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Visual Function, Organization, and Development of the Mouse Superior Colliculus

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Abstract

The superior colliculus (SC) is the most prominent visual center in mice. Studies over the past decade have greatly advanced our understanding of the function, organization, and development of the mouse SC, which has rapidly become a popular model in vision research. These studies have described the diverse and cell-type-specific visual response properties in the mouse SC, revealed their laminar and topographic organizations, and linked the mouse SC and downstream pathways with visually guided behaviors. Here, we summarize these findings, compare them with the rich literature of SC studies in other species, and highlight important gaps and exciting future directions. Given its clear importance in mouse vision and the available modern neuroscience tools, the mouse SC holds great promise for understanding the cellular, circuit, and developmental mechanisms that underlie visual processing, sensorimotor transformation, and, ultimately, behavior.

INTRODUCTION

The superior colliculus (SC), as well as its nonmammalian homolog, the optic tectum, is a midbrain structure important for multimodal integration and sensorimotor transformation. It is an evolutionarily conserved structure that receives direct retinal input in all known taxa of vertebrates, and even in nonvertebrate chordates (Kusunoki & Amemiya 1983). It was the most sophisticated visual center until the neocortex recently evolved in mammals. In mice, a mammal that has become a productive model in vision research in recent years (Huberman & Niell 2011), more than 85% of retinal ganglion cells (RGCs) project to the SC (Ellis et al. 2016), making it by far the most prominent visual center in this species.

With the advances in mouse genetics, it is now possible to identify subtypes of neurons within a given brain structure, to trace synaptic connectivity, and to manipulate gene expression and neuronal activity in a spatially and temporally controlled manner (Callaway & Luo 2015, Huang & Zeng 2013, Kim et al. 2017, Sjulson et al. 2016). These advances, together with the recent development of two-photon Ca^{2+} imaging (Svoboda & Yasuda 2006) and large-scale electrophysiology recording (Buzsaki et al. 2015), have enabled rapid progress in functional studies of the mouse visual system. Even though most of these studies are still focused on the retina and cortex (Demb & Singer 2015, Diamond 2017, Glickfeld & Olsen 2017, Niell 2015, Wei & Feller 2011), the mouse SC has received rapidly increasing attention in vision research owing to its clear importance in visually guided behaviors and the rich literature of SC studies in other species.

Here, we first provide a brief background of the SC based on decades of studies in numerous species. This section is limited to information that is essential for understanding the rest of the review. Readers are encouraged to read a number of recent reviews on these topics (e.g., Basso & May 2017, Cang & Feldheim 2013, Gandhi & Katnani 2011, Krauzlis et al. 2013, May 2006). We then summarize recent results on the function, organization, and development of the mouse SC, with a particular focus on visual processing and visually guided behaviors. Comparisons with findings in other mammalian species are made whenever necessary. We conclude by outlining a number of outstanding questions and exciting future directions.

BACKGROUND INFORMATION ON THE SUPERIOR COLLICULUS

The SC has been studied in numerous mammalian species, including nonhuman primates, tree shrews, cats, hamsters, squirrels, rats, and mice, making it one of the most studied structures in neuroscience research (Basso & May 2017). These studies reveal two key features of SC organization that are conserved among different species (**Figure 1**). First, the SC is a layered structure with alternating strata of fibers and cell bodies. Inputs to the SC are organized according to modality along the superficial to deep axis, with superficial layers being visual and deeper layers multimodal and premotor (May 2006, Stein 1984). Second, individual SC layers contain topographic maps of the sensory periphery or motor commands, and these maps are in register across layers (Cang & Feldheim 2013). The alignment of these maps allows the SC to integrate multisensory information and to initiate orienting movements toward salient stimuli.

The most superficial cellular layer of the SC is the stratum griseum superficiale (SGS), or the superficial gray layer. SGS neurons receive direct retinal input from ganglion cell (RGC) axons that course in the deeper stratum opticum (SO), or the optic layer. While the SO consists mostly of white matter, it contains some cell bodies as well. Retinal inputs are mapped topographically such that SGS and SO neurons represent the two-dimensional visual field along the anterior-posterior and medial-lateral axes of the SC (**Figure 1*a***). The SC also receives inputs from the visual cortex

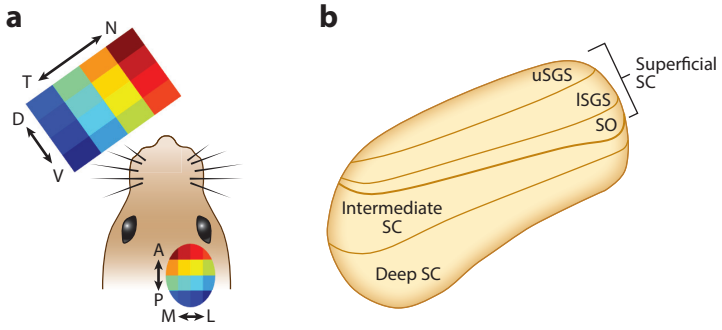

Figure 1

Retinotopic and laminar organization in the superior colliculus (SC). (*a*) The dorsal-ventral (D-V) and temporal-nasal (T-N) axes of visual space are mapped onto the medial-lateral (M-L) and posterior-anterior (P-A) axes of the contralateral SC. (*b*) The SC is divided into superficial, intermediate, and deep layers. The superficial layers are visually responsive and can be further subdivided following anatomical and functional criteria. Additional abbreviations: lSGS, lower stratum griseum superficiale; SO, stratum opticum; uSGS, upper stratum griseum superficiale.

that terminate in the lower SGS and deeper layers (Wang & Burkhalter 2013). The cortical inputs are also topographically organized and aligned in register with retinal inputs (Triplett et al. 2009).

The deeper SC can be further subdivided into intermediate and deep layers. Collectively, these layers contain neurons that receive sensory inputs from several modalities, such as inputs from the primary somatosensory cortex, the auditory nuclei of the midbrain, the trigeminal nucleus of the brainstem, and visual inputs from the superficial SC and visual cortex (May 2006). As a result, many neurons in these layers are multimodal. Deep layers of the SC also contain premotor neurons that control rapid eye movements known as saccades. Studies in primates and cats revealed a map of saccadic eye movements in the deep layers that encode the direction and amplitude based on the location in the SC (Robinson 1972, Robinson & Fuchs 1969, Roucoux & Crommelinck 1976, Schiller & Stryker 1972, Sparks et al. 1990, Stein et al. 1976, Wurtz & Albano 1980, Wurtz & Goldberg 1972). The movement fields of neurons in the motor map overlap with the receptive fields of corresponding visual neurons in the superficial layers, supporting the SC's role in shifting the gaze toward sites of visual stimulation.

In addition to saccadic eye movements, electrical stimulation of the SC has also been shown to induce movement of other body parts, orienting either toward or away from sensory stimuli. These include head movement, pinnae and whisker movement, reaching, and sonar vocalization (Gandhi & Katnani 2011). More recently, studies have started to reveal that the SC may also mediate higher cognitive functions, such as spatial attention, target selection, and decision making (Basso & May 2017, Krauzlis et al. 2013, Wolf et al. 2015). We do not cover these topics in this review because they have not been studied as extensively in the mouse SC. It is worthwhile to point out, however, that the mouse SC holds great promise for future studies of these functions, given the available genetic tools and the prominence of the SC in mice (Basso & May 2017).

