Review

Binocular Circuitry as a Model for Understanding Experience-Dependent Circuit Development across the Mammalian Cortex

Jingxi Zhao,[1] Chuying Zhou,[2,3] Na Zhou,[1] Yi Wang,[4] Xin Zhang,[1] and Liming Tan[2,3]*

[1]School of Pharmacy, Laboratory of Drug Discovery from Natural Resources and Industrialization, State Key Laboratory of Mechanism and Quality of Chinese Medicine, Macau University of Science and Technology, Taipa, Macau 999078, China, [2]Shenzhen Key Laboratory of Neuropsychiatric Modulation, Shenzhen-Hong Kong Institute of Brain Science, Shenzhen Institutes of Advanced Technology, Chinese Academy of Sciences, Shenzhen 518055, China, [3]Guangdong Provincial Key Laboratory of Brain Connectome and Behavior, the Brain Cognition and Brain Disease Institute, Shenzhen Institutes of Advanced Technology, Chinese Academy of Sciences, Shenzhen 518055, China, and [4]Department of Stomatology, First Medical Center, Chinese PLA General Hospital, Beijing 100853, China

The binocular circuitry in mammals (e.g., mice, cats, and primates) integrates two distinct visual cortical circuitries—the contralateral and ipsilateral eye circuitries—into a cohesive functional system for three-dimensional vision. These two circuitries, differing in their developmental timing and trajectories, demonstrate the intricate interplay between innate genetic programs and experience. The contralateral eye cortical circuitry, largely laid down by intrinsic mechanisms and maturing earlier, establishes an initial framework, whereas the later-developing ipsilateral eye circuitry, established and refined through visual experience, aligns with and is integrated into this framework to achieve precise functional connectivity. We propose that this mechanism of binocular circuitry development, wherein distinct circuits are progressively refined and integrated under the influence of environmental stimuli, exemplifies a fundamental organizing principle governing the development of the entire cortical architecture. Such integration enables different cortical areas to combine diverse streams of information, improving processing capabilities and optimizing neural circuits to support more sophisticated functions, ultimately facilitating advanced sensory–motor coordination and complex behaviors.

Key words: **circuit integration; cortical plasticity; critical periods; experience; visual system**

Significance Statement

The hallmark of mammalian brain wiring is that postnatal experience plays a fundamental role in the maturation of neural circuits laid down by genetic programs. However, the precise role of experience in circuit development has been elusive. Binocular vision is increasingly being studied as a model for visually guided behaviors. Using experience-dependent development of binocular circuitry as an example, we propose a new model in which experience refines and integrates circuits of different modalities into specialized functional circuits that allow animals to improve their performance in the environment. This review should be of interest to researchers of computational, systems, developmental, cellular, and molecular neuroscience as well as those in fields related to developmental neuropsychiatric disorders (ASD, ADHD, etc.).

Introduction

Binocular vision, which involves merging independent retinal images acquired from two eyes to forge a unified visual representation, is pivotal for robust perception of three-dimensional space and critical for efficient foraging (Cumming and Parker, 1997; Scholl et al., 2013; Xu et al., 2020; Boone et al., 2021; Johnson et al., 2021; La Chioma and Hubener, 2021; Fu et al., 2023). Achieving this advanced visual capacity requires a structured developmental process. First, precise functional–anatomical maps [i.e., retinotopic, orientation, and ocular dominance

---

Received Feb. 13, 2025; revised Oct. 10, 2025; accepted Jan. 8, 2026.

Author contributions: J.Z., C.Z., N.Z., Y.W., X.Z., and L.T. wrote the paper.

This work was funded by the National Key R&D Program of China 2022YFA1105503, Shenzhen Medical Research Fund B2402005, National Natural Science Foundation of China (NSFC) 32371019, Guangdong Provincial Key Laboratory of Brain Connectome and Behavior 2023B1212060055, and Shenzhen Science and Technology Program (Grant Number SYSPG20241211173950073) to L.T. and Macau Science and Technology Development Fund [FDCT(003/2022/ALC, 0102/2023/AMJ)] to X.Z.

*Lead contact.

The authors declare no competing financial interests.

Correspondence should be addressed to Xin Zhang at xinzhang@must.edu.mo or Liming Tan at lm.tan@siat.ac.cn.

This paper contains supplemental material available at: https://doi.org/10.1523/JNEUROSCI.0326-25.2026

https://doi.org/10.1523/JNEUROSCI.0326-25.2026

(OD) maps] must form from the inputs of each eye along the visual pathways. This step is followed by maturation of the binocular circuitry that integrates these inputs (Leamey et al., 2007; Mazziotti et al., 2017; Seabrook et al., 2017; Min et al., 2023). A comprehensive understanding of the mechanisms underlying the development of the binocular circuitry requires the investigation of the distinct maturation profiles of the contralateral and ipsilateral visual pathways, particularly their contributions to cortical responsiveness and their integration to form binocular neurons (Creel, 1971; Michalski et al., 1994; Zhao et al., 2013; Herrera et al., 2024). Such analysis is crucial for deciphering the molecular and cellular mechanisms that underpin the emergence of high-acuity stereoscopic vision and visually guided natural behaviors (Johnson et al., 2021; Broersen et al., 2025).

