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REVIEW ARTICLE

The mouse pulvinar nucleus: Organization of the tectorecipient zones

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Abstract

Comparative studies have greatly contributed to our understanding of the organization and function of visual pathways of the brain, including that of humans. This comparative approach is a particularly useful tactic for studying the pulvinar nucleus, an enigmatic structure which comprises the largest territory of the human thalamus. This review focuses on the regions of the mouse pulvinar that receive input from the superior colliculus, and highlights similarities of the tectorecipient pulvinar identified across species. Open questions are discussed, as well as the potential contributions of the mouse model for endeavors to elucidate the function of the pulvinar nucleus.

Keywords: Thalamus, Synapse, Superior colliculus, Visual

The pulvinar nucleus is considered one of the most enigmatic thalamic regions. Factors that contribute to its mystery are the vast array of anatomical connections that involve the pulvinar nucleus, its reduced activity in anesthetized or restrained animals, and the resulting difficulties in determining the circuits and stimuli that contribute to its receptive field properties. Additionally, although the pulvinar is commonly considered a single thalamic nucleus, it contains a number of distinct subregions which may be differentially involved in various functions ascribed to the pulvinar (e.g., visual attention, decision making, motor planning, perceptual suppression, synchronization of cortical activity, detection of faces, or fearful stimuli; Wilke et al., 2009, 2010, 2013; Van Le et al., 2014; Le et al., 2014, 2016; Grimaldi et al., 2016; Zhou et al., 2016*b*; Dominguez-Vargas et al., 2017; McFadyen et al., 2017; Soares et al., 2017). In order to understand how the pulvinar contributes to these various tasks, the synaptic circuits within each subregion must first be defined.

This review focuses on circuits of the mouse lateral posterior nucleus (LPN), a region considered to be the homologue of the primate pulvinar nucleus (Harting et al., 1972). As schematically illustrated in Fig. 1, this homology is based to a large extent on commonalities in the projections of the superficial (visual) layers of the superior colliculus (SC), or optic tectum, to the primate pulvinar nucleus, rodent/carnivore LPN, and avian nucleus rotundus (Harting et al., 1973; Robson and Hall, 1977; Berson and Graybiel, 1978; Mooney et al., 1984; Takahashi, 1985; Abramson and Chalupa, 1988; Luppino et al., 1988; Hutsler and Chalupa, 1991; Kelly et al., 2003; Marín et al., 2003; Chomsung et al., 2008; Masterson et al., 2009, 2010; Baldwin et al., 2011, 2013; Fredes et al., 2012; Wei et al., 2011*a*). Because of these similarities, we will refer to this region of the mouse thalamus as the pulvinar nucleus. We hope that this nomenclature will assist in comparative studies that may contribute to our understanding of the organization and function of the pulvinar nucleus across species, including that of humans. In order to most explicitly relate the organization of the mouse pulvinar to that of other species, this review emphasizes the regions that receive input from the SC. Although the size of the tectorecipient zones relative to the entire extent of the pulvinar nucleus varies across species, there are a number of similarities in the organization of these zones as discussed below.

Tectopulvinar cells

The SC projections to the pulvinar nucleus originate from a unique class of cells, termed widefield vertical (WFV) cells (Fig. 2). WFV cells have been identified in a variety of species (chicken, pigeon, mouse, rat, ground squirrel, gray squirrel, tree shrew; Mooney et al., 1988; Karten et al., 1997; Luksch et al., 1998, 2001; Major et al., 2000; Marín et al., 2003; May, 2006; Chomsung et al., 2008; Endo et al., 2008; Isa and Hall, 2009; Fredes et al., 2012; Kaneda et al., 2011; Gale and Murphy, 2014); in each case these cells display very large dendritic fields that cover significant regions of the SC or optic tectum. Based on the configuration of their dendritic arbors, and interaction with retinotectal inputs *in vitro* (Luksch et al., 2001; Endo et al., 2008), WFV cells have been referred to as motion detectors (Major et al., 2000). This concept has been corroborated *in vivo* in the mouse, where it has been demonstrated

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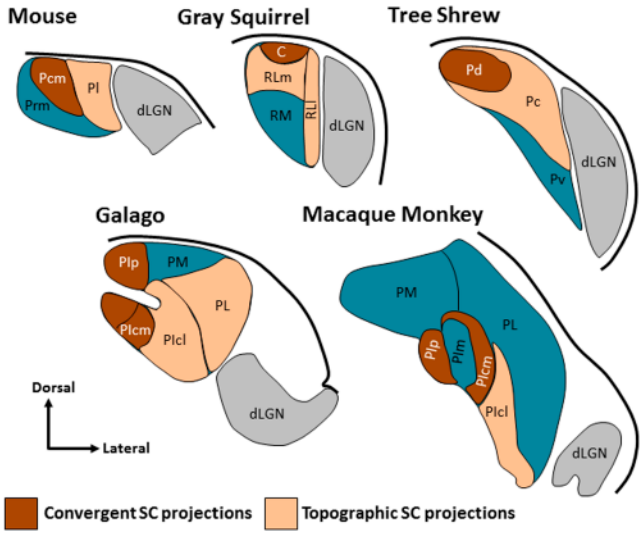

Fig. 1. The pulvinar nucleus contains two tectorecipient zones. Schematic illustrations indicate regions of the pulvinar nucleus in the mouse, squirrel, tree shrew, galago and macaque monkey that have been shown to receive dense convergent input (brown) or less dense topographic projections (peach) from the SC. The non-tectorecipient zones of the pulvinar are indicated in blue, and the location of the dorsal lateral geniculate nucleus (dLGN, gray) is indicated for reference. Illustrations are not to scale (adapted from Stepniewska et al., 2000; Chomsung et al., 2008; Baldwin et al., 2011, 2013; Day-Brown et al., 2017). Subdivisions for **mouse**: Pcm, caudal medial pulvinar, Pl, lateral pulvinar, Prm, rostral medial pulvinar, **squirrel**: C, caudal pulvinar, RL, rostral lateral pulvinar, RLm, medial rostral lateral pulvinar, RLl, lateral rostral lateral pulvinar, RM, rostral medial pulvinar, **tree shrew**: Pc, central pulvinar, Pd, dorsal pulvinar, Pv, ventral pulvinar, **galago and macaque**: PIcm, central medial inferior pulvinar, PIcl, central lateral inferior pulvinar, PIp, posterior inferior pulvinar, PIpl, posterior lateral inferior pulvinar, PL, lateral pulvinar, PM, medial pulvinar, **macaque**: PIm, medial inferior pulvinar.

that WFV cells respond best to a small visual stimulus moving in any direction within a large visual field (Gale and Murphy, 2014, 2016).

In the ground squirrel, two types of WFV cells have been identified. Type I WFV cells extend their dendrites to the most superficial extent of the SC (within the most dorsal regions of the stratum griseum superficiale, or SGS), while type II WFV cell dendrites end in the middle of the SGS (Major et al., 2000). These two cell types have been found to project to different regions of the pulvinar nucleus (Fredes et al., 2012; described in more detail below). Similar to type I and type II WFV cells, the dendrites of type I and type II tectorotundal cells end in different lamina of the chick optic tectum (Luksch et al., 1998), and each type responds differentially to electrical stimulation of retinal input (Luksch et al., 2001).