RECEPTIVE FIELD PROPERTIES IN THE MOUSE SUPERIOR COLLICULUS

As in other visual areas, neurons in the superficial SC respond to specific stimulus features in their receptive fields. Studies over the years have revealed diverse response properties in these cells.

Basic Response Properties

Dräger and Hubel were the first to study receptive field properties of individual SC neurons and their organization in mice. In a series of papers published in the 1970s (Dräger & Hubel 1975a,b; 1976), they described the superficial SC neurons as responding "best to a small dark or light object of any shape moved slowly through the receptive-field center or to turning a small stationary spot on or off" (Dräger & Hubel 1975b, p. 711). They also reported that a small number of these visual neurons displayed direction-selective responses to moving stimuli. The vast majority of cells responded only through the contralateral eye, consistent with the pattern of retinocollicular projections in mice. In addition, Dräger and Hubel described several features of SC organization that are similar to those seen in other mammalian species (Wallace & Stein 1996). These include the distribution of exclusively visual neurons in the superficial SC, and auditory, somatosensory, and multimodal neurons in deeper SC; retinotopic organization of the visual receptive fields; and topographic maps of other sensory modalities that are largely aligned with the superficial visual map.

Even though these early studies laid the groundwork, the mouse SC was not subject to much functional investigation until several decades later, when mice were established as a promising model for vision research. In 2010, Wang et al. (2010) performed a quantitative and thorough analysis of visual response properties of superficial SC neurons (i.e., SGS and SO) in urethane-anesthetized wild type C57BL/6 mice. Using flashing spots, they showed that the vast majority of the recorded neurons (~90%) have spatially overlapped ON and OFF subfields (**Figure 2*a***). Most of these neurons preferred flashes with the radius of 6–10°, similar to the size of their receptive fields; and they were suppressed by larger stimuli. Similar ON-OFF overlap and surround suppression had been observed in the SC of a number of other species, including primates, cats, hamsters, and rats, even though their receptive fields are smaller than in mice (Cynader & Berman 1972, Girman & Lund 2007, McIlwain & Buser 1968, Prevost et al. 2007, Rhoades & Chalupa 1976, Schiller & Stryker 1972).

Wang et al. (2010) determined the tuning properties of individual SGS and SO neurons using drifting sinusoidal gratings (**Figure 2*a***), including selectivity for stimulus direction and orientation, spatial frequency tuning, temporal frequency tuning, and response linearity. Across the entire population, ~30% of cells displayed highly direction-selective responses. No bias toward certain directions was seen across this population, contradictory to the Dräger & Hubel (1975b) report that the vast majority of direction-selective neurons preferred upward motion in mouse SC. It is important to note that direction selectivity has been observed in the visual SC neurons of all mammalian species that have been studied, including monkeys, tree shrews, cats, hamsters, squirrels, rabbits, and rats (Albano et al. 1978, Cynader & Berman 1972, Fortin et al. 1999, Masland et al. 1971, McIlwain & Buser 1968, Michael 1972, Rhoades & Chalupa 1976), albeit to different degrees. The conservation of direction-selective responses in the SC across species is suggestive of a specialized function of this structure in visual signal processing.

Interestingly, ~20% of mouse SGS and SO neurons were selective for the orientation but not the direction of the drifting gratings (Wang et al. 2010). Such orientation-selective or axis-selective responses were not observed in primate and cat SC but seen in the more closely related rats (Girman & Lund 2007, Prevost et al. 2007). In addition, mouse SC cells are tuned to higher spatial frequencies (~0.08 cycles per degree) than neurons in the dorsal lateral geniculate nucleus (dLGN) and V1 recorded under similar conditions (Zhao et al. 2013). The presence of orientation selectivity and preference for higher spatial frequency suggest that the SC may play a greater role in image-forming vision in mice than in other species.

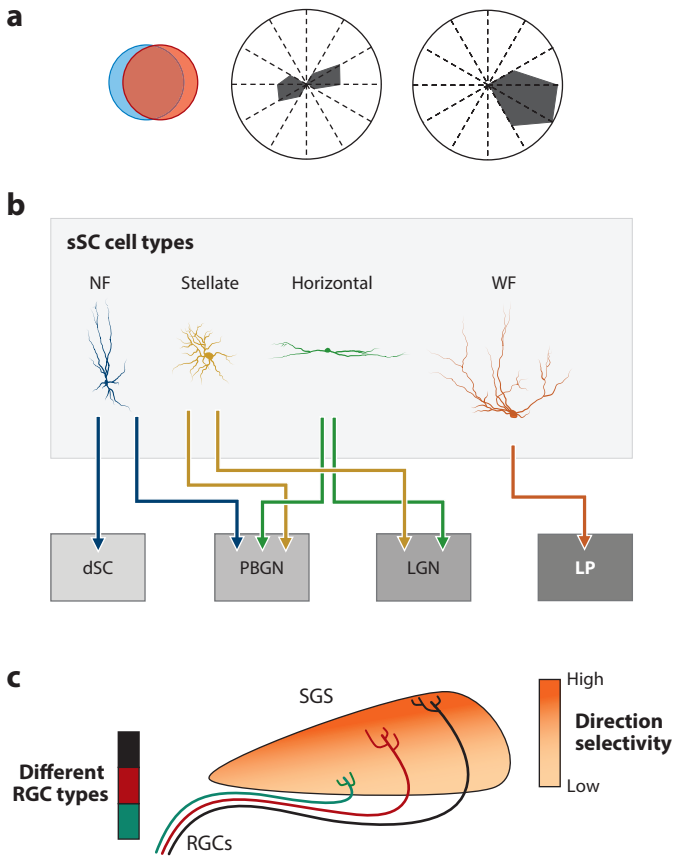

Figure 2

Visual function and organization of the mouse superior colliculus (SC). (*a*) Most visual neurons in the mouse SC have overlapping ON and OFF subfields (*left*); and many display orientation- (*middle*) or direction-selective (*right*) responses (Wang et al. 2010). (*b*) Four morphological cell types in the superficial layers of the mouse SC and their projection targets, according to Gale & Murphy (2014). (*c*) Different retinal ganglion cell (RGC) types project to distinct depths in the stratum griseum superficiale (SGS) (Dhande & Huberman 2014), and the degree of direction selectivity in SGS neurons declines with depth (Inayat et al. 2015). Additional abbreviations: dSC, deep superior colliculus; LGN, lateral geniculate nucleus; LP, lateral posterior nucleus; NF, narrow field; PBGN, parabigeminal nucleus; sSC, superficial superior colliculus; WF, wide field.