In this review, we explore the development of the binocular circuitry in the primary visual cortex (V1) of mice and higher mammals (i.e., cats, ferrets, and primates), tracing its progression from the pre-eye–opening phase to the end of the classical critical period, with a specific focus on the distinct timing and trajectories of maturation of the contralateral eye and ipsilateral eye cortical circuitries. We conceptualize these two circuitries as distinct modalities, with the binocular circuitry developing through the integration of a slower-developing, experience-dependent modality (i.e., the ipsilateral eye circuitry) into a preestablished scaffold formed by a more rapidly maturing, genetically hardwired modality (i.e., the contralateral eye circuitry). We propose that this experience-dependent multimodal integration process may universally underlie postnatal circuit development across the mammalian cortex.

Experience-Dependent Development of the Binocular Circuitry

Retinotopic map

Topographic mapping is a fundamental principle of nervous system organization (Cang and Feldheim, 2013). A key example is the retinotopic map, a spatially organized neural representation in which adjacent locations on the retina correspond to adjacent locations within a visual area of the brain. Retinotopic maps have recently been shown to exist outside the visual cortex to ubiquitously scaffold cognition by providing a whole-brain–level reference frame for perception–action loops (Groen et al., 2022). Importantly, the foundation of this widespread functional and anatomical map across brain areas is built by topographic projections of retinal ganglion cells (RGCs). This orderly topographic organization is guided by patterned spontaneous neuronal activity and graded expression of the repulsive guidance cues EphA and ephrin-A (McLaughlin et al., 2003; Cang et al., 2005a,b). RGCs from the temporal retina project ipsilaterally, whereas nasal RGCs decussate at the optic chiasm to reach the contralateral side (Huberman et al., 2008; Guido, 2018). These projections terminate in the lateral geniculate nucleus (LGN), which relays the spatially organized input to the V1. The V1 binocular region (called V1b hereafter) is the initial site where the retinotopic maps from the contralateral and ipsilateral eyes converge, enabling the integration of topographically matched inputs from the two eyes into the same neurons in V1 (Fig. 1). Thus, the retinotopic map serves as the most basic anatomical foundation for the formation of binocular neurons (Espinosa and Stryker, 2012).

Orientation and OD maps

In V1 of higher mammals, neurons with similar orientation preferences cluster into iso-orientation patches (Hubel and Wiesel, 1962; Chapman et al., 1996). The preferred orientation of these patches varies smoothly across the cortical surface and is organized into radial “pinwheel” patterns centered on singularities called orientation centers, thus forming a continuous orientation map (Bonhoeffer and Grinvald, 1991, 1993; Koulakov and Chklovskii, 2001). Similarly, in V1 of higher mammals, neurons that respond more strongly to stimulation of either the contralateral or ipsilateral eye tend to cluster together and form alternating bands across the cortical sheet; this pattern is termed an OD map (Hubel and Wiesel, 1969; Crair et al., 1997; Horton and Hocking, 1998). The orientation and OD maps reflect the anatomical and functional organization of eye-specific inputs in the cortex and serve as neural substrates for establishing the binocular circuitry.

Visual experience is required for ipsilateral but not contralateral map formation in mice and cats

Visual experience exerts markedly different influences on the formation, refinement, and maintenance of cortical maps for the contralateral and ipsilateral visual pathways. In mice, under

