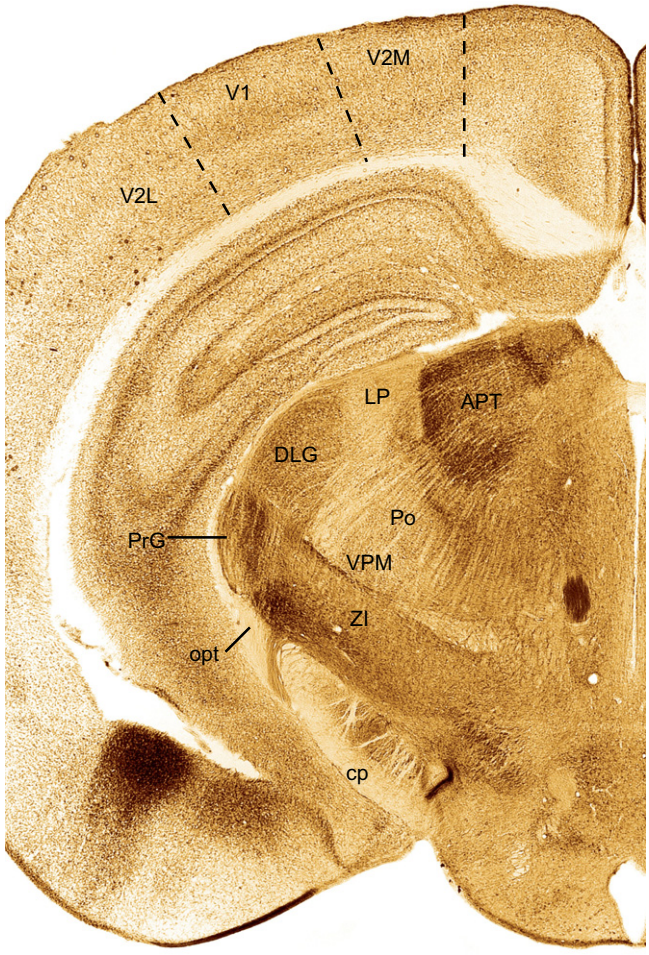

FIGURE 25.2 A photograph of a coronal section of mouse brain through the middle of the dorsal lateral geniculate nucleus. The section is stained with acetylcholinesterase, which helps to define the primary visual cortex (V1) from the adjacent visual association areas (V2M and V2L). (APT=anterior pretectal area; cp=cerebral peduncle; LP=lateral posterior nucleus of thalamus; opt=optic tract; Po=posterior nucleus of thalamus; PrG=pregeniculate nucleus (formerly ventral lateral geniculate nucleus); VPM=ventral posteromedial nucleus of thalamus; ZI-zona incerta). *The photograph is taken from the atlas of Franklin and Paxinos (2008).*

THE PRETECTUM AND ACCESSORY OPTIC TRACT NUCLEI

The nuclei of the pretectum which receive a direct input from the contralateral retina are the olivary pretectal nucleus (OPT), posterior pretectal nucleus (PPT), and the nucleus of the optic tract (OT) (Pak et al., 1987).

The accessory optic system of mammals is formed by two small branches of the optic tract – the superior and inferior fasciculi of the accessory optic tract (Hayhow,

1959; de Renzi et al., 1959). The retinal projections to the accessory optic system are almost entirely contralateral. The superior fasciculus supplies the dorsal and lateral terminal nuclei and part of the medial terminal nucleus, and the inferior fasciculus supplies the medial terminal nucleus (Pak et al., 1987). Of the three terminal nuclei, the medial terminal nucleus receives the largest projection. The medial terminal nucleus is developed from prosomeres 1 and 2 of the diencephalon, whereas the dorsal terminal nucleus and the lateral terminal nucleus are developed in prosomere 1 alone.