Cell-Type-Specific Responses

A major goal in vision science is to link the diverse functional properties seen in individual neurons with genetically identified specific cell types. Such progress is highlighted by recent discoveries that visual information is processed and transmitted by dozens of functionally defined RGC subtypes (Baden et al. 2016), many of which are already genetically identified (Dhande et al. 2015). Similarly, how different types of cortical inhibitory neurons mediate gain control (Atallah et al. 2012), surround suppression (Adesnik et al. 2012), and state-dependent modulation (Fu et al. 2014) is being elucidated. In comparison, cell-type-specific analysis in the SC is still very limited.

SGS neurons are traditionally classified into several types based on their morphology in many mammalian species (May 2006). Narrow-field (NF) and wide-field (WF) cells are the two major

excitatory (glutamatergic) outputs of the SGS. NF cell bodies fall in the lower SGS and extend their dendritic fields in a narrow column around the soma, in both upward and downward directions. WF cell bodies are found in the lower SGS and the SO, and their oblique dendrites extend toward the SC surface, covering a very large area in comparison to their NF counterparts. Horizontal cells, predominantly found in the upper SGS, are perhaps the only unambiguously inhibitory (GABAergic) neurons in the SC. They possess an oblong cell body with horizontally extended dendrites, giving these cells a bipolar morphology. These dendrites can extend for large distances and are capable of dendro-dendritic interactions (Mize 1992). Stellate cells have smaller dendritic fields, and although they can be immunoreactive to GABA antibodies, they are usually classified as excitatory neurons. Piriform cells are possibly GABAergic neurons with a pear-shaped soma and ascending dendrites (Mize 1992). They are found at the separation between the horizontal and vertical (NF/WF) cell layers in rats (Langer & Lund 1974). Finally, marginal cells are located on the dorsal surface of the SGS and extend their processes downward, and they may include both excitatory and inhibitory neurons.

In a heroic effort, Gale & Murphy (2014) succeeded in describing the visual response properties of some of these cell types in mice. They showed that WF and horizontal cells had large receptive fields, whereas those of NF and stellate cells were small, consistent with their dendritic structures. Interestingly, even though WF cells have large receptive fields, they still prefer small moving objects. A later study by the same authors (Gale & Murphy 2016) demonstrated that this selectivity was due to WF cells' active dendritic properties and local inhibition. Perhaps more importantly, they discovered three transgenic mouse lines in which Cre recombinase was expressed in WF, NF, and horizontal cells, respectively. This made it possible to perform cell-type-specific analysis and manipulation. Indeed, by expressing GFP and ChR2 in the Cre+ cells, Gale & Murphy (2014) were able to reveal the downstream target of these genetically defined cells (**Figure 2*b***). Specifically, they showed that WF cells project to the lateral posterior nucleus (LP), a rodent pulvnar-like structure that innervates both V1 and higher visual cortical areas (Sherman & Guillery 2002). NF cells were shown to project to deeper SC and parabigeminal nucleus (PBGN), which has reciprocal connections with the SC and projects to the amygdala. Finally, stellate and horizontal cells project to the LGN (both dorsal and ventral) and PBGN. It is important to point out that some of these findings were inconsistent with the cell-type projection patterns in other species. For example, NF cells were found to project to the dLGN in rats and tree shrews (May 2006). The discrepancies between the new findings in the mouse SGS and earlier studies will need to be resolved in future investigations. Nevertheless, this study (Gale & Murphy 2014) represented a major advance in linking cell types in the mouse SGS with their response properties and projection targets. With more sophisticated and extensive molecular and genetic studies (e.g., Byun et al. 2016), the classification of SC cell types will be further subdivided and refined, which will subsequently facilitate our understanding of cell-type-specific function, organization, and development in the mouse SC.

More Complex Responses and Behavioral Modulation

In addition to responding to flashes, sweeping bars, moving dots, and uniform grating, mouse SGS neurons also display interesting response properties to more complex visual stimuli. Zhao et al. (2014) showed that almost all SGS neurons respond robustly to looming stimuli that mimic approaching objects. The evoked responses were higher in awake mice than in anesthetized mice, but tuned similarly to high looming speeds under both conditions. These SGS responses likely mediate the animal's escape or freezing behaviors in response to looming predators (see the section below titled Visually Guided Behaviors Mediated by the Mouse Superior Colliculus).

SGS neurons can also perform feature-specific saliency computation by comparing the visual stimuli in their receptive field center and surround. It was recently shown that SGS neurons were strongly suppressed when the center stimulus was surrounded by gratings of the same orientation, but the suppression was reduced by an orthogonal surround (Ahmadlou et al. 2017). Even more interestingly, by imaging transgenic mice with labeled GABAergic neurons, our lab has revealed striking differences in the responses of excitatory and inhibitory neurons to motion contrast (J. Barchini, X. Shi, H. Chen, and J. Cang, unpublished data). The responses of superficial excitatory neurons are bidirectionally modulated, increasing monotonically as a function of the direction difference between the center and surround, from suppression by the same-direction surround to maximal potentiation by an oppositely moving surround. Such a response profile is likely important for the animal to detect object motion in the environment and distinguish it from self-induced full-field motion in the background.

Most of the above studies were performed in anesthetized mice. Given the recent discoveries that behavioral states such as locomotion modulate visual responses in V1 (Niell & Stryker 2010), it is of great interest to study SC responses in awake mice and in different behavioral states. A recent study by Ito et al. (2017) addressed some of these topics using large-scale silicon probe recording in awake mice. Several of the response properties seen in the superficial SC neurons of anesthetized mice were qualitatively confirmed in this study, such as relatively small receptive fields compared to deeper neurons, overlapping ON/OFF responses, and direction- and orientation-selective responses. In addition, they showed that many deep SC neurons were suppressed by contrast or by certain orientations/directions of gratings (negative orientation/direction selectivity). Finally, they reported that locomotion modulated the responses in both the superficial and deep SC. The circuit basis of these interesting properties will likely be the focus of many studies in the years to come.

ORGANIZATION OF THE MOUSE SUPERIOR COLLICULUS: MAPS, LAMINAE, AND COLUMNS

Neurons in the brain are often grouped into maps or layers according to their functional properties and/or developmental origin. The SC is well known for its topographic and laminar organization and has been the subject of extensive studies.

Retinotopy

Retinotopy in the visual system is a prime example of topographic representations, where visual space is systematically mapped onto image-forming retinorecipient structures through precise projections from the retina to these targets. In the mouse SC, retinotopic maps were readily revealed in the early studies by Dräger & Hubel (1975b). The nasal-temporal (N-T) axis of the visual field (azimuth) is represented along the anterior-posterior axis of the SC and the dorsal-ventral (D-V) axis (elevation) along the medial-lateral axis (**Figure 1*a***), consistent with the maps seen in other mammals (Feldon & Kruger 1970, Siminoff et al. 1966).

Retinotopic maps in the SC have been mostly studied by anatomical methods. Focal injections of lipophilic fluorescent dyes (e.g., DiI) in the retina would label a small number of neighboring RGCs, allowing their axons to be traced to the SC (Simon & O'Leary 1992). By comparing the labeled axon termination zones in wild type and mutant mice, a number of labs have identified many guidance cues and developmental processes that are important in retinocollicular map development (see the section below titled Development of Layers and Maps). These developmental studies were greatly facilitated by the introduction of optical imaging of intrinsic signals to reveal the functional retinotopic map in the mouse SC (Cang et al. 2008, Mrsic-Flogel et al. 2005). An

imaging session of a few hours reveals a complete set of high-quality cortical and SC maps from the same animals, making it an ideal tool for screening molecules required for retinotopic map formation and refinement (Cang & Feldheim 2013).