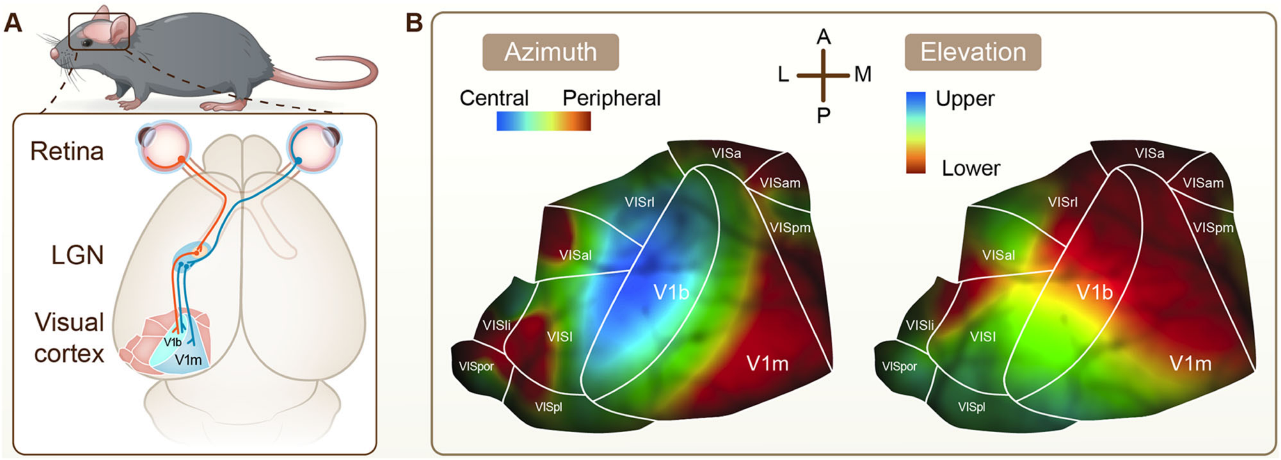

Figure 1. Schematic of the mouse visual pathway and retinotopic maps of visual cortical areas. ***A***, Schematic of the visual pathway for the left hemisphere. ***B***, Retinotopic maps, including azimuth (left) and elevation (right) maps, throughout the left visual cortex, with visual areas and V1b labeled. LGN, lateral geniculate nucleus; V1b, primary visual cortex, binocular zone; V1m, primary visual cortex, monocular zone; VISal, anterolateral visual area; VISam, anteromedial visual area; VISpm, posteromedial visual area; VISpl, posterolateral visual area; VISrl, rostrolateral visual area, VISli, laterointermediate visual area, VISpor, postrhinal visual area; VISl, lateromedial visual area; VISa, anterior visual area.

conditions of contralateral monocular deprivation (cMD) following eye opening, the retinotopic map for the contralateral eye still forms and gradually improves but becomes slightly less organized than it is in normally reared mice (Smith and Trachtenberg, 2007). In contrast, under the same cMD conditions, even though the ipsilateral eye remains open, the ipsilateral eye map fails to develop properly: it appears poorly organized, exhibiting reduced precision in receptive field organization and weaker responsiveness across development.

In cats, orientation maps show a similar differential dependence on visual experience. The contralateral eye orientation map forms and is refined normally without visual input during the early postnatal period, as evidenced by the well-organized pinwheels in binocularly deprived (BD) cats from postnatal day (P)14–P26 (Crair et al., 1998). However, maintaining this organization into adulthood requires normal visual input, as the map deteriorates markedly by P45 under continued binocular suture. In contrast, the ipsilateral eye orientation map remains severely disorganized throughout the P14–P45 period under BD conditions.

The development of eye-specific orientation maps in the ferret V1b follows a markedly different trajectory. Ferrets are altricial—born at an early stage of development, with the establishment of retinothalamic and thalamocortical connectivity occurring mostly after birth, unlike in mice and cats, where this process occurs largely before birth (Issa et al., 1999). Ferrets' eyes typically open at approximately P30. At eye opening, oriented stimuli delivered monocularly or binocularly elicit three well organized but mismatched monocular or binocular orientation maps in the ferret V1b. During the first week following eye opening, the binocular orientation map remains relatively stable, and both the contralateral and ipsilateral eye maps undergo vision-dependent shifts to match the binocular map (Chang et al., 2020). The discrepancies in the maturation trajectory and experience dependence of the monocular and binocular circuitries between ferrets and cats remain unresolved but may be attributable to the extended postnatal development of the entire visual pathway occurring in ferrets prior to eye opening (Issa et al., 1999).

These findings demonstrate the conserved principle in mice and cats that functional maps for the ipsilateral eye are more susceptible to alterations in visual experience than are those for the contralateral eye, whereas in ferrets, experience serves primarily to align monocular maps with binocular representations.

Visual experience is required for the establishment of ipsilateral and binocular neurons but not for contralateral neurons in mice

The formation of normal numbers of highly tuned binocular neurons involves the integration of functionally refined inputs from the contralateral and ipsilateral visual pathways. Binocular neurons are not simply refined from a fixed population of gradually developing poorly tuned counterparts; instead, the cellular composition of the binocular circuitry undergoes continuous drift (Jenks and Shepherd, 2020; Tan et al., 2020, 2021). That is, early monocular contralateral neurons that exhibit highly selective orientation tuning and high spatial frequency preferences often acquire matched inputs from the ipsilateral eye and become highly tuned and stable binocular neurons. Conversely, early binocular neurons characterized by poor tuning properties typically lose responsiveness to the weaker eye and are rendered monocular.

In mice, few binocular neurons are present at eye opening, but near-adult numbers of binocular neurons are established just 4 d after eye opening (Jenks and Shepherd, 2020). This developmental progression occurs as cortical responses to contralateral and ipsilateral eye stimulation emerge and are refined via distinct trajectories. The vast majority of visually responsive neurons in V1b are driven by contralateral eye inputs at eye opening (Tan et al., 2021, 2022). At this time, these monocular contralateral neurons already exhibit decent orientation selectivity and spatial frequency tuning, with these properties rapidly maturing to adult levels by P18. In contrast, ipsilateral and binocular neurons are very limited in both number and tuning quality at eye opening. After 4 d, the number of ipsilateral neurons increases substantially, whereas their tuning properties, particularly orientation selectivity, develop slowly and attain the same level of maturity as contralateral neurons at approximately P36 (Tan et al., 2022). In parallel, binocular neurons exhibit a near-adult level of binocular matching of orientation preference at P18 but are broadly tuned and strongly biased toward cardinal orientations (Tan et al., 2022). By P36, binocular neurons in V1b layers 2/3 (L2/3) achieve mature tuning properties, characterized by sharp orientation tuning with a marked reduction in cardinal bias, a high spatial frequency preference and a complex cell-like modulation index, through the population drift described in an earlier paragraph (Tan et al., 2022; Brown and McGee, 2023; Fig. 2).