In the mouse, WFV cells have not been subdivided. However, the availability of transgenic mouse lines (e.g., Gale and Murphy, 2014, 2016; Byun et al., 2016) may help to facilitate the categorization of these cells. If subclasses of WFV cells exist in the mouse, those that extend dendrites most superficially within the SC (Fig. 2C) could potentially be innervated by populations of retinal axons that are restricted to the most superficial regions of the SGS (e.g., those that originate from direction-selective ganglion cells; Rivlin-Etzion et al., 2011). Future studies in mice may take advantage of ganglion cell-specific transgenic lines to determine whether WFV cells are innervated by single ganglion cell subtypes (to form dedicated parallel channels of information flow to the pulvinar) or whether they receive convergent input from multiple classes of ganglion cells.

Tectopulvinar projection patterns

The projections of WFV cells target specific subregions of the pulvinar. In the mouse, the caudal medial pulvinar (Pcm) receives bilateral input from WFV cells and the lateral pulvinar (Pl) receives input from ipsilateral WFV cells (Fig. 3). Similar projection patterns have previously been identified in the rat (Takahashi, 1985), and these two subdivisions can be distinguished with a variety of immunocytochemical markers (Nakamura et al., 2015). In the mouse, the Pcm contains a dense population of terminals that contain substance P (Fig. 4). Similarly, the primate posterior (PIp) and central medial (PIcm) subdivisions of the inferior pulvinar (Fig. 1) also contain a dense population of terminals that stain for substance P (Stepniewska et al., 2000). The mouse Pcm can also be defined based on cells that contain both the calcium-binding protein calretinin and express the substance P receptor neurokinin 1 (NK1, Fig. 3); in contrast, the Pl does not stain with antibodies against substance P, NK1, or calretinin (Figs. 3 and 4).

The organization of tectorecipient zones in the mouse pulvinar is very similar to that identified in the ground squirrel, where the caudal pulvinar receives bilateral, nontopographic SC projections that originate from type I WFV cells, while the rostral pulvinar receives topographic, ipsilateral SC projections that originate from type II WFV cells (Fredes et al., 2012). As illustrated in Fig. 1, two types of tectopulvinar projections, nontopographic or "diffuse" projections and topographic "specific" projections, have also been identified in gray squirrels (Baldwin et al., 2011), tree shrews (Luppino et al., 1988; Chomsung et al., 2008), and galagos (Baldwin et al., 2013). In the tree shrew, the nontopographic tectal projections are highly convergent. These tectopulvinar terminals form dense clusters that surround and synapse on single pulvinar dendrites. In contrast, the topographic projections are less convergent and form smaller, more discrete, synaptic clusters (Chomsung et al., 2008; Wei et al., 2011*b*). These two tectopulvinar innervation patterns have been revealed across species using antibodies against the type 2 vesicular glutamate transporter (vGLUT2, contained in tectopulvinar terminals; Wei et al., 2011*b*); vGLUT2 staining is very dense in regions of the pulvinar that receive convergent tectal input, and lighter in regions that receive topographic tectal projections (Chomsung et al., 2008; Baldwin et al., 2011, 2013). Multiple tectopulvinar pathways that originate from separate SC cell types have also been identified in the cat (Abramson and Chalupa, 1988; Kelly et al., 2003), and in the pigeon, a unique interdigitated pattern of tectorotundal projections originate from separate optic tectum cell types (Marín et al., 2003).

The precise organization of tectopulvinar projections has not been studied in mice. Tracing the axonal projections of single WFV cells would facilitate our understanding of the organization and potential topography of this pathway. Monosynaptic circuit tracing (Wickersham et al., 2007) in transgenic mice (e.g., calretinin-cre mice), could also help to determine whether subclasses of WFV cells target distinct pulvinar subdivisions. In many species, the pulvinar has been subdivided using histochemical staining for the enzyme acetylcholinesterase and/or immunohistochemical staining for the neuromodulator substance P (Graybiel and Berson, 1980; Abramson and Chalupa, 1988; Luppino et al., 1988; Hutsler and Chalupa, 1991; Stepniewska et al., 1999; Kelly et al., 2003; Chomsung et al., 2008; Baldwin et al., 2011, 2013; Fredes et al., 2012). Where examined, these two stains overlap to a great extent, perhaps due to involvement of acetylcholinesterase in the hydrolysis of substance P (Goebel and Pourcho, 1992*a*, 1992*b*). Studies in the cat and rat suggest that the expression of substance P in tectopulvinar

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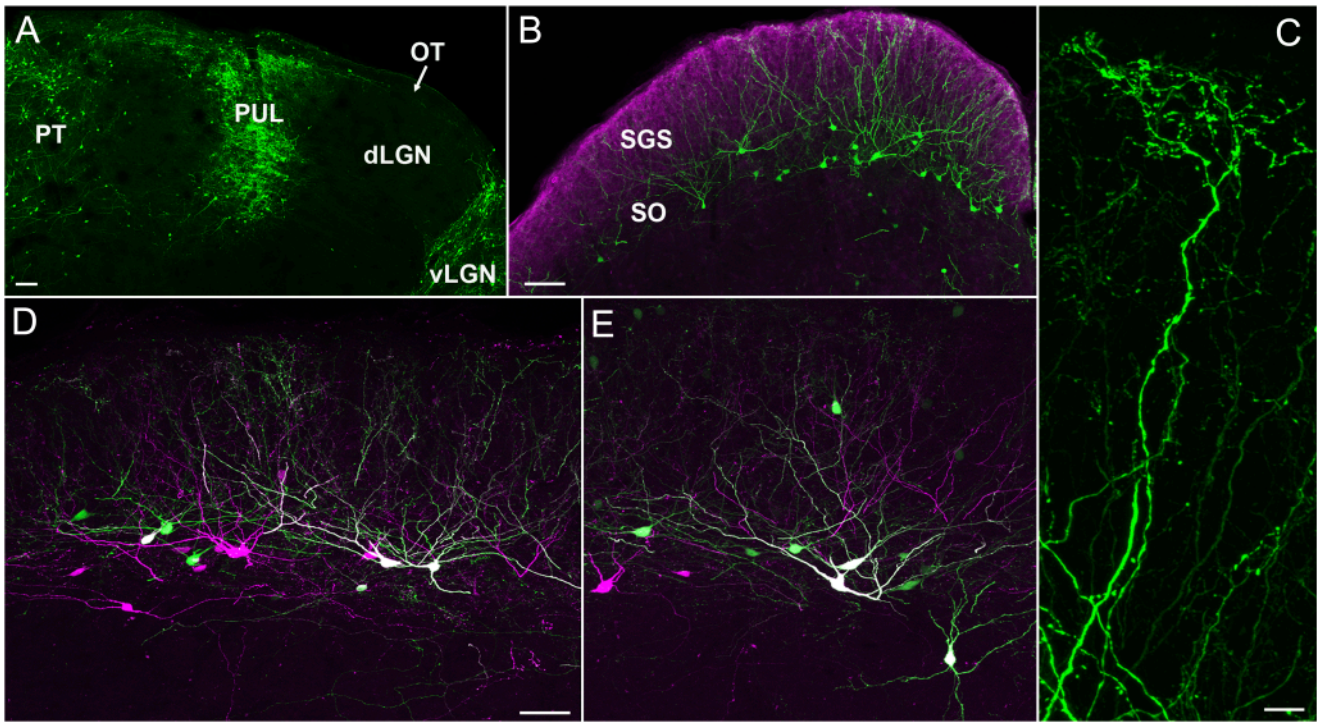