Retinotopic maps can also be studied by two-photon Ca^{2+} imaging, which allows analysis at cellular resolution. Inayat et al. (2015) imaged the most superficial lamina of the mouse SGS after removing the cortex and confirmed retinotopic organization, where, on average, neighboring cells have receptive fields that are closer in visual space compared to cells farther away. However, similar to what was observed in mouse V1 (Bonin et al. 2011), a great deal of scatter exists at finer scale, where neighboring cells could have receptive fields as far apart as 10°. Importantly, this study imaged only small fields of view, ~130 μm in diameter. Future experiments are needed to reveal the entire SC retinotopic maps at cellular resolution. This will be especially interesting considering that different visual field locations (front versus peripheral; near horizontal versus overhead) likely serve different ethological functions in mice.

Eye Movement Maps

It had long been thought that rodents primarily use their heads rather than their eyes to orient toward salient stimuli. However, saccade-like eye movements have been recently observed in mice with speed and amplitude similar to that in other mammals (Sakatani & Isa 2004, 2007). Furthermore, in head-fixed mice, saccadic eye movements can be evoked by microstimulation in the deep layers of the SC (Wang et al. 2015). Importantly, the amplitude of these eye movements depends on the stimulation locations: Stimulating anterior SC evoked small and nasally directed (ipsiversive) saccades, and stimulating posterior SC evoked temporally directed (contraversive) movements. In other words, the eye movement map in the mouse SC has the same global polarity as the overlaying visual map, just like in cats and primates (Wang et al. 2015). However, the retinotopic and eye movement maps appear to not be precisely aligned in mice, although the quantification of alignment is difficult because of their lack of fovea. This suggests that mice may normally move both eyes and heads during natural orienting movements, which remains to be investigated in future studies. Nevertheless, the fact that mouse SC contains motor maps that control saccadic eye movements should facilitate future studies of sensorimotor transformation and its development.

Laminar Organization

The SC is well known for being a layered structure. Even within the visual SGS, studies in a number of species demonstrated that this layer can be further divided into sublaminae based on histological properties and termination zones of different types of RGCs (Brun et al. 2014; Gabriel et al. 2012; Girman & Lund 2007; Huberman et al. 2008, 2009; Inoue & Sanes 1997; Kim et al. 2010; Zhang et al. 2015). Such an anatomic pattern suggests depth-specific functional organizations in the SGS, which can be best revealed by cellular-resolution imaging. Indeed, using two-photon Ca^{2+} imaging in anesthetized mice, Inayat et al. (2015) examined the response properties of the most superficial lamina of the SGS (within ~50 μm from the surface). Interestingly, the superficial SGS lamina (sSGS) is enriched with neurons that are highly direction selective, with ~80% of cells having a direction selectivity index greater than 0.5 (Inayat et al. 2015). This is in striking contrast with the results obtained with single-unit recordings across all depths of the SGS, where ~30% of cells are direction selective (Wang et al. 2010). The obvious explanation for this difference is that direction selectivity declines with depth in the SGS (**Figure 2*c***), which was directly confirmed by single-unit recordings in this study (Inayat et al. 2015), and then later by large-scale recordings in awake

mice (Ito et al. 2017). Notably, very few neurons are orientation selective in the sSGS, suggesting that orientation-selective neurons are more concentrated in the deeper laminae. Together, these findings suggest that the SGS may contain a stack of superimposed maps, each encoding a different feature of the visual world, largely consistent with the differential projection patterns of RGC subtypes (**Figure 2*c***) (Dhande & Huberman 2014).

In addition to allowing for depth-specific analysis with a higher precision than electrophysiology, two-photon Ca^{2+} imaging also makes it easier to examine cell-type-specific responses. No striking differences in receptive field structure or direction selectivity were seen between excitatory and inhibitory neurons in the sSGS (Inayat et al. 2015). This is different from the result in the electrophysiology study mentioned in the above section showing that the horizontal neurons, which are inhibitory, were rarely direction selective (Gale & Murphy 2014). This difference is likely due to the fact that cells in the most superficial lamina are often severely undersampled in physiology studies. In contrast, the morphology of the sSGS neurons has not been reconstructed, and thus how they fit into the four classes of cells in the previous study is not clear.

The depth-specific organization of direction-selective neurons in the SGS is reminiscent of the finding in the dLGN, where direction-selective neurons appear to be enriched in the dorsal shell (Piscopo et al. 2013). Direction-selective dLGN neurons project their axons to V1 (Kondo & Ohki 2016, Sun et al. 2016), with a possible bias toward the more superficial layers (Cruz-Martin et al. 2014, Kondo & Ohki 2016; but see Sun et al. 2016). Intriguingly, many superficial SGS neurons, likely including direction-selective neurons, project to the dorsal shell of the dLGN (Bickford et al. 2015). Together, the direction-selective responses seen in all these visual centers may be linked in a colliculo-thalamo-cortical loop that is critical for motion processing.

Columnar Organization in the Mouse Superior Colliculus?

On top of retinotopy, neurons in the visual system can be arranged in higher-order maps according to their response properties. For example, orientation-selective cells in V1 of primates, cats, ferrets, and tree shrews are arranged in columns (Blasdel 1992, Bosking et al. 1997, Chapman et al. 1996, Grinvald et al. 1986, Hubel & Wiesel 1962, Ohki et al. 2005), where neurons in each column prefer the same orientation, and these columns are arranged in a pinwheel structure that systematically represents the full range of orientations. Interestingly, orientation columns are not observed in the V1 of mouse, rat, or gray squirrels (Bonin et al. 2011, Ohki et al. 2005, Van Hooser et al. 2005), raising an intriguing question regarding the role of columnar organization in visual processing (Horton & Adams 2005).

Curiously, two recent studies suggest that orientation columns may exist in the mouse SC, even though they do not agree with each other regarding the patterns of these columns. In one study (Feinberg & Meister 2015), two-photon microscopy was used to image the posterior and medial corner of the SGS in awake mice, and cells with similar orientation preferences were found to form large patches spanning the SGS depth. The other study (Ahmadlou & Heimel 2015), which was done in anesthetized mice using electrophysiology and wide-field Ca^{2+} imaging, found that neurons at each retinotopic location spanning the SGS often preferred similar orientations that were parallel to the concentric circle around the center of the animal's visual field. Although the discrepancy between the two reports needs to be resolved before we can have an accurate picture of orientation selectivity organization in the mouse SGS, both studies suggest that stimulus orientation is not evenly represented at all visual field locations. This is different from the columnar organization seen in primate and cat V1, where all orientations are systematically represented for a particular region of visual space. It is important to point out that orientation-selective neurons constitute only a small population in the mouse SGS (~20%), and their tuning curves tend to be

wider than in V1 (Niell & Stryker 2008, Wang et al. 2010). Consequently, such columns, if they indeed exist, would not result in orientation blindness at any location in the SC.