Notably, although monocular contralateral neurons emerge independent of visual experience, as their proportional abundance is unaffected by cMD between P14 and P18, their tuning properties (i.e., orientation selectivity, spatial frequency preference, and modulation index) are slightly impaired by early cMD, mirroring the minor defect in the contralateral eye retinotopic map in V1b induced by early cMD (Smith and Trachtenberg, 2007). These results indicate that the refinement but not the emergence of contralateral neurons requires visual experience (Tan et al., 2020, 2021). In contrast, both the emergence and the refinement of ipsilateral and binocular neurons are critically dependent on visual experience from eye opening to the critical period. Visual deprivation during either of these two stages can lead to a markedly reduced quantity and quality of both ipsilateral and binocular neurons (Tan et al., 2020, 2021). In the absence of visual experience, the orientation selectivity of monocular ipsilateral neurons does not improve and remains much poorer than that of contralateral neurons. Consequently, monocular neurons that become binocular exhibit

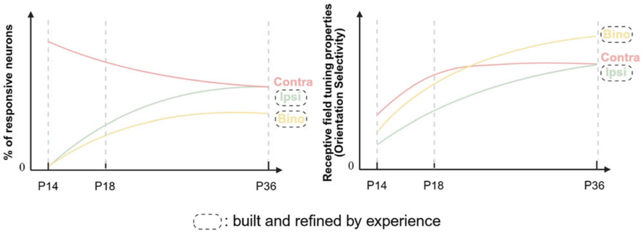

Figure 2. Developmental progression of visual responsiveness and receptive field tuning in V1b L2/3 neurons from eye opening to P36. ***A***, Line plots showing changes in the fraction of visually responsive neurons in mouse. At eye opening, most responsive neurons are driven by contralateral eye inputs, whereas the number of ipsilateral and binocular neurons is limited. From P14 to P36, the proportion of contralateral neurons decreases, whereas those of ipsilateral and binocular neurons increase, resulting in a balanced distribution of contralateral- and ipsilateral-driven neurons by P36. ***B***, Line plots showing the developmental trajectories of receptive field tuning (orientation selectivity) in mouse V1b L2/3 neurons. Monocular contralateral tuning (red) matures rapidly from P14 to P18, whereas monocular ipsilateral tuning (green) improves gradually from P14 to P36. Binocular tuning (yellow) progressively increases and surpasses contralateral tuning around P20. Contra, contralateral neurons; Ipsi, ipsilateral neurons; Bino, binocular neurons.

tuning properties that are no better than those of monocular neurons that remain monocular, and these newly formed binocular neurons are less complex cell-like than their monocular counterparts, indicating that the formation of highly tuned binocular neurons requires visual experience (Tan et al., 2020, 2021).

In naive ferrets at eye opening, the majority of L2/3 neurons are binocularly responsive but commonly display different monocular orientation preferences, and patterned visual experience during the first week post eye opening shifts monocular orientation preferences to align with the binocular preference (Chang et al., 2020). Compared with that in mice, the normal development of contralateral eye responses in V1b L2/3 in ferrets is more strongly dependent on visual experience (Gorzek and Trachtenberg, 2025). Studies have shown that visual deprivation following eye opening in ferrets strongly impairs the maturation of orientation selectivity in L2/3 neurons (Chapman and Stryker, 1993; White et al., 2001).

Taken together, these observations indicate that to achieve binocular circuitry maturation in mice, normal visual experience beginning at eye opening is required to continuously build and refine the ipsilateral eye cortical circuitry and facilitate the integration of well-tuned ipsilateral eye inputs with their matched contralateral eye counterparts, driving the dynamic neuronal population drift toward a well-tuned binocular neuron ensemble.

Distinct binocular plasticity and orientation selectivity in V1 L2/3 and L4

The traditional view of cortical development holds that L2/3 development is contingent upon L4, with changes in L2/3 reflecting an amplified version of the alterations occurring in L4 (Espinosa and Stryker, 2012; Hooks and Chen, 2020). In other words, the development of the visual system seems to follow a structured hierarchical progression, with neural networks in the early segments of the visual pathway maturing before those in later segments and being essential for the development of networks in later segments. Thus, it is thought that the maturation of binocular circuitry follows the order of dLGN to V1 L4 to L2/3 (Gu and Cang, 2016; Sommeijer et al., 2017).

However, recent findings in mice suggest that binocular circuitry development may not adhere to this hierarchical sequence. Bauer et al. (2021) demonstrated that the vast majority of dLGN neurons are driven by monocular inputs, with only a minimal percentage (~1%) driven comparably by both eyes. Furthermore, studies have shown that the tuning properties (i.e., direction and orientation tuning) of V1 L2/3 and L4 are established de novo and not directly inherited from afferent inputs (Lien and Scanziani, 2018; Rossi et al., 2020). In line with these findings, distinct developmental and plasticity profiles have been observed between L2/3 and L4 in mice. Specifically, while population drift of binocular neurons occurs in both layers, as age increases, the number of monocular neurons in L4 increases, whereas the proportion of binocular neurons in L2/3 increases (Huh et al., 2020; Tan et al., 2022). Moreover, the orientation selectivity of neuronal responses elicited by the contralateral eye is similar in both layers, whereas orientation tuning for the ipsilateral eye is less selective in L4 neurons and does not undergo the same refinement process with age as it does in L2/3. This discrepancy in orientation selectivity between the two eyes in L4 neurons may, in turn, account for the progressive decline in binocularity observed in this layer. Chapman and Stryker (1993) demonstrated that in ferrets, the role of visual experience differs by layer, such that orientation tuning in L2/3 is strongly dependent on the quality of visual input, whereas tuning in L4 is established largely through intrinsic mechanisms.