Fig. 2. WFV cells project to the ipsilateral and contralateral pulvinar. Panel **A** illustrates an injection of a retrogradely transported virus (MIT viral vector core: hEF1α-EYFP-IRES-cre) in the pulvinar (PUL) of a wild type mouse that induced the expression of yellow fluorescent protein (YFP, green) in WFV cells of the SC. Cells labeled by this injection are illustrated in panel **B** in a contralateral SC section that was stained with an antibody against calretinin (purple), which delineates the stratum griseum superficiale (SGS). The WFV tectopulvinar cells are located in the stratum opticum (SO) and lower SGS and extend dendrites to the surface of the SC, where they end in complex dendritic tufts (panel **C**). Panels **D** and **E** illustrate WFV cells labeled by injections of retrogradely transported cre-dependent viruses (MIT-viral vector core: hEF1α-LS1L-mCherry and hEF1α-LS1L-EYFP) in the left and right pulvinar of a substance P-cre mouse (Jackson Labs stock number 021877) to induce the expression of either YFP (green, left pulvinar injection) or mCherry (purple, right pulvinar injection) in cre-expressing neurons. Many WFV cells expressed both YFP and mCherry (white), demonstrating that a subpopulation of WFV cells bilaterally innervate the pulvinar, and that WFV cells express substance P. Scale bars: **A** and **B** = 100 μm, **C** = 10 μm, **D** = 50 μm and also applies to **E**. dLGN, dorsal lateral geniculate nucleus, PT, pretectum, OT, optic tract. Virus injection methods as in Bickford et al. (2015).

pathways is developmentally regulated, and influenced by visual input (Miguel-Hidalgo et al., 1990, 1991; Behan et al., 1993). The mouse is an ideal model to further define the role of substance P in tectopulvinar pathways by using transgenic lines, optogenetics, and/or designer receptors exclusively activated by designer drugs (DREADD) to manipulate substance P pathways and characterize any resulting behavioral effects.

Synaptic properties of tectopulvinar terminals

Tectopulvinar terminals have consistently been found to form clusters of relatively large terminals that surround and synapse on the proximal dendrites of pulvinar neurons (Partlow et al., 1977; Robson and Hall, 1977; Crain and Hall, 1980*a*; Kelly et al., 2003; Chomsung et al., 2008; Masterson et al., 2009; Wei et al., 2011*b*; Bickford, 2016); tectopulvinar terminals in the mouse exhibit similar characteristics (Fig. 5B). *In vitro* slice studies in the rat and tree shrew have demonstrated that multiple tectopulvinar axons can converge on single cells (Masterson et al., 2010; Wei et al., 2011*b*), presumably contributing to the large receptive fields of pulvinar neurons (Chalupa et al., 1983; Mooney et al., 1984; Chalupa and Abramson, 1988; Casanova et al., 2001; Dumbrava et al., 2001; Berman and Wurtz, 2011; Roth et al., 2016).

Tectopulvinar terminals release glutamate to activate ionotropic glutamate receptors on postsynaptic neurons (Masterson et al., 2010; Wei et al., 2011*b*). Stimulation of tectopulvinar terminals at frequencies of up to 20 Hz elicits postsynaptic responses that maintain relatively stable amplitudes (unlike the frequency-dependent amplitude changes demonstrated in other thalamic pathways; for review see Bickford, 2016). This frequency-independence may be due to the synaptic arrangements of these terminals and/or the presynaptic proteins contained within them (synapsin I and synapsin II; Wei et al., 2011*b*). Another unique feature of tectopulvinar terminals is that stimulation at 100 Hz can elicit their release of substance P which, through activation of neurokinin 1 receptors, can boost tectopulvinar responses (Masterson et al., 2010).

Again, the mouse is an ideal model to study further details of the synaptic properties of tectopulvinar terminals. These terminals can be specifically activated using optogenetic techniques (Maire et al., 2015) and transgenic lines (e.g., mice that lack synapsins; Kielland et al., 2006; Song and Augustine, 2015) can potentially be used to determine the mechanisms that underlie their unique frequency-independence. Studies in mice may also reveal whether substance P is contained in all tectopulvinar projections, or confined to those originating from specific WFV subclasses. Our previous *in vitro* studies in the rat suggested that

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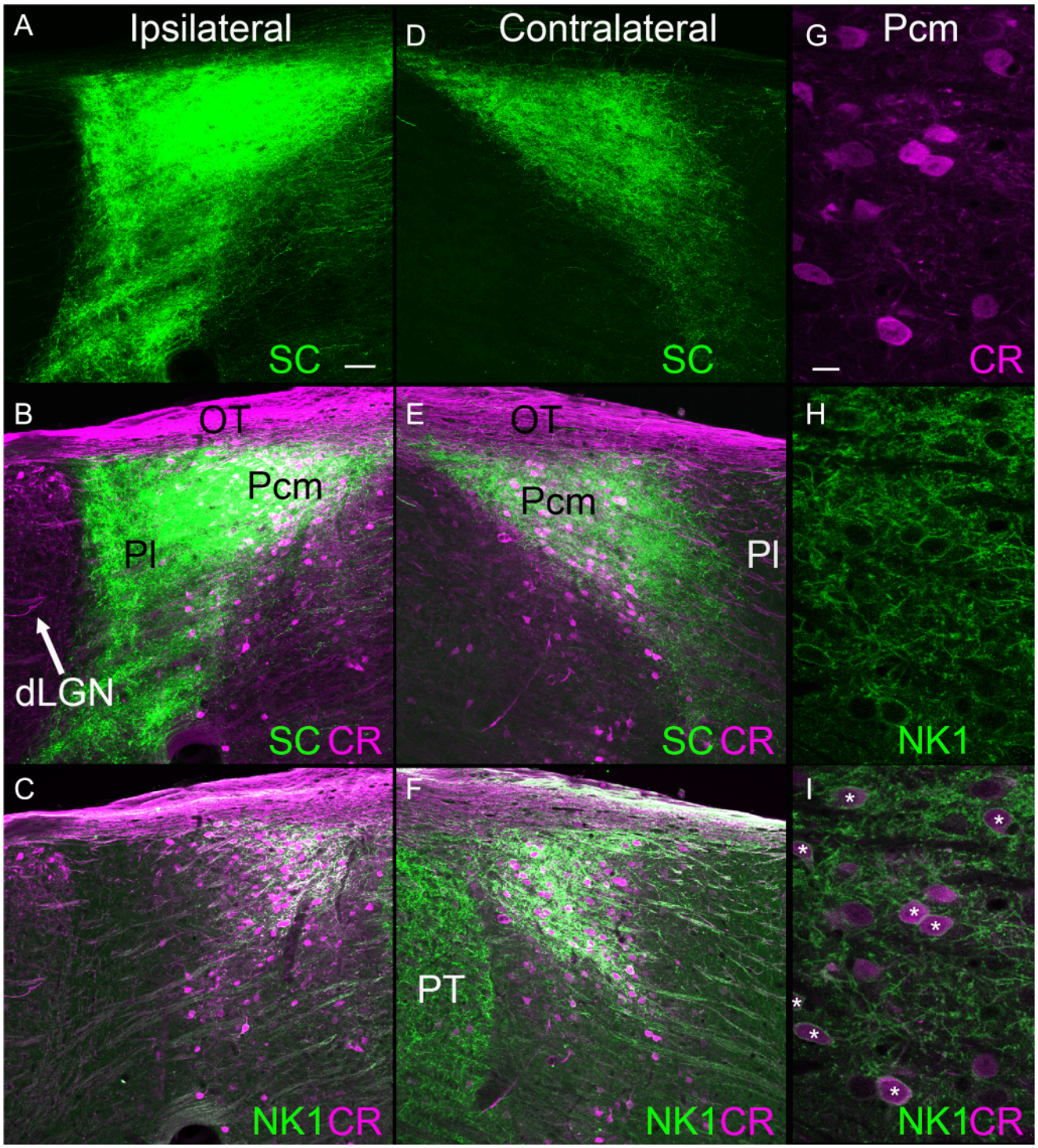