What about direction selectivity organization in the SGS? As described in the previous section, direction selectivity is high in the most superficial lamina (sSGS) and declines with depth in the mouse SGS. No clustering of cells of similar directional preference was seen in the sSGS, although slightly more cells preferred anterior and upward directions in the imaged area (Inayat et al. 2015). Interestingly, recordings in the ground squirrel showed that SGS cells in a vertical electrode penetration tend to prefer similar directions (Michael 1972). Taken together, these observations suggest that a region-specific organization may exist in the SGS, which would give the SC a biased filter toward detecting particular stimulus features in a given region of space. These findings have tantalizing implications for understanding the behavioral and ethological functions of the mouse SC.

RETINAL AND CORTICAL CONTRIBUTION TO SUPERIOR COLLICULUS RESPONSE PROPERTIES

Most, if not all, RGC types project to the SC in mice. How do these rich sets of visual information contribute to the response properties seen in the SC? This question has now been addressed for direction selectivity, a ubiquitous feature of the SC in all species, thanks to the available optogenetic, genetic, physiological, and imaging techniques. Specifically, light-sensitive channelrhodopsins were expressed in SGS inhibitory neurons, which, upon optogenetic activation, would silence excitatory neurons in the SGS. This would remove local excitatory input to the neurons being recorded under voltage clamp, thereby isolating their retinal input (**Figure 3*a***). Using this method, Shi et al. (2017) demonstrated that the retinal input to individual direction-selective SGS neurons is already selective as a result of precisely converging similarly tuned direction-selective RGCs. The selective retinal input is then linearly amplified by intracollicular circuits without changing preferred direction or level of selectivity. This finding thus predicts decreased SGS direction selectivity when retinal selectivity is compromised, a prediction also tested in the same study. Two-photon imaging of transgenic mice that had reduced retinal direction selectivity (Pei et al. 2015) revealed that many fewer cells were still direction selective in the sSGS of these mice (**Figure 3*b***) (Shi et al. 2017). Similarly, Kay & Triplett (2017) made a clever use of transgenic mice where direction-selective and non-direction-selective retinal inputs appear to preferentially target different halves of the SGS (Triplett et al. 2014). They found more direction-selective SGS responses in the region targeted by the putative selective retinal input, supporting the retinal origin of direction selectivity in the SC. Finally, it is worthwhile to note that the precise connectivity suggested by these studies, both retinocollicular convergence and intracollicular connectivity, requires certain developmental mechanisms that are not yet studied (Shi et al. 2017).

The SC also receives projections from the visual cortex, including both V1 and higher visual areas (Wang & Burkhalter 2013). These corticotectal projections originate from a subclass of layer 5 pyramidal cells, which in mice appear to respond somewhat differently from other projection neurons in the same layer (Lur et al. 2016). These inputs terminate in the deeper SGS in a topographic manner, aligning with retinal inputs that terminate more superficially (Triplett et al. 2009). In rats, it has been shown that most cortical inputs target non-GABAergic cells in the SGS (Boka et al. 2006).

The impact of cortical input on the SC's visual response has been studied in a number of species, but they were mostly done in anesthetized animals. Anesthesia could have a profound effect on the function of corticotectal projections. To address this issue, Zhao et al. (2014) compared the effect of silencing the visual cortex in both awake and anesthetized mice. Cortical silencing was

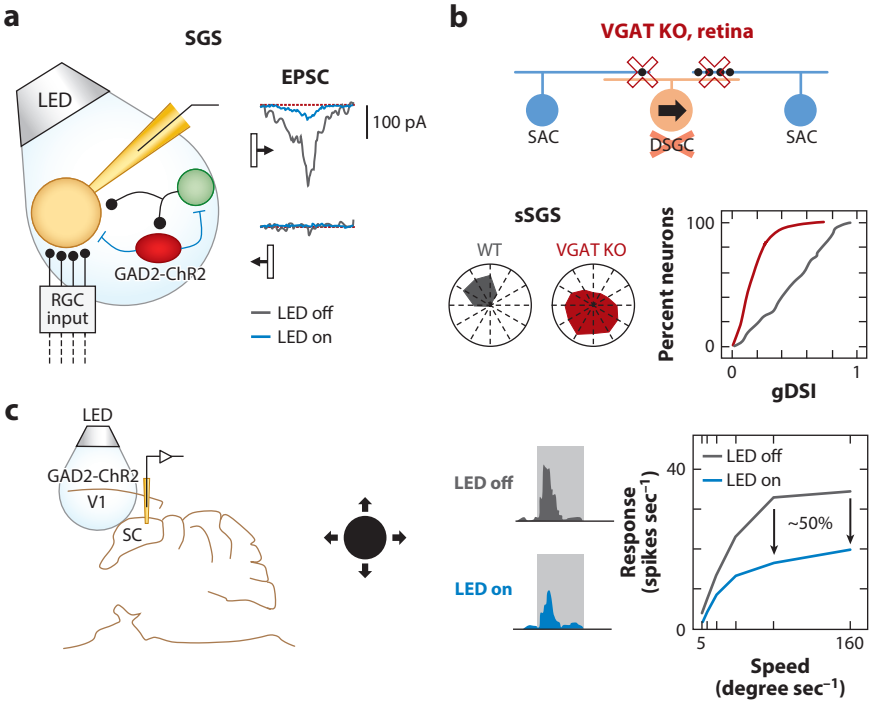

Figure 3

Retinal origin and cortical control of superior colliculus (SC) responses. (*a*) Optogenetic silencing of local circuits in the stratum griseum superficiale (SGS) reveals tuned retinal inputs to direction-selective SGS neurons. The excitatory postsynaptic current (EPSC) amplitude is reduced upon optogenetic silencing, but the tuning remains. (*b*) Vesicular GABA transporter knockout (VGAT KO) in starburst amacrine cells (SACs) leads to decreased selectivity of direction-selective ganglion cells (DSGCs) and to a subsequent decline of selectivity in the superficial SGS (sSGS), compared to littermate wild type (WT) controls. (*Bottom left*) Example polar plots of sSGS responses to drifting gratings in WT (*gray*) and VGAT KO (*red*). (*Bottom right*) Cumulative distribution of the global direction selectivity index (gDSI) of WT and VGAT KO. (*c*) The visual cortex modulates the gain of looming-evoked SGS responses. (*Left*) Experimental setup: blue light activation of ChR2-expressing GAD2+ (GABAergic) neurons to silence cortical excitatory neurons, including those projecting to the SGS. (*Middle*) In response to a looming disk expanding at different speeds, an SGS neuron's peristimulus time histogram when V1 is active (LED off) or silenced (LED on). (*Right*) Population tuning curves of SGS neurons to different looming speeds, showing ~50% reduction when the visual cortex is inactivated, without changing the speed tuning. Panels *a* and *b* are adapted from Shi et al. (2017). Panel *c* is adapted from Zhao et al. (2014). Additional abbreviation: RGC, retinal ganglion cell.

achieved by an optogenetic method, which is reversible and allows for tracking the same SGS cells before and after the manipulation. A visual looming stimulus was used, which mimics approaching objects and is behaviorally relevant (see the section titled Visually Guided Behaviors Mediated by the Mouse Superior Colliculus). The looming stimulus evoked strong responses in most SGS neurons. Importantly, the looming-evoked responses were reduced by almost half when the visual cortex was silenced in awake, but not in anesthetized, mice. This effect was seen across all looming speeds and proportional to the response magnitude (**Figure 3*c***). Consequently, silencing cortex did not change the speed tuning of SGS neurons or their response temporal dynamics. In other words, the effect of cortical input to the SGS is largely a gain control. A similar gain control was also observed for SGS's response to sudden light flashes, which induce a temporary suspension

of locomotion in mice (Liang et al. 2015). Behaviorally, optogenetic silencing of the corticotectal projection reduces the light-induced locomotion arrest, whereas their activation was sufficient to elicit the behavior (Liang et al. 2015).