By combining in vivo imaging in ferrets and computational modeling, Lempel et al. (2024) identified potential mechanisms underlying the stronger orientation selectivity in L2/3 and further delineated its developmental interplay with L4. In naive animals, L2/3 neurons demonstrated greater orientation selectivity than did L4 neurons, a difference attributable to recurrent connectivity within L2/3 prior to the onset of visual experience. At this developmental stage, L4 supplies L2/3 with poorly selective feedforward projections, and consequently, the mismatch in orientation preference between the feedforward inputs and the established recurrent connectivity leads to considerable variability in the responses of L2/3 neurons. With subsequent visual experience, the recurrent connections in L2/3 become synchronized with specific feedforward inputs from L4, resulting in selective connections between L4 and L2/3 neurons and more stable orientation preferences of L2/3 neurons. Thus, the heightened orientation selectivity of L2/3 neurons at the time of eye opening is not inherited from L4, whereas the later-acquired response stability and reliability of these neurons rely on L4 inputs. While this phenomenon remains to be demonstrated in the mouse visual cortex, a recent study in the mouse primary motor cortex (M1) revealed that thalamic inputs enable reliable tuning of M1 L2/3 neurons after motor learning, which is consistent with the role of feedforward inputs in stabilizing the tuning of cortical L2/3 neurons (Ramot et al., 2025).

Furthermore, the horizontal connections in the cat and ferret L2/3 can be significantly impacted by alterations in visual experience, as either binocular eyelid suture or dark rearing results in less extensive and less clustered horizontal connections than normal, leading to reduced orientation selectivity of L2/3 neurons (Callaway and Katz, 1991; White et al., 2001). These observations, along with the findings of studies on OD plasticity in cats (Trachtenberg et al., 2000), indicate that L2/3 neurons possess a greater degree of inherent plasticity than do L4 neurons. This plasticity, which increases their binocularity relative to that of L4 neurons, is likely underpinned by their distinctive recurrent connectivity that matures precociously and depends on experience.

Mechanisms Regulating the Development of the Binocular Circuitry

The role of gamma-aminobutyric acid (GABA)ergic interneurons (INs) in binocular circuit development

The development of the binocular circuitry is shaped not only by eye-specific sensory inputs but also by the progressive maturation of intracortical inhibitory networks. The mouse visual cortex hosts a diverse population of GABAergic INs, originating primarily from the medial ganglionic eminence (MGE) and caudal ganglionic eminence (CGE; Gouwens et al., 2020). MGE-derived INs include the parvalbumin (PV) and somatostatin (SST) subclasses, whereas CGE-derived progenitors give rise to vasointestinal peptide (VIP)- and lysosome-associated membrane glycoprotein 5 (Lamp5)-expressing subclasses (Inan et al., 2012; Wamsley and Fishell, 2017; De Marco Garcia and Fishell, 2025). Here, we focus specifically on PV- and SST-expressing INs, detailing their development from eye opening to the onset of the critical period and examining how their maturation and interactions may facilitate the alignment and integration of binocular inputs within V1 L2/3.

Development and role of PV–INs during the critical period

INs that express PV account for nearly 40% of all GABAergic neurons in the cortex and form synaptic contacts primarily on the somatic and perisomatic regions of pyramidal neurons (PNs; Di Cristo et al., 2004). Previous research revealed that PV–INs regulate the critical period of OD plasticity, with their intrinsic fast-spiking properties and efficacy of synaptic transmission to PNs increasing from eye opening to the onset of the critical period (Lazarus and Huang, 2011; Kuhlman et al., 2013; Severin et al., 2021). Additionally, perisomatic GABAergic innervation reaches a state of near-complete maturation by approximately P20, indicating a correlation between the maturational trajectory of PV–INs and the onset of the classical critical period (Gordon and Stryker, 1996; Chattopadhyaya et al., 2004). Beyond their potential involvement in the onset of the classical critical period, PV–INs are also involved in the refinement of orientation and direction selectivity within V1. Lee et al. (2012) demonstrated that optogenetic activation of PV–INs but not SST–INs or VIP–INs resulted in increased orientation selectivity of V1 PNs and a marked increase in orientation discrimination performance in mice. Furthermore, optogenetic suppression of PV–INs results in an increased firing rate of less-active PNs and a decreased firing rate of PNs with higher activity (Zhu et al., 2015). This dual effect on the PN firing rate affects the reliability of visual cortical representations to natural stimuli, implying that response reliability in L2/3 does not depend solely on the alignment between feedforward inputs and recurrent connectivity, as previously mentioned, but is also regulated by PV–INs.