Fig. 3. Caudal medial pulvinar (Pcm) cells express calretinin (CR) and neurokinin 1 (NK1) and align with bilateral SC projections. Confocal images illustrate ipsilateral (**A**, **C**, green) and contralateral (**D**, **F**, green) projections to the pulvinar that were labeled by a unilateral virus injection in the SC. These sections were also stained with antibodies against CR (**B**, **E**, purple) to define the Pcm (which contains CR) and the lateral pulvinar (Pl, which does not contain CR). Adjacent sections (**C**, **F**) stained for CR (purple) and NK1 (green) illustrate that CR-positive Pcm cells express NK1. This expression pattern is shown at higher magnification in half micron optical sections in panels **G** (CR, purple), **H** (NK1, green) and **I** (CR, purple, and NK1, green, asterisks indicate cells labeled with both antibodies). Scale in **A** = 50 μm and applies to **A**–**F**. Scale in **G** = 10 μm and applies to **G**–**I**. dLGN, dorsal lateral geniculate nucleus, OT, optic tract, PT, pretectum. Methods as in Masterson et al. (2010) and Bickford et al. (2015).

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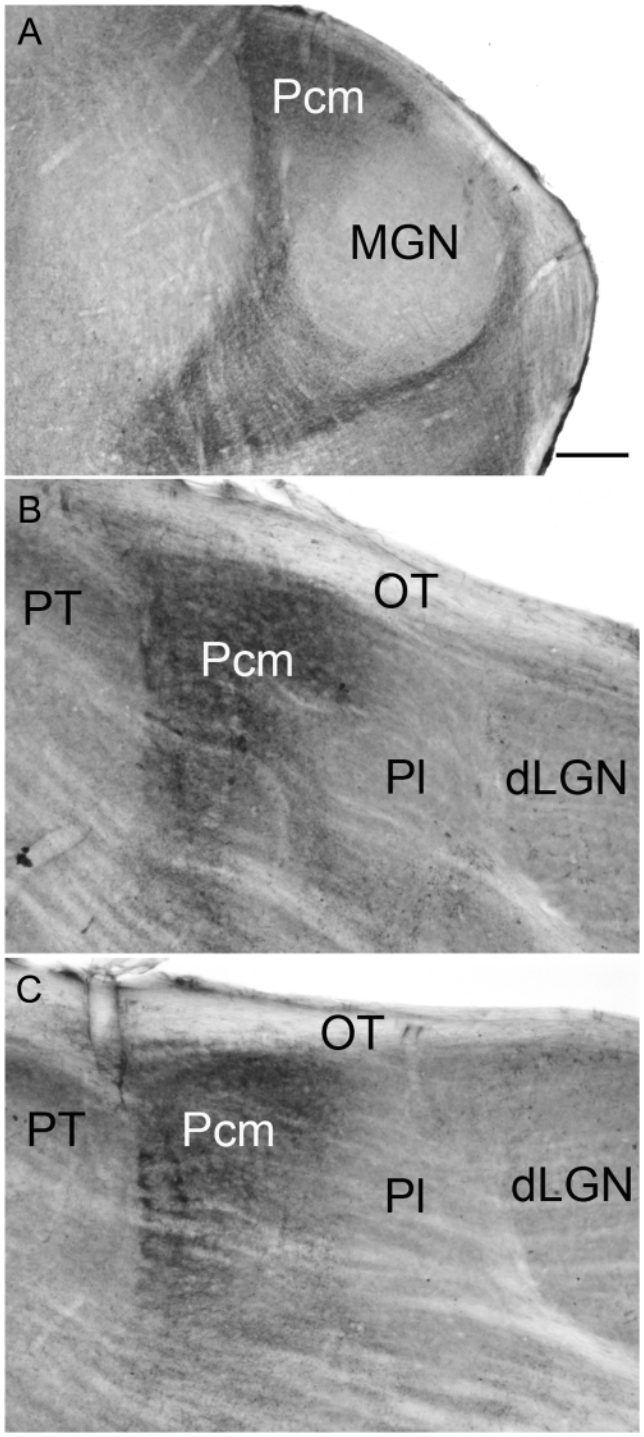

Fig. 4. The Pcm contains a dense population of terminals that contain substance P. (**A**–**C**) Caudal to rostral sections stained with an antibody against substance P (visualized with a diaminobenzidine reaction). Staining is densest in the caudal and medial pulvinar (Pcm). Little staining is observed in the lateral pulvinar (Pl). Scale = 100 μm and applies to all panels. dLGN, dorsal lateral geniculate nucleus, MGN, medial geniculate nucleus, OT, optic tract, PT, pretectum. Methods as in Masterson et al. (2010).

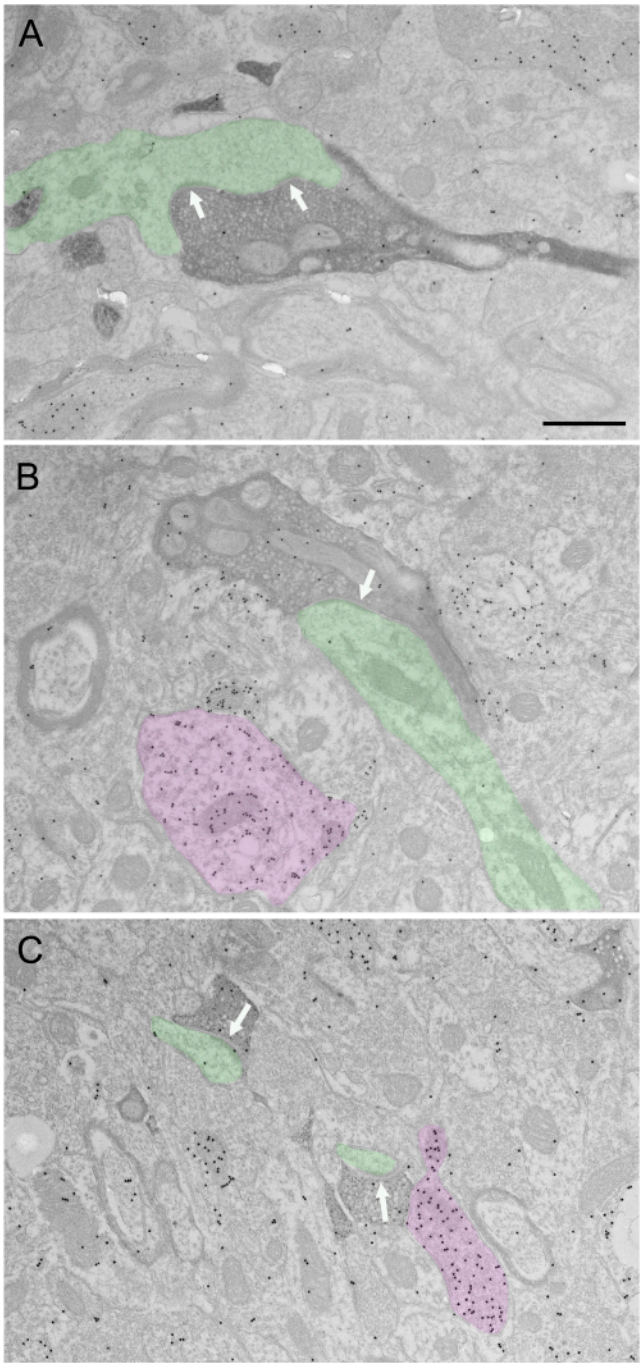

Fig. 5. Ultrastructure of cortical and tectal terminals in the mouse pulvinar. Terminals labeled by the anterograde transport of biotinylated dextran amine injected in V1 (**A**), superior colliculus (**B**) or the posterior/postrhinal cortex (**C**) contact (white arrows) the proximal (**A**, **B**) and distal (**C**) dendrites of pulvinar neurons (green overlay). Sections were additionally stained with gold particles to reveal the distribution of GABA. This identifies two types of GABAergic terminals (purple overlay) in the mouse pulvinar: F2 profiles (**B**) contain a low density of vesicles and F1 profiles (**C**) contain a high density of vesicles. Scale = 600 nm and applies to all panels. Methods as in Li et al. (2003*a*).

all tectopulvinar projections contain substance P (Masterson et al., 2010). However, our investigation was limited to the caudal most regions of the pulvinar (likely corresponding to the mouse Pcm; Fig. 4).