Together, these studies support the notion that SGS neurons inherit basic feature selectivity from the retina and modulate their response magnitude depending on cortical input. However, there remain many gaps in our knowledge, and revisions of this idea are likely. For example, even though the orientation selectivity seen in the SGS could come from the newly discovered orientation-selective retinal ganglion cells in mice (Nath & Schwartz 2016, Zhao et al. 2013), it has not yet been directly tested. Similarly, and somewhat surprisingly, no experiment has been performed to examine the effects of silencing cortex on basic properties like direction/orientation selectivity in awake mice. A recent study suggests that silencing the visual cortex may affect the SGS differently when center and surround stimuli were of orthogonal orientations (Ahmadlou et al. 2017), although the difference was very subtle. Finally, an exceedingly high proportion of SGS neurons are GABAergic [~50% (Mize 1992)]. These inhibitory neurons have been shown to be involved in surround suppression, including in mice (Kasai & Isa 2016). It is likely that they contribute to other functional properties, especially in response to more complex visual stimuli. Future studies are needed to address these important issues regarding circuit mechanisms of visual processing in the SGS.

VISUALLY GUIDED BEHAVIORS MEDIATED BY THE MOUSE SUPERIOR COLLICULUS

In addition to its well-studied function in controlling saccadic eye movement, the SC is also known to be involved in the generation of both approaching and defensive responses in rodents. For example, in rats, collicular stimulation can elicit biting and gnawing (Redgrave et al. 1981) while bilateral lesion of the SC impairs prey capture behavior (Furigo et al. 2010). Excitingly, prey capture has also been recently demonstrated in laboratory mice and shown to require vision (Hoy et al. 2016). Whether, and more importantly how, prey capture is mediated by the SC in mice remains to be determined. An encouraging clue comes from observations of the so-called "cortexless" transgenic mice (Diao et al. 2018, Shanks et al. 2016, Whelan et al. 2012). Much of the neocortex, including the entire visual cortex, fails to develop in these mice due to genetic defects. Yet, these mice can survive and reproduce, at least in a laboratory setting, and perform reflexive visual behaviors (Shanks et al. 2016), highlighting the importance of subcortical visual structures, including the SC, in visually guided behaviors.

Visually evoked defensive response is another example of such behaviors in rodents (**Figure 4*a***). These responses can be triggered by overhead stimuli that are believed to mimic an approaching aerial predator (Yilmaz & Meister 2013). The behavioral outcome could be either freezing or rapid escape, depending on the stimulus type: A looming disc will evoke an escape, while a sweeping stimulus will trigger a freezing response (De Franceschi et al. 2016).

The SC's involvement in such defensive behaviors was already established by a number of early studies. For example, wild rats with collicular lesions displayed a decreased responsiveness to visual stimuli and reduced flight behavior to visual threats, such as an approaching human (Blanchard et al. 1981). Injection of the GABA antagonist picrotoxin to stimulate the superficial layers of the SC could evoke freezing, escape, or jumping in rats (Redgrave et al. 1981). It was later shown that for superficial layers, avoidance responses were obtained from stimulating regions representing the upper visual filed (Sahibzada et al. 1986). Also in rats, microinjection of glutamate in the rostro-medial SC (all layers) and both medial and lateral parts of the caudal deeper layers could evoke defensive behaviors (Dean et al. 1988). These results are consistent with anatomical findings

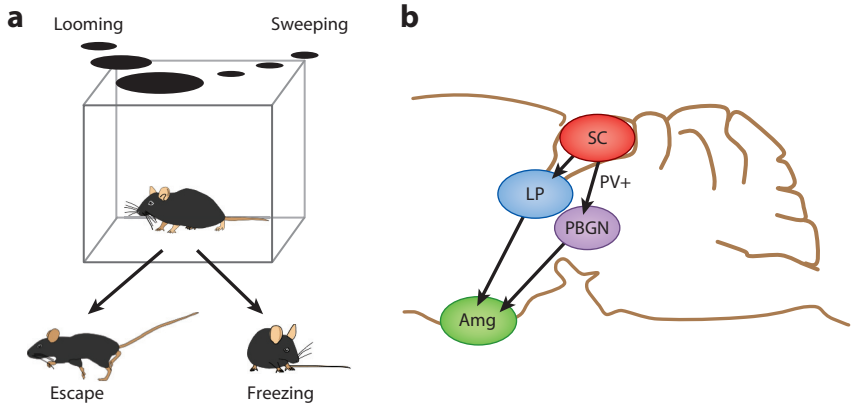

Figure 4

Visually evoked defensive behavior mediated by the mouse superior colliculus (SC). (*a*) An expanding disk (looming stimulus), mimicking an approaching aerial predator, triggers flight response, while a sweeping dot, mimicking a soaring bird, triggers freezing (Yilmaz & Meister 2013 and De Franceschi et al. 2016). (*b*) Pathways involved in visually evoked defensive behavior. Activation of SC cells projecting to the lateral posterior nucleus (LP) then to the amygdala (Amg) can elicit freezing response (Wei et al. 2015, Zingg et al. 2017). SC parvalbumin-positive cells (PV+) projecting to the parabigeminal nucleus (PBGN), when activated, can induce rapid escape followed by freezing (Shang et al. 2015).

that reveal that a difference in inputs can be found in the deeper layers as a function of the location along the lateral-medial axis in both rats (Comoli et al. 2012) and mice (Savage et al. 2017).

More recent efforts in mice have been focused on the identification of the cellular substrates and neural pathway in the SC that mediate visually evoked defensive behaviors. SGS neurons respond to visual looming stimuli (Zhao et al. 2014), and optogenetic inhibition of the excitatory SC cells in the medial region of the intermediate layer reduced looming-induced freezing (Wei et al. 2015). Similarly, silencing the SC suppressed the animal's temporary arrest response to light flashes, another innate defense behavior (Liang et al. 2015). A separate study suggested that parvalbumin-positive (PV+) neurons in the SGS, which are excitatory, could be so-called looming detectors, since their activation induces rapid escape followed by freezing (Shang et al. 2015). However, given that almost all SGS neurons respond to looming stimulus (Zhao et al. 2014), the special features that distinguish PV+ neurons remain to be explored.