THE SUPERIOR COLLICULUS

The superior colliculus in all mammals consists of seven layers, six of which are labeled in Fig. 25.3. The projection from the retina in the mouse terminates in the three superficial layers – the stratum zonale, stratum griseum superficiale, and the stratum opticum (Drager and Hubel, 1975). The relatively small ipsilateral projection to the superior colliculus terminates in a series of patches in the rostromedial portion of the superior colliculus (Drager and Hubel, 1975). The retinotopic organization of the superior colliculus is consistent among mammals: the zero vertical meridian is represented rostrally and the most peripheral part of the contralateral visual field is represented caudally; the upper visual field is represented medially in the superior colliculus and the lower visual field is represented laterally (Drager and Hubel, 1975, 1976). As noted above, the representation of the ipsilateral hemifield is restricted to the most rostral area of the superior colliculus. The retinal representation is the same in all retina recipient layers. The superior colliculus receives substantial input from the ipsilateral primary visual cortex (Stein and Meredith, 1991). In the deeper layers of the superior colliculus, many cells respond to somatosensory and auditory stimuli as well as visual input. The main somatosensory input to the superior colliculus is from the whiskers (Drager and Hubel, 1975).

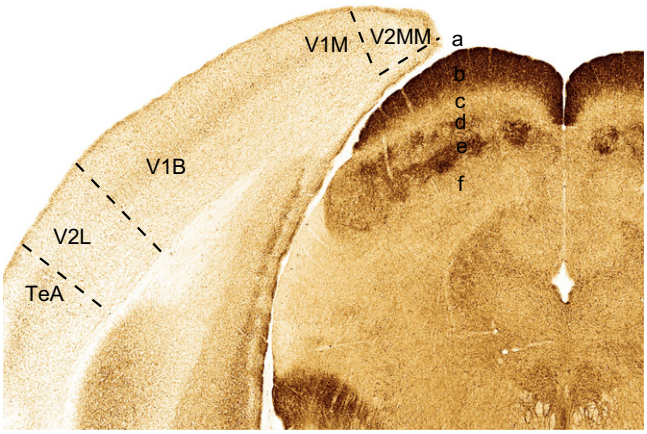

FIGURE 25.3 A photograph of a coronal section of mouse brain through the middle of the superior colliculus. The section is stained with acetylcholinesterase, which helps to define the primary visual cortex (V1M and V1B) from the adjacent visual association areas (V2MM and V2L). The layers of the superior colliculus are labelled a to f. (a=stratum zonale; b=superficial gray layer; c=optic nerve layer; d=intermediate gray layer; e=intermediate white layer; f=deep gray layer; TeA=temporal association cortex; V1B=primary visual cortex, binocular area; V1M=primary visual cortex, monocular area; V2L=secondary visual cortex, lateral area; V2MM=secondary visual cortex, mediomedial area). *The photograph is taken from the atlas of Franklin and Paxinos (2008).*

THE DORSAL LATERAL GENICULATE NUCLEUS

The dorsal lateral geniculate nucleus (DLG) receives input from the retina and projects to the visual cortex. This nucleus has been intensively studied in the cat and monkey, but with the advent of gene targeting technology, increasing attention is being paid to the DLG of the mouse. The DLG is the only thalamic nucleus in the mouse that contains both glutamatergic (excitatory) cells and GABAergic (inhibitory) cells. Other thalamic sensory nuclei in the mouse do not contain GABAergic interneurons (Arcelli et al., 1997). In primates, all thalamic projection nuclei contain both glutamatergic and GABAergic neurons.

The mouse DLG lies dorsomedial to the ventroposterior somatosensory complex and the medial geniculate nucleus (Figs. 25.3 and 25.4). Ventral to the DLG is the pregeniculate nucleus (PrG) (formerly called the ventral lateral geniculate). Separating the DLG and PrG is a band of neurons called the intergeniculate leaf (IGL). The surface of the DLG is covered by the optic tract.

The mouse DLG has a retinotopic organization in which the ipsilateral temporal visual field is represented in the rostrolateral region, and the nasal visual field is represented in the caudal part of the DLG (Wagner et al., 2000). A characteristic feature of the DLG of primate and carnivore mammals is a separation of neurons into layers that receive either ipsilateral or contralateral input. Such layers are not seen in histological sections of the mouse DLG, consistent with the near absence (2–3%) of ipsilaterally projecting RGCs. The neurons of the mouse DLG are relatively homogeneous in size (Grubb and Thompson, 2003), in contrast with the variety of types found in primates and carnivores.