Retinal innervation and plasticity of pulvinar pathways

Tecto-pulvinar pathways have often been cited as the substrate mediating "blindsight": the ability, in the absence of visual perception, to navigate using visual cues and respond to negative or

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fearful facial expressions (Leopold, 2012; Schmid and Maier, 2015). However, it has recently been demonstrated that during development, the pulvinar transiently receives substantial direct input from the retina, which diminishes to sparser levels in adults. This pathway shows considerable plasticity: in situations where V1 is lost at an early age, this retinopulvinar pathway does not regress, and may account for the preservation of vision when lesions to V1 occur during infancy (Warner et al., 2012; Kaas, 2015; Bridge et al., 2016).

In the mouse, it has been demonstrated that at least some of the retinopulvinar projections arise from intrinsically photosensitive (melanopsin-containing) ganglion cells, and a portion of pulvinar neurons are functionally influenced by melanopsin-derived signals (Allen et al., 2016). A melanopsin-dependent light aversion response in neonatal mice activates pulvinar cells, as well as cells in the amygdala (which as discussed below, receives input from the pulvinar; Delwig et al., 2012). Perhaps, as in primates, direct retinopulvinar projections in the mouse are also more robust during development and function to initiate basic movements in response to light. However, it is still unknown how direct retinopulvinar *versus* indirect retino-tecto-pulvinar pathways contribute to melanopsin-dependent pulvinar responses, and motor behaviors.

Lesion studies in the hamster demonstrated that terminals originating from the retina, SC and cortex all compete for territory in the developing pulvinar nucleus; retinopulvinar terminations expand after SC lesions and/or combined SC and cortex lesions (Crain and Hall, 1980*b*, 1980*c*, 1981). Further investigations in mice may help to define mechanisms underlying the developmental competition between retinopulvinar, tectopulvinar, and corticopulvinar projections, and how this might correlate with transitions from the simple light-aversive movements of neonates to the more complex visually-guided escape, freezing or prey capture behaviors of adult mice (Yilmaz and Meister, 2013; De Franceschi et al., 2016; Hoy et al., 2016).

The striate-recipient zones of the pulvinar

Across mammalian species, the pulvinar also contains zones that are innervated by the striate cortex (cat; Berson and Graybiel, 1983; Guillery et al., 2001; Huppé-Gourgues et al., 2006; rat; Li et al., 2003*c*; macaque; Ogren and Hendrickson, 1979*a*). In rodents, terminals that originate from V1 innervate the Pl, as well as more rostral thalamic regions (the rostral medial pulvinar, Prm, and lateral dorsal nucleus, LD; Bourassa and Deschênes 1995). These more rostral regions are well segregated from the tectorecipient zones. However, the mouse Pl shows considerable overlap in the distribution of terminals originating from the SC and V1 (Figs. 6L and 7B). The striate- and tectorecipient zones of the pulvinar are also well segregated in other species, but may contain some zones of overlap (e.g. the cat LPl-2; Abramson and Chalupa, 1988; Chalupa and Abramson, 1989; Kelly et al., 2003; Huppé-Gourgues et al., 2006).

The striate-recipient zones of the mouse pulvinar form reciprocal connections with V1, with pulvinocortical projections to V1 ending primarily in layers I and V (Fig. 8B; Herkenham, 1980; Roth et al., 2016; Rubio-Garrido et al., 2009). Retrograde tracing studies in the mouse indicate that the pulvinocortical projections to V1 are organized in a roughly topographic manner, but this organization is clearly different from the precise topography of connections between V1 and the dorsal lateral geniculate nucleus (dLGN; Roth et al., 2016). In addition, tracing of single axons in the rat indicates that individual pulvinar cells that project to V1 also send projections to various areas of the extrastriate cortex, as well as the striatum (Nakamura et al., 2015).

V1 projections to the pulvinar have been shown to arise from cells in layer V, as well as cells in lower layer VI (cat; Abramson and Chalupa, 1985; rat; Bourassa and Deschênes, 1995; galago; Conley and Raczkowski, 1990; macaque; Lund et al., 1975; mouse; Roth et al., 2016). The terminals that arise from layer V cells are significantly larger than corticogeniculate terminals or tectopulvinar terminals (rat; Bourassa and Deschênes, 1995; tree shrew; Chomsung et al., 2008; Day-Brown et al., 2017; cat; Guillery et al., 2001; Huppé-Gourgues et al., 2006; Kelly et al., 2003; rat; Li et al., 2003*c*; Masterson et al., 2009), and similar large V1 corticopulvinar terminals are found in the mouse (Figs. 5A and 7A).

Extrastriate connections of the mouse pulvinar nucleus

Visual areas of the mouse cortex have been defined on the basis of corticocortical connections with V1 (Wang and Burkhalter, 2007). In this way nine distinct visual areas that surround V1 have been identified: posterior (P), postrhinal (POR), lateromedial (LM), laterointermediate (LI), anterolateral (AL), rostrolateral (RL), anterior (A) anteromedial (AM), and posterormedial (PM). All of these extrastriate visual areas are reciprocally connected to the mouse pulvinar nucleus (Tohmi et al., 2014), and also innervate the SC (Wang and Burkhalter, 2013). The tectorecipient zones of the pulvinar are primarily connected with the lateral extrastriate cortex (LES, Fig. 6C and 6G; primarily areas P, POR, LM, and LI). These connections are roughly topographic, with the Pcm forming reciprocal connections primarily with more ventral regions (P and POR) and the Pl primarily forming connections with more dorsal regions adjacent to V1 (LM and LI; Figs. 8 and 9; Tohmi et al., 2014). However, given the widespread projections of single pulvinocortical axons identified in the rat (Nakamura et al., 2015), the exact organizational scheme of pulvinocortical projections remains an open question.