These studies also investigated what pathways downstream of the SC mediate looming-evoked behavioral response (**Figure 4*b***). In one study (Shang et al. 2015), PV+ cells were shown to project to the amygdala through the PBGN, and activation of this pathway was sufficient to elicit escape followed by freezing. The other, however, identified the SC–LP–amygdala pathway as mediating the freezing response to looming (Wei et al. 2015). This result was supported by a recent study (Zingg et al. 2017) that found that optogenetic activation of LP-projecting SC neurons could evoke freezing, while activation of PBGN-projecting neurons did not trigger any response. It remains possible that both pathways could be involved in looming-evoked fear responses, dependent upon the specific visual stimuli or behavioral context.

DEVELOPMENT OF LAYERS AND MAPS

Although the mouse SC only recently became a popular model in vision research, it had been widely used in developmental studies for many decades. These studies have provided a general understanding of how the SC acquires its characteristic laminar and topographic organization.

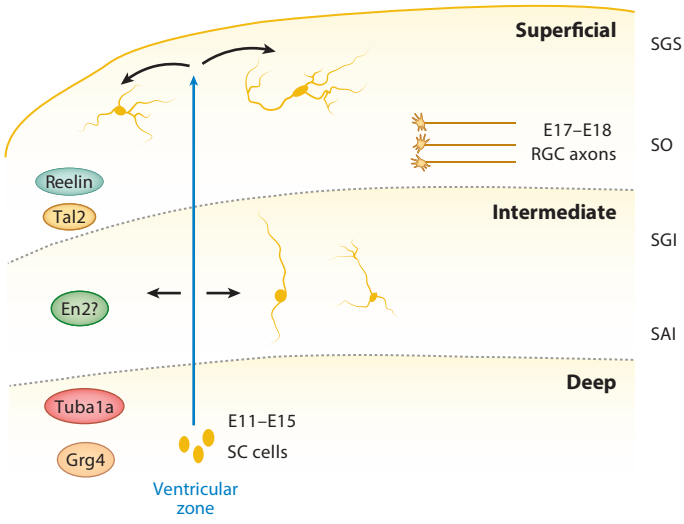

Figure 5

A simplified schematic of mouse superior colliculus (SC) laminar development. A majority of SC cells are born between embryonic day 11 (E11) and E15 and ascend radially from the ventricular zone (*blue arrow*). Tangential dispersions of a small number of cells are observed in the superficial and deeper layers (*black arrows*). RGC axons enter the stratum opticum (SO) around E17 to E18. Molecules involved in cell migration and layer formation in early SC development are listed on the left side. Additional abbreviations: RGC, retinal ganglion cell; SAI, stratum album intermediale; SGI, stratum griseum intermediale; SGS, stratum griseum superficiale.

Layers

The SC and its nonmammalian homolog, the optic tectum (OT), derive from the dorsal midbrain. In chicks, the tectal swelling expands like a balloon during the initial phase of development, around embryonic day 5.5 (E5.5), and the numbers of tectal layers dramatically increase between E8.5 and E16.5. As in other brain areas, layer formation in the tectum depends primarily on radial migration of postmitotic precursor cells from the ventricular zone (Watanabe & Yaginuma 2015). Two waves of tangential migrations in the middle and superficial layers were also observed to populate the tectum (Gray & Sanes 1991; LaVail & Cowan 1971a,b; Puelles & Bendala 1978; Watanabe & Yaginuma 2015; Watanabe et al. 2014).

In rodents, the generation of SC cells peaks around E13, with superficial layers slightly delayed compared to deeper layers (Altman & Bayer 1981, Edwards et al. 1986a). Within each subregion, the events of neurogenesis, cell migration, and early morphological differentiation of neurons largely follow an inside-out order (Edwards et al. 1986a,b; Pierce 1973; Puelles & Bendala 1978). Similar to what is seen in the chick, radial cell dispersion was the predominant form of cell migration from the germinal zones (**Figure 5**) (Brückner et al. 1976, Tan et al. 2002). Two streams of tangential dispersions in the superficial and deeper layers from radially migrating cells are also reported in the developing mouse SC (Edwards et al. 1986a, Tan et al. 2002). Radial cell dispersion in the middle layers is primarily associated with the differentiation of glutamatergic neurons, while the scattered cells in the superficial layers often express GABA (Tan et al. 2002). By birth, when cell migration is largely complete, optic nerve fibers have already invaded the SC (Bovolenta & Mason 1987; Edwards et al. 1986a,b). By the end of the first postnatal week, the developing SC exhibits adult-like layered architecture, with ~70% of the final thickness for each layer. The SC eventually reaches its adult size and shape within the first postnatal month (Edwards et al. 1986a).

Several transcription factors were shown to be involved in controlling cell migration and laminar formation in early development. For example, Grg4, a member of the Gro/Grg/TLE family of transcriptional repressors (Cavallo et al. 1998, Koop et al. 1996, Roose et al. 1998), regulates postmitotic cell migration and laminar formation in the chick tectum (Sugiyama & Nakamura 2003). Targeted deletion of Tal2, a basic helix–loop–helix (bHLH) transcription factor involved in T cell leukemogenesis (Baer 1993), led to missing SGS and reduced SO in mice (Bucher et al. 2000), indicating its role in the formation of the superficial layers. Similarly, targeted deletion of Barhl1, another transcription factor involved in sensory neuron development (Kojima et al. 1991, Li et al. 2002, Mo et al. 2004, Saito et al. 1998), resulted in the loss of a large population of neurons from the most superficial SC (Li & Xiang 2006). In contrast, the transcription factor engrailed-2 (En2) is strongly expressed in the middle layers of chick tectum and absent from the superficial layers. Misexpression of En2 in the superficial neurons caused them to migrate back toward the middle layers (Omi et al. 2014). En2 was shown to be involved in mid- and hindbrain development in mice (Joyner et al. 1991, Millen et al. 1994, Simon et al. 2005) and the formation of the retinotectal map in lower vertebrates (Friedman & O'Leary 1996, Itasaki & Nakamura 1996, Logan et al. 1996, Wizenmann et al. 2015), but its role in mouse SC laminar development remains to be established.

Cytoskeleton proteins are also involved in cell migration and laminar formation in the SC. The α-tubulin gene *Tuba1a* is important in neuronal migration during early brain development (Keays et al. 2007). In the *Tuba1a* "Jenna" mutant mouse, the radial migration of SC neurons is impaired with increased apoptotic cell death (Edwards et al. 2011). The SC layers are significantly thinner, with an apparent fusion of the intermediate gray and white layers (Edwards et al. 2011). Reelin, a large extracellular protein, was first implicated in neuronal migration in the *reeler* mouse (D'Arcangelo et al. 1995). Reelin is expressed in the developing SC and has been shown to control lamination of the rodent SC (Ikeda & Terashima 1997, Sakakibara et al. 2003). In addition to having inverted cortex and disorganized hippocampus and cerebellum, Reelin knockout mice exhibit a complete disorganization of the SC superficial layers with tangled RGC projections, but their deep layers are largely normal (Sakakibara et al. 2003). Notably, these different lines of mutant mice provide an interesting opportunity to study how SC function and visual behaviors are affected when the molecular signaling for migration and lamination is disrupted. This should be an important and exciting opportunity for future studies.