VISUAL CORTEX

The primary visual cortical area in the mouse, area V1, is the homolog of area 17 of humans. V1 is bordered

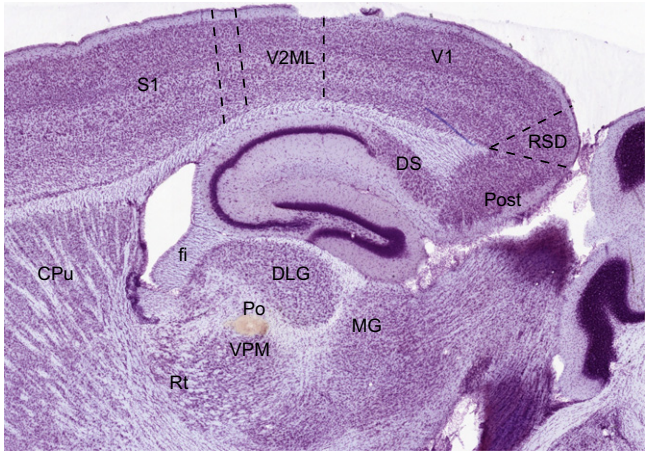

FIGURE 25.4 A photograph of a Nissl stained sagittal section of mouse brain through the middle of the dorsal lateral geniculate nucleus (DLG). The primary visual cortex (V1) is bounded by the adjacent visual association area (V2ML) and the retrosplenial dysgranular cortex (RSD). (CPu=caudate putamen; DS=dorsal subiculum; fi=fimbria hippocampus; MG=medial geniculate nucleus; Po=posterior nucleus of thalamus; Post=postsubiculum; Rt=reticular nucleus of thalamus; S1=primary somatosensory cortex; VPM=ventral posteromedial nucleus of thalamus). *The photograph is taken from the atlas of Franklin and Paxinos (2008).*

medially, laterally and rostrally by visual association areas, which seem to be equivalent to area 18 of humans (Figs. 25.2, 25.3, 25.4, and 25.5). The medial association area, V2ML (Franklin and Paxinos, 2008), is equivalent to areas PM and AM of Wang and Burkhalter (2007), and Vm-r and Vm-c of Wagor et al. (1980). The lateral association area, V2L (Franklin and Paxinos, 2008), is broadly equivalent to areas RL, AL, LM, LI, P, and POR of Wang and Burkhalter (2007). Areas V2 and V3 of Wagor et al. (1980) (area 18a) seem to be equivalent to area V2L in the atlas of Franklin and Paxinos (2008). As in other mammals, the commissural connections of the visual areas are mostly restricted to the visual association areas. Direct commissural connections in V1 are restricted to the most lateral margin of V1, adjacent to V2L.

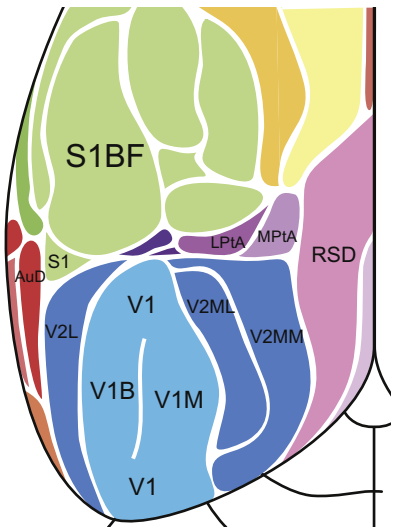

FIGURE 25.5 A diagram of a dorsal view of the primary visual cortical areas (V1, V1B, and V1M) and the secondary visual cortical areas (V2L, V2MM, and V2ML). Surrounding cortical areas are labeled for reference. (AuD=secondary auditory cortex, dorsal area; LPtA=lateral parietal association cortex; MPtA=medial parietal association cortex; RSD=retrosplenial dysgranular cortex; S1=primary somatosensory cortex; S1BF=primary somatosensory cortex, barrel field). *The diagram was constructed by Dr Matthew Kirkcaldie of the University of Tasmania from a three dimensional reconstruction of the mouse brain atlas of Franklin and Paxinos (2008).*

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