Within the extrastriate cortical areas connected with the tectorecipient pulvinar, pulvinocortical terminals are concentrated in layer IV, and corticopulvinar cells are concentrated in layer VI (Fig. 8D; Herkenham, 1980; Abramson and Chalupa, 1985; Masterson et al., 2009; Chomsung et al., 2010; Nakamura et al., 2015; Roth et al., 2016). Cortical terminals that innervate the tectorecipient zones of the pulvinar nucleus primarily form smaller terminals that innervate smaller, distal dendrites (Fig. 5C; Robson and Hall, 1977; Masterson et al., 2009; Chomsung et al., 2010). Electrical stimulation of corticopulvinar terminals in tectorecipient zones of the rat initially elicits small amplitude glutamatergic excitatory postsynaptic potentials (EPSPs), but repetitive stimulation rapidly increases EPSP amplitudes in a frequency-dependent manner (Masterson et al., 2010). This contrasts with electrical activation of corticopulvinar terminals in more rostral regions of the rat pulvinar nucleus, where a second type of large amplitude EPSP can also be elicited, which exhibits a frequency-dependent decrease in amplitude (Li et al., 2003*b*). These two types of EPSPs, which presumably result from the activation of terminals that originate from layer V or layer VI corticopulvinar cells, also differ in the degree of convergence onto single pulvinar neurons. Electrical stimulation of layer VI corticopulvinar axons with increasing current levels results in a graded increase in the amplitude of postsynaptic responses, demonstrating that many terminals converge on postsynaptic neurons. In contrast, electrical stimulation of layer V corticopulvinar axons with increasing current levels results in "all or none" changes in the

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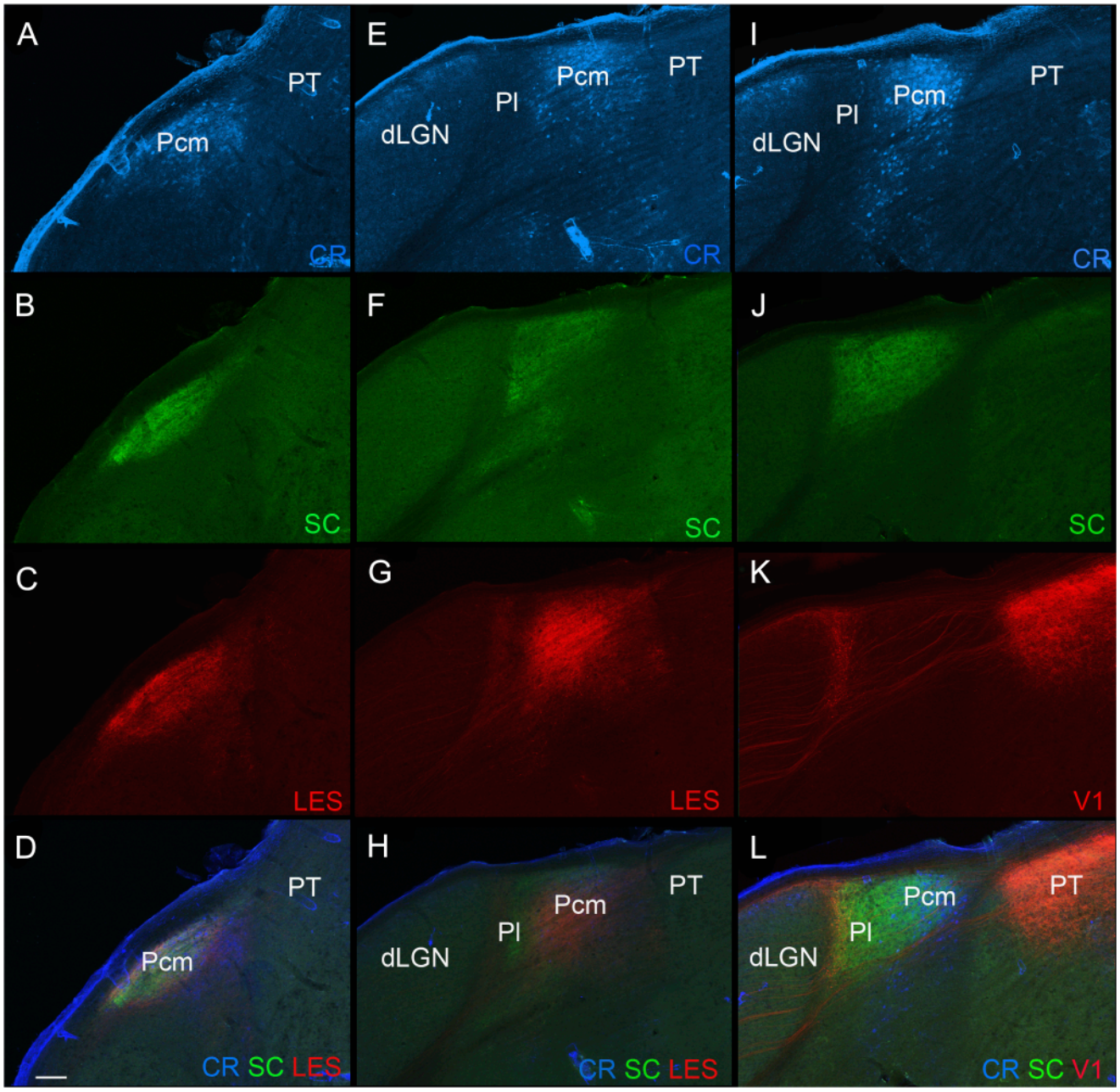

Fig. 6. Tectopulvinar and corticopulvinar terminals overlap in the caudal medial (Pcm) and lateral (Pl) subdivisions of the mouse pulvinar. This overlap is demonstrated *via* dual virus injections in the SC and lateral extrastriate cortex (LES, first 2 columns, **A**–**D** and **E**–**H**), or SC and V1 (last column, **I**–**L**). The Pcm and Pl subdivisions are defined using immunocytochemical staining for calretinin (CR, blue, first row, **A**, **E**, **I**). Virus injections were placed in the SC to induce the expression of yellow fluorescent protein (green, panels **B**, **F**, **J**), and in the cortex (V1 or LES) to induce the expression of TdTomato (red, panels **C**, **G**, **K**), overlap of the CR and virus labeling patterns (panels **D**, **H**, **L**) show that the Pcm is innervated by the SC and LES, while the Pl is innervated by the SC, V1 and LES (panels **D**, **H**, **L**). Scale bar in **D** = 100 μm and applies to all panels. dLGN, dorsal lateral geniculate nucleus, PT, pretectum. Methods as in Jurgens et al. (2012) and Bickford et al. (2015).

amplitude of postsynaptic responses, demonstrating that each postsynaptic neuron receives input from only a few of these axons (Li et al., 2003*b*; Masterson et al., 2010).

The function of layer V *versus* layer VI corticopulvinar projections is still unclear. It has been proposed that layer V corticopulvinar projections function to transfer signals from one cortical area to another (Guillery and Sherman, 2002). It has also been suggested that layer V corticothalamic projections could function to detect the relative timing of sensory events and ongoing cortical activity (Groh et al., 2008). Experiments in mice could be designed to specifically manipulate the activity of layer V *versus* layer VI corticopulvinar projections to determine the effects on pulvinar activity, cortical activity and/or behavior. Such experiments would be particularly important for testing the hypothesis that layer V corticopulvinar projections are the primary determinant ("drivers") of pulvinar neuron receptive field properties (Sherman and Guillery, 1998).