Maps

As described above, the SC contains a retinotopic representation of the visual space as a result of precise targeting of RGC axons. How this spatial ordering is established during development has been the subject of extensive studies and numerous reviews. Here, we provide only a brief and general account of this process without diving into the vast literature. Readers are recommended to consult the numerous recent reviews on this topic (Ackman & Crair 2014, Cang & Feldheim 2013, Feldheim & O'Leary 2010, Luo & Flanagan 2007, Triplett 2014).

In mice, RGC axons reach the rostral edge of the SC between E17 and E18. By postnatal day 0 (P0) to P1, individual retinal axons overshoot their termination zones and extend to the caudal end of the SC, almost filling the entire collicular space. By P8, all arborizations except those in the topographically correct location are eliminated, and the retinocollicular map reaches its adult precision. It has been well established that both molecular guidance cues and structured activity work in concert in this process, instructing RGC axons to find their correct target locations.

The best-studied guidance cues in mapping retinocollicular projections are the EphA and ephrin-A family of proteins. EphAs are receptor tyrosine kinases that bind to ephrin-As. They are

both membrane bound and induce contact-dependent repulsion. Several members of the EphA and ephrin-A families are expressed in complementary gradients along the temporal-nasal axis of the retina and the rostral-caudal axis of the SC. These gradients induce differential levels of repulsion between RGC axons and SC cells and possibly attraction at low concentrations (Hansen et al. 2004), which, together with other forces such as axon-axon competition, set up a coarse retinotopic map along the rostral-caudal axis of the SC. This map is then refined through activity-dependent processes driven by the spontaneous, wave-like, correlated activity in the retina. Recent studies have revealed the patterns of these retinal waves in vivo (Ackman et al. 2012) and investigated which features of the waves are critical for map refinement (Xu et al. 2015). The exact cellular and molecular mechanisms underlying this refinement process remain to be determined, although correlation-based Hebbian plasticity is a possible candidate (Munz et al. 2014).

Importantly, the retinocollicular projection is not just a single map. Instead, it is a superimposition of individual maps where different RGC subtypes target specific laminae within the SGS. The same guidance cues and activity-dependent processes could mediate the formation of all these maps, thereby achieving map alignment. Alternatively, one or some of these maps could work as a template to guide the alignment of other maps (Cang & Feldheim 2013). Recent studies have provided clues for these possibilities (Liu et al. 2014, Sweeney et al. 2015), but no definitive discovery has been made.

The retinocollicular map is also aligned with topographic projections from the visual cortex to the SGS. This process seems to also use a combination of correlated activity and molecular cues (Savier et al. 2017, Triplett et al. 2009). Finally, these visual maps are also aligned with other sensory and motor maps in the SC. Although the mechanisms underlying alignment of these maps are still poorly understood, there is evidence for the common use of EphA- and ephrin-A-family molecules in the development of aligned inputs from primary somatosensory cortex (Triplett et al. 2012). In contrast, the recent study that revealed an eye movement map in the mouse SC also showed that this motor map was degraded in mice reared in complete darkness during development (Wang et al. 2015). In particular, the dark-reared mice exhibited larger saccades than did control mice, suggesting that visual experience is required for fine-tuning saccade precision and for aligning visual and motor maps. This finding is consistent with the studies in barn owls and ferrets, where the visual map in the SC or OT is used as a topographic template to align the auditory map in an experience-dependent manner (Brainard & Knudsen 1998; King et al. 1996, 1998).

CONCLUSIONS AND FUTURE DIRECTIONS

The past decade has seen much progress in the studies of mouse SC. With an increasing number of labs joining the effort, the mouse SC has become a popular model in vision research. It is now well established that the mouse SC shares the same characteristic laminar and topographic organization as in other mammals. Many general principles have been revealed about SC laminar development and map formation from mouse studies. Also as in other species, the SC in mice displays diverse visual response properties in its superficial layers and contains a motor map in deep layers that initiates saccadic eye movements. Studies have started to reveal the circuit mechanisms of visual responses seen in the mouse SC, especially regarding the contributions of retinal and cortical inputs. Excitingly, the SC is clearly demonstrated to mediate visually triggered fear responses in mice, and the underlying neural pathways have been revealed.

Despite such progress, however, our understanding of the function, organization, and development of the mouse SC is still rather primitive. New genetic tools and novel paradigms are needed to answer many outstanding questions. We outline below a few of the most important directions that, in our opinion, will significantly move the field forward.

First, simple visual stimuli such as light flashes, drifting gratings, or moving dots are used in most studies, either in anesthetized mice or in awake mice under passive viewing condition. This has severely limited our understanding of visual processing that the mouse SC performs. Sophisticated visual stimuli and computational analyses will help address some of these issues. But more importantly, conditions that are more natural than passive viewing are needed to answer certain fundamental questions regarding SC functions. For example, how would the direction-selective cells in the SGS respond to self-generated optical flow when the mouse is allowed to run? The virtual reality system recently designed for studying mouse V1 (Keller et al. 2012, Roth et al. 2016, Zmarz & Keller 2016) will be a powerful paradigm to answer such questions.

Second, the current classification of cell types and available mouse driver lines does not capture the diverse functions seen in the SC. In addition to different morphology, excitatory neurons in the SGS have different tuning properties, projection patterns, and intracollicular connectivity. Consequently, they will likely be further divided from the current narrow-field, wide-field, and stellate cell types. Similarly, the inhibitory neurons in the SGS, which make up a much higher population than in the cortex, are unlikely a single homogeneous cell type. The well-established classification of cortical inhibitory neurons [e.g., PV+, somatostatin-positive, and vasoactive intestinal peptide (VIP)-positive] does not apply to the SC. Instead, new genomic technologies such as single-cell RNA sequencing may allow the identification of specific SC cell types and generation of new mouse lines.

Novel stimulation paradigms and mouse lines will facilitate several directions of circuit-level investigation of the SC function and organization. For example, what are the mechanisms underlying visual response properties in the mouse SGS, and if they are modulated by behavioral context, what neural circuits give rise to such modulation? In addition, SGS neurons project to a number of structures, such as dLGN, LP, and PBGN. Do SGS neurons display projection-specific response properties? In other words, what information do they each carry to different targets in visually guided behaviors? Moreover, what function, if any, does depth-specific or columnar organization serve in visual processing? It would be informative to determine, for example, the effect of silencing the topmost SGS lamina on visual behavior.

Finally, on top of the global retinotopy, more precise patterns of connectivity are established during development, but the underlying mechanisms are completely unknown. For example, what cues and receptors are responsible for laminar-specific targeting of RGCs? Furthermore, similarly tuned direction-selective RGCs must converge to give rise to direction selectivity in the SGS, and excitatory SGS neurons that prefer similar directions are also preferentially connected within the colliculus (Shi et al. 2017). The developmental mechanisms for such precise and selective connectivity remain to be discovered. As a result, with its long history in developmental studies and with the help of new technologies, the mouse SC will again become a productive model, now for studying circuit-level development.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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