Development and role of SST–INs during the critical period

SST–INs, which account for ∼20–30% of all neocortical GABAergic INs, preferentially inhibit the distal dendrites of PNs, as well as PV–INs (Pfeffer et al., 2013; Urban-Ciecko and Barth, 2016; Guan et al., 2017). At eye opening, there is a notable reduction in the inhibition of PNs by SST–INs, a modification that is anticipated to increase the efficacy of visual input and may contribute to experience-dependent developmental processes within the visual cortex (Guan et al., 2017). From eye opening to the onset of the critical period, SST–INs undergo a significant increase in input resistance, coupled with depolarization of their resting membrane potential (Lazarus and Huang, 2011). These alterations result in heightened excitability of SST–INs, suggesting their major contributions to the distal dendritic inhibition and somatic disinhibition of PNs, which further regulate visual cortical plasticity (Lazarus and Huang, 2011). Consistent with this idea, dampening the activity of SST–INs during the critical period hinders binocular matching and the maturation of the ipsilateral eye responses of L2/3 PNs (Yaeger et al., 2019).

Inhibitory microcircuits formed by PV–INs and SST–INs facilitate PN plasticity

The maturation of PV–INs, leading to their strong somatic inhibition of PNs, is well accepted as a prerequisite for both the onset of the classical critical period and the development of the binocular circuitry. However, systemic diazepam administration during P15–P16 in mice, which was shown to initiate the classical critical period precociously (Fagiolini and Hensch, 2000; Iwai et al., 2003), did not facilitate the maturation of binocular circuitry (Tan et al., 2021). Instead, diazepam-treated mice exhibited impaired receptive field tuning of binocular neurons, with manifestations including reduced binocular matching of orientation preference, a lower spatial frequency preference, and decreased complexity of the ipsilateral eye response. Thus, the strong somatic inhibition of PNs by PV–INs may not be universally important to all aspects of critical period plasticity.

Consistent with this idea, studies have shown that dynamic modulation of PV–IN activity, rather than sustained strong PV–IN inhibition, plays a pivotal role in facilitating PN plasticity. Kuhlman et al. (2013) delineated a model of disinhibition that is integral to critical period plasticity. They reported that cMD results in a reduced firing rate of PV–INs, thereby attenuating PV-mediated perisomatic inhibition. Notably, this reduced inhibition facilitated a shift in the OD of PNs. Moreover, pharmacological augmentation of PV inhibition during periods of visual deprivation impeded the OD shift of PNs, whereas the converse—pharmacogenetic suppression of the PV–IN firing rate—prolonged the critical period of OD plasticity. Thus, the heightened plasticity of PNs relies at least partially on decreased PN inhibition by PV–INs. Furthermore, this somatic disinhibition of PNs can be mediated physiologically by SST–INs. During the peak of the critical period for binocular plasticity, the activity of SST–INs can be markedly elevated by increased acetylcholine release from neurons in the basal forebrain when mice are running. This transient increase in SST–IN activity augments the branch-specific dendritic inhibition and somatic disinhibition of PNs, which are two key factors for PN plasticity. In adulthood, however, this locomotion-induced activation of SST–INs diminishes, and compartmentalized PN dendritic responses disappear (Yaeger et al., 2019).

On the basis of the abovementioned microcircuitry formed by PNs and PV– and SST–INs, transient cholinergic activation of SST–INs by heightened arousal or active processing of visual information can result in increased dendritic inhibition and decreased somatic inhibition of PNs. According to the differential developmental timing and trajectories of the two visual pathways, it is conceivable that during the critical period of development in V1b, the input to SST–INs may be dominated by the contralateral eye. In this way, transient cholinergic activation of SST–INs leads to two concomitant consequences: (1) inputs from the contralateral eye are transiently suppressed by SST–INs, while inputs from the ipsilateral eye are prompted by cholinergic activation of particular PN dendrites, and (2) the firing rate of PNs driven by transiently balanced binocular inputs increases. These two processes could ultimately lead to the integration of matched binocular inputs onto PNs, the hallmark of visual cortical developmental plasticity during the critical period (Tsimring et al., 2025). This hypothetical model, although requiring further verification, proposes the intricate interplay among cholinergic modulation, SST–IN-mediated dendritic inhibition and somatic disinhibition, PV–IN-mediated somatic inhibition, and experience-dependent integration of the contralateral and ipsilateral eye cortical circuitries, all of which are essential for the maturation of the binocular circuitry in the visual cortex (Bear and Singer, 1986; Fig. 3).

Molecular mechanisms regulating the development of the binocular circuitry

A plethora of molecular mechanisms have been found to underlie the critical period for OD plasticity by orchestrating the maturation of inhibitory circuits and synaptic remodeling (Levelt and Hubener, 2012). However, the cellular and molecular mechanisms regulating the normal development of the binocular circuitry remain less well understood.

Mazziotti et al. (2017) reported that mice lacking miR-132/212 exhibited a deficit specifically in binocular matching of orientation preferences without changes in orientation or direction selectivity, leading to impaired depth perception. Wang et al. (2013) demonstrated that environmental enrichment (EE)

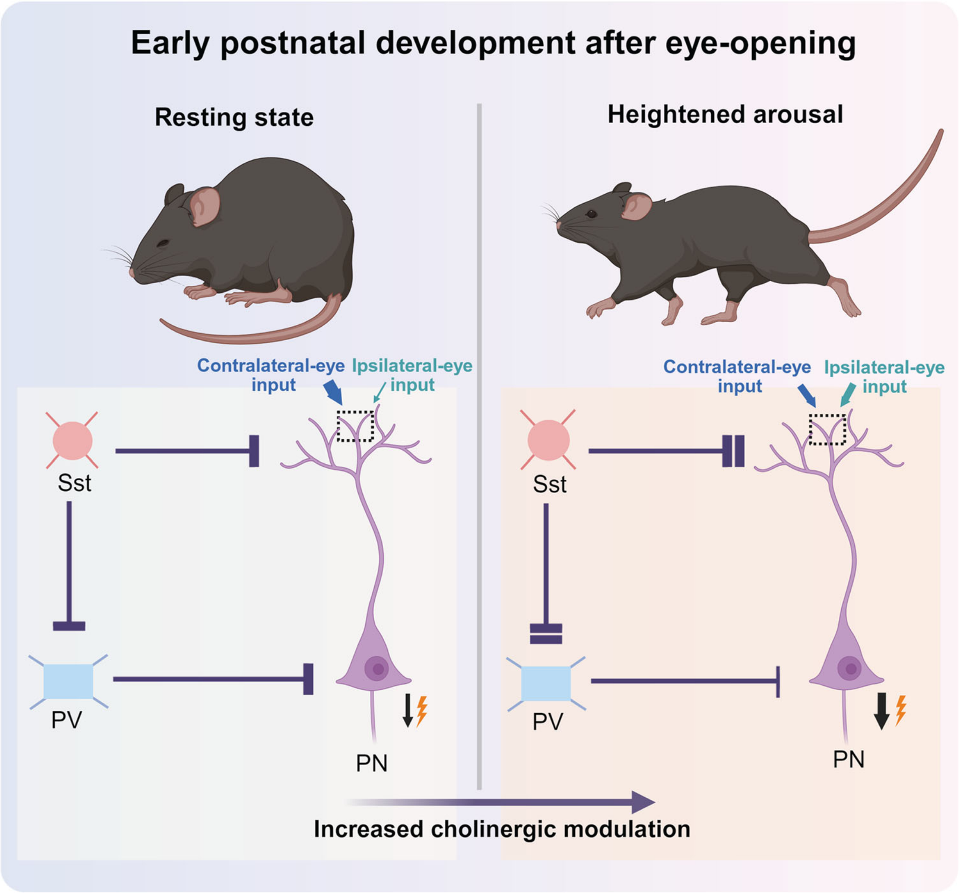

Figure 3. A cortical disinhibitory microcircuit model of state-dependent cholinergic modulation driving binocular integration in V1 L2/3 after eye opening. Resting state during early postnatal development (left): strong contralateral eye inputs and weak ipsilateral eye inputs to PNs. Heightened arousal (right): during active states, such as locomotion or visual engagement, cholinergic input from the basal forebrain increases. This state-dependent cholinergic modulation could ultimately lead to balanced eye-specific inputs and their functional integration onto PNs. Sst–IN, somatostatin-expressing interneuron; PV–IN, parvalbumin-expressing interneuron; PN, pyramidal neuron.

restored binocular matching in mice with a precocious critical period induced by increased inhibition. This restoration occurred through increased acetylation of histone H4 (H4K5) in the visual cortex, a process likely mediated by an elevated level of insulin-like growth factor 1 (IGF-1). Jenks and Shepherd (2020) reported that the absence of Arc in V1 L2/3 neurons of mice resulted in an increased proportion of binocular neurons and a reduced number of neurons responding exclusively to the contralateral eye, although other aspects of visual responsiveness remained unaltered.

The critical effects of microRNAs, histone acetylation, and the plasticity gene Arc on the maturation of the binocular circuitry in V1b L2/3 revealed by the above studies suggest the fine spatiotemporal regulation of the expression levels of key synaptic molecules in L2/3 PNs from eye opening to the end of the critical period. Consistent with this idea, Cheng et al. (2022) reported that *Igsf9b*, a cell adhesion molecule that promotes the formation of perisomatic inhibitory synapses onto PNs through its binding to neuroligin-2 (Woo et al., 2013), is required for the maturation of binocular neurons in L2/3. They also reported a marked reduction in the signal-to-noise ratio of L2/3 neuronal responses to visual stimuli in *Igsf9b*-KO mice, mirroring the finding of impairment of the response reliability of L2/3 PNs by optogenetic suppression of PV inhibition (Zhu et al., 2015). Thus, *Igsf9b* could regulate the development of the binocular circuitry by promoting the formation of PV-mediated inhibitory synapses onto L2/3 PNs.

Beyond the mechanisms described above that regulate V1 L2/3 binocular neuron development, it is important to recognize that cortical L2/3 neurons are not a homogeneous population. Their transcriptomic, morphological, electrophysiological, and connectivity properties exhibit continuous or discrete variations along cortical depth. Single-cell transcriptomic analyses have revealed continuous cellular transcriptomic variation with cortical depth (Zhang et al., 2021, 2023). Consistent with this continuous variation in gene expression, Weiler and colleagues reported that V1b L2/3 neurons display structural, physiological, and functional heterogeneity with cortical depth at cellular resolution, including variations in apical and basal dendrite morphology, subthreshold and suprathreshold electrophysiological properties, horizontal connectivity, and GABAergic inputs (Weiler et al., 2023). Their findings regarding the dendritic morphology and synaptic input variation of PNs were further verified and refined by the recent MICrONS project (Schneider-Mizell et al., 2025). Notably, the expression level of *Igsf9b* in V1 L2/3 exhibited a continuous increase with cortical depth. The reductions in the expression of inhibitory synaptic markers and the number of visually responsive neurons were also exacerbated with cortical depth in KO mice, mirroring the spatially graded *Igsf9b* expression pattern (Cheng et al., 2022).

Thus, the normal phenotypic variation of L2/3 neurons with cortical depth could be regulated by genes with continuous spatial expression variations that are associated with neuronal development and function. Recent advances in spatially resolved techniques for phenotypic and transcriptomic analyses at single-cell resolution provide a unique opportunity to study the molecular mechanisms underlying the development of the binocular circuitry—or the functional cortical circuitry more generally—in the context of the experience-dependent cellular organization of the cortex (Wang et al., 2019; Siegle et al., 2021; Qin and Tape, 2024).

Organizing Principles of Binocular Integration and Beyond

Conserved organizing principles of the visual circuitry between mice and higher mammals (cats/primates)

In this section, we discuss evidences to support the proposal that the experience-dependent development of the binocular circuitry, which aims to establish high-acuity and position-invariant binocular feature detectors, is highly conserved at the level of fundamental organizing principles of the visual system between mice and higher mammals (mostly cats).

The first similarity in binocular circuitry development between mice and cats lies in the differential developmental timing and vision dependence of the contralateral and ipsilateral eye cortical circuitries (Crair et al., 1998; Smith and Trachtenberg, 2007; Tan et al., 2020, 2021).

The second similarity is that normal visual experience is required for the formation of highly tuned binocular feature detectors via the selective integration of sharply tuned inputs from the two eyes in both mice and cats. In mice, as previously described, visual experience progressively refines the ipsilateral eye circuit and selectively integrates the best features of this circuit with the matched contralateral eye inputs to form binocular neurons. Similarly, in cats with normal experience, OD borders are located as far from orientation pinwheel centers as possible, indicating the establishment of well-tuned binocular neurons, as neurons farther away from pinwheel centers have sharper orientation tuning, and neurons closer to OD borders are more binocular (Cloherty et al., 2016). In kittens reared with orthogonally oriented cylindrical lenses placed over each eye, however, OD borders are located as close to orientation pinwheel centers as possible, indicating the prominent presence of poorly selective binocular neurons.

In addition to similarities in vision-dependent development of the binocular circuitry, the basic organization of the visual system that is foundational for establishing the binocular circuitry also appears to be conserved between mice and higher mammals (Table 1).

The abovementioned cross-species similarities in the development of the binocular circuitry and the fundamental visual system organization suggest that mice and higher mammals (cats/primates) employ shared spatiotemporal regulatory principles to construct the visual cortical circuitry during experience-dependent development (discussed in the next subsection). However, the functional implementation of these visual circuits for behavior can differ substantially across species (Luongo et al., 2023). Such fundamental differences in visually guided behaviors between mice and higher mammals may arise from divergence of the structural and functional properties of RGCs, the diversity and organization of visual cortical cell types, and the number and complexity of cortical areas, as well as overall brain volume and computational capacity.

Table 1. Cross-species similarities in the basic organization of the visual system

Organizational features of the visual system	Higher mammals (cat/primate)	Rodents (mouse)
Limited functional binocular convergence in the LGN	Neurons in the LGN are monocular, with binocular responses confined to the koniocellular layer (Zeater et al., 2015; Dougherty et al., 2019)	Few functionally binocular neurons were identified in the dLGN (Bauer et al., 2021)
Fovea and fovea-like region in the visual cortex	The foveal region exhibits smaller population receptive fields (pRFs) and enhanced spatial resolution (Godat et al., 2022)	Cortical "focea" region shows smaller pRFs and improved visual spatial resolution, largely overlapping with binocular visual cortical region (van Beest et al., 2021)
OD columns	Well-defined OD columns extend vertically across cortical layers and are most pronounced in L4 (Hubel and Wiesel, 1968; Crair et al., 2001)	Neurons preferring ipsilateral eye stimulation form discrete clusters that are most prominent in L4 and extend into L2/3 and L5, giving rise to columnar organization (Goltstein et al., 2025)
Spatial organization of orientation-tuned neurons	Orientation-selective neurons form iso-orientation columns organized in pinwheel-like map across cortical surface (Bonhoeffer and Grinvald, 1993)	Local clustering of V1 neurons with similar tuning preferences across layers (Ringach et al., 2016), with a global map of orientation bias organized around a single pinwheel across visual cortical areas (Fahey et al., 2019)
Covariation of