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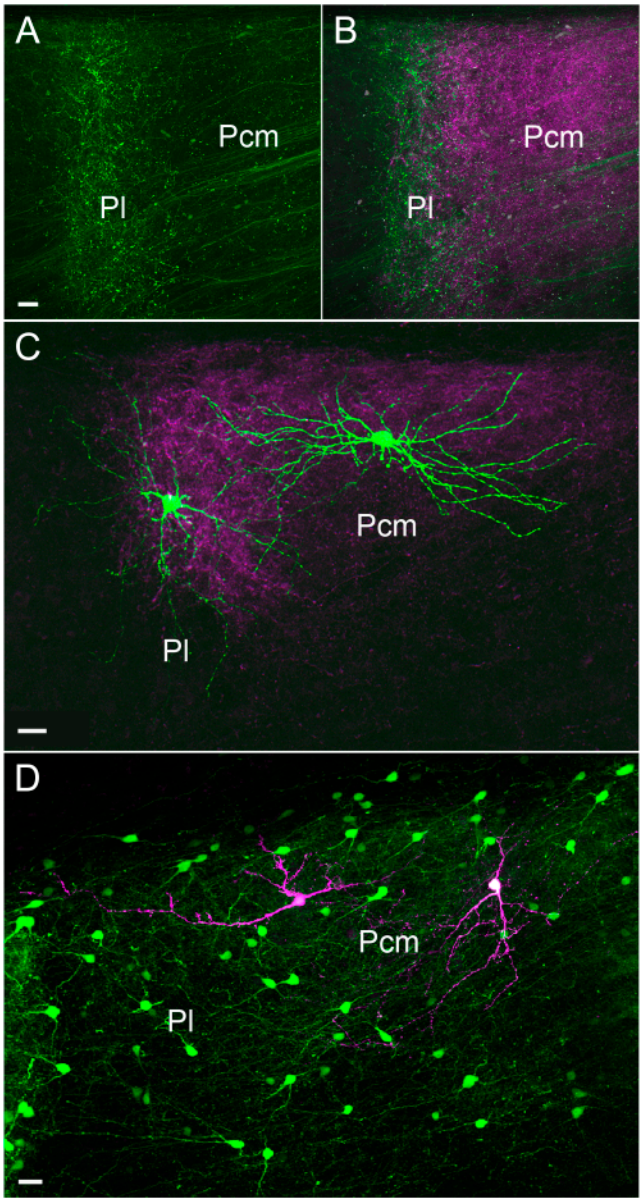

Fig. 7. Potential input integration in the mouse pulvinar. Terminals labeled by a virus injection in V1 (green, **A**, **B**) and the ipsilateral SC (purple, **B**) overlap in the Pl. (**C**) Two biocytin-filled pulvinar neurons (green) and surrounding tectopulvinar terminals (purple, labeled by a virus injection in the ipsilateral SC). The dendrites of the pulvinar neurons extend across subdivisions. (**D**) Biocytin-filled pulvinar interneurons (purple) identified in a mouse line (Jackson Laboratories stock number 007677) that expresses green fluorescent protein in GABAergic neurons (green) extend dendrites across subdivisions. Scale bars = 20 μm. Methods as in Bickford et al., (2015).

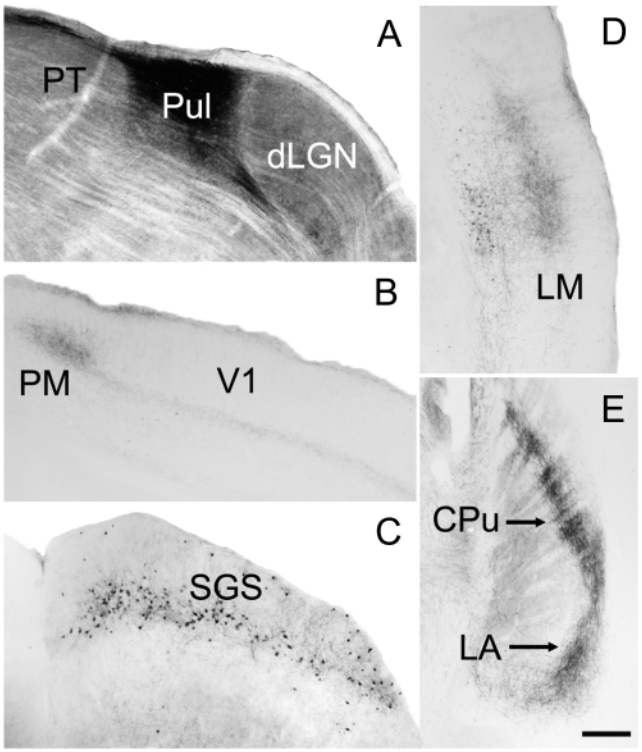

Fig. 8. The mouse pulvinar projects to the cortex, striatum and amygdala. Injections of biotinylated dextran amine in the mouse pulvinar (**A**) label terminals in V1 (**B**) and extrastriate cortex regions including the posterior medial area (PM, panel **B**) and the lateral medial area (LM, panel **D**). Cells in the superior colliculus (**C**) and LM (**D**) are also labeled by retrograde transport. (**E**) The pulvinar also projects to the caudate and putamen (CPu) and lateral amygdala (LA). Scale = 200 μm and applies to all panels. Methods as in Chomsung et al. (2010).

Pulvinar projections to the striatum and amygdala

The tectorecipient zones of the pulvinar also project to the striatum and lateral amygdala (Takahashi, 1985; Harting et al., 2001*a*,*b*; McHaffie et al., 2005; Day-Brown et al., 2010; Nakamura et al., 2015; Roth et al., 2016), suggesting pulvinar involvement in the visual guidance of movement. Recently, activation of the mouse SC-pulvinar-amygdala pathway has been shown to elicit freezing responses, while inactivation of this pathway inhibits the innate freezing response to overhead looming stimuli (Wei et al., 2015). Similar pathways have been implicated in visually-triggered fear responses across species (Carr, 2015).

In the tree shew, pulvinar-amygdala cells are concentrated in the regions of the pulvinar that receive the nontopographic projections from the SC (Pd, Fig. 1, Day-Brown et al., 2010). Likewise, mouse pulvinar-amygdala cells appear to be concentrated in the Pcm (Wei et al., 2015). In the rat, SC contacts on pulvinar-amygdala cells have been identified (Linke et al., 1999), and cells in regions corresponding to the Pcm branch to innervate the ventral temporal cortex and amygdala (Doron and Ledoux, 2000), or caudal striatum (Nakamura et al., 2015). Thus, the bilateral SC-pulvinar-amygdala pathway (Fig. 9A) may primarily function to activate freezing or escape responses. Mice could be used for future studies to determine whether the unilateral SC-pulvinar-striatum projections (Fig. 9B) trigger distinct motor responses, such as prey capture (Hoy et al., 2016).

Cell types within the pulvinar nucleus

Our understanding of the organization of the dLGN was greatly advanced by the identification of morphological cells types that correlate with functional cell classes (e.g. Friedlander et al., 1981); identification of structure/function correlations for pulvinar neurons is expected to similarly advance our understanding of this nucleus. The pulvinar contains projection cells (Fig. 7C; Nakamura et al., 2015), GABAergic interneurons (Fig. 7D; Carden and Bickford,

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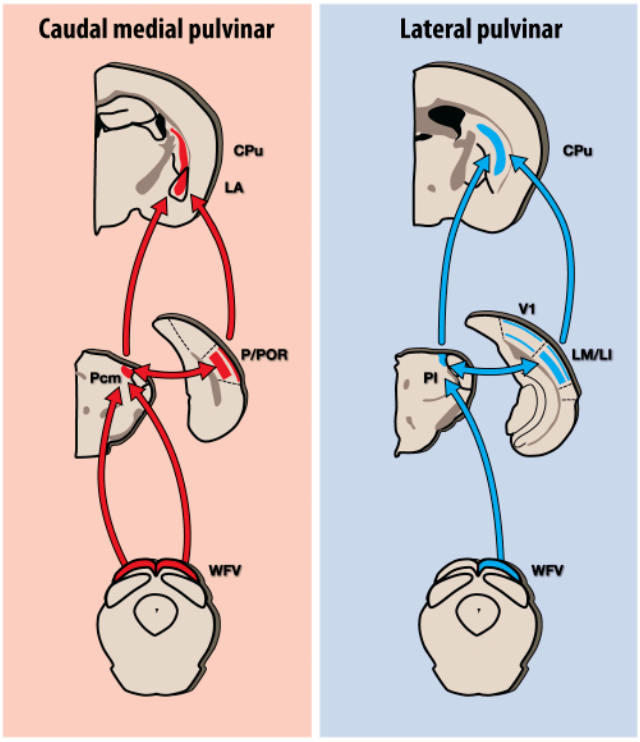

Fig. 9. The tectorecipient mouse pulvinar forms interconnected loops with the cortex, striatum and amygdala. The schematic diagrams illustrate the main connections of the tectorecipient subdivisions of the mouse pulvinar. The caudal medial pulvinar (Pcm, red) receives bilateral input from WFV cells of the SC, and is reciprocally connected to the posterior (P) and postrhinal (POR) regions of the cortex, where it innervates layers I and IV–VI. Both the Pcm and P/POR project to the caudal caudate/putamen (CPu) and lateral amygdala (LA). The lateral pulvinar (Pl, blue) receives ipsilateral input from WFV cells, and is reciprocally connected to V1 and the lateral medial (LM) and lateral intermediate (LI) regions of the cortex. Within V1, the Pl projects to layers I and Va. Within LM and LI, the Pl projects to layer I and IV. The Pl, LM and LI project to the middle regions of the CPu.

2002; Chomsung et al., 2008; Li et al., 2003*c*), and a dense population of glial cells (glial to neuron ratio of approximately 3:1 in the tree shrew pulvinar; Wei et al., 2011*a*). In the rat, the axons of individual projection cells have been shown to innervate multiple cortical areas, multiple cortical lamina, as well as the striatum and amygdala (Nakamura et al., 2015). Evidence in the cat and primate also suggests that pulvinar axons innervate widespread cortical areas (Kaufman et al., 1984; Baleydier and Mauguière, 1987; Rockland, 2002). Therefore, the subdivision of pulvinar neurons based on projection targets is not straightforward.

In addition, the dendrites of pulvinar neurons are not restricted to specific input zones (Fig. 7C and 7D; Ogren and Hendrickson, 1979*b*; Imura and Rockland, 2006; Nakamura et al., 2015). The widespread distribution of pulvinar dendritic arbors may explain why SC cells are transynaptically labeled after pseudorabies virus injections in the middle temporal cortical area (Lyon et al., 2010), even though tectopulvinar terminals do no overlap the distribution of pulvinar somata labeled by retrograde tracer injections in the same cortical regions (Stepniewska et al., 1999). The distribution of pulvinar neuron dendritic arbors suggests that a substantial integration of inputs may occur even when the distributions of pulvinar afferents are largely segregated. For example, the dendritic fields of individual mouse pulvinar neurons can extend across both the Pcm and Pl (Fig. 7C and 7D), potentially receiving input from bilateral and ipsilateral tectopulvinar projections (Fig. 3A and 3D), V1 (Figs. 6K and 7A), as well as extrastriate cortical areas (Fig. 6C and 6G). Therefore, it may be challenging to identify subclasses of pulvinar neurons based on presynaptic inputs.

Comparison of neurons recorded within tectorecipient and striate-recipient zones of the cat pulvinar complex have revealed differences in receptive field sizes, direction- and orientation selectivity (Chalupa et al., 1983; Abramson and Chalupa, 1988; Chalupa and Abramson, 1988, 1989). However, analysis of spatiotemporal receptive field properties in these two zones using white noise and reverse correlation analysis suggests a significant integration of V1 and SC inputs across subdivisions (Piché et al., 2015). Furthermore, as discussed above, retrograde tracing techniques demonstrated that mouse pulvinocortical projections to V1 are coarsely topographic (Roth et al., 2016). However, this same study revealed that individual pulvinocortical boutons are activated by widely dispersed locations across the visual field, suggesting that while pulvinocortical axon projections may be aligned with the retinotopic organization of V1, they can contribute a surround modulation of cortical neurons that extends well beyond what their anatomical topography might imply.

Again, the mouse may be a useful model to dissect potential structure/function relationships within the pulvinar. Transgenic mouse lines (e.g., calretinin-cre) may provide a starting point for subdividing neuron groups, and whole cell recordings may identify differences in membrane properties (Monckton and McCormick, 2002; Li et al., 2003*a*; Ramcharan et al., 2005; Wei et al., 2011*a*). However, perhaps the most important step in this process is the characterization of pulvinar receptive field properties in moving animals, as discussed below.

Pulvinar activity and visual context

In the anesthetized mouse, spontaneous activity in the pulvinar is significantly lower than that recorded in the dLGN (Roth et al., 2016), and even in awake but inactive primates, the spontaneous activity of pulvinar neurons is less than half that of dLGN neurons (Ramcharan et al., 2005). In addition, in anesthetized mice the proportion of pulvinar neurons that respond to simple visual stimuli is approximately half that of dLGN neurons (Allen et al., 2016). These differences in activity levels/visual responsiveness likely reflect functional distinctions between these two visual pathways. Recently, imaging studies in actively-moving mice have demonstrated that pulvinocortical projections to V1 signal discrepancies between optic flow and running speed (Roth et al., 2016). A similar role for the pulvinar in visuomotor coupling is supported by primate studies, where inactivation of the pulvinar nucleus disrupts the planning of visually-guided eye and hand movements (Wilke et al., 2010). Thus, the activity of the pulvinar nucleus reflects vision in the context of movement, and this activity appears to be critical for the subsequent planning and execution of appropriate visually-guided action.

Given this evidence, it appears to be essential to characterize pulvinar receptive field properties in the context of movement. To accomplish this, experiments must be carried out in awake behaving animals. While across-species comparative studies are needed, mice can be used to efficiently address a number of initial open questions. For example, what is the source of the motor signals in the pulvinar nucleus? It has been established that premotor cells in the deep SC provide corollary discharge signals to the

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mediodorsal nucleus to signal impending movements (Bickford and Hall, 1989; Sommer and Wurtz, 2002; Wurtz et al., 2011). *In vitro* slice studies have shown premotor cells in the deep layers of the SC can affect the activity of tectothalamic cells in the superficial layers (Phongphanphanee et al., 2011); in this way WFV cells could potentially provide contextual signals to the pulvinar nucleus. Recordings from WFV cells in awake behaving mice could determine whether internally-generated movement commands modify their responses to moving visual stimuli.

The pulvinar projects directly to the striatum and amygdala (discussed above), and preliminary studies indicate that pulvinocortical terminals target corticostriatal and corticoamygdala cells (Zhou et al., 2016*a*). Thus, the pulvinar is at the center of a hub connecting the cortex, striatum, and amygdala (Fig. 9). The interconnected nature of these circuits (as well as their potential influence on SC circuits *via* the substantia nigra and/or zona incerta; Bickford and Hall, 1992; Kim et al., 1992; McHaffie et al., 2005), suggests that the pulvinar actively participates in the dynamic coordination of body movements with the perception of visual signals. However, it is still unclear how activity levels in the striatum and amygdala might affect pulvinar activity. Recording visual receptive field properties of pulvinar neurons during optogenetic manipulation of the amygdala (Tye et al., 2011; Wei et al., 2015), or subpopulations of striatal projection cells (Kravitz et al., 2012), may help to reveal mechanisms that impart context to pulvinar signals.

Summary

Many similarities have been identified in the organization of the pulvinar nucleus across species, and the mouse provides a very useful model to continue to unravel the function of this puzzling structure. The tectorecipient pulvinar forms interconnected loops with the cortex, striatum and amygdala, and emerging evidence suggests that these circuits may be designed to code visual signals in the context of ongoing movement. Thus, the pulvinar nucleus may play a key role in the planning and execution of appropriate visually-guided movements, which require the precise coordination of perception and action. Future studies designed to manipulate circuits may shed light on the repertoire or behaviors mediated by the pulvinar nucleus, and mechanisms underlying their selection. In this way, the mouse model may be a particularly useful tool to inform and guide our understanding of the human pulvinar nucleus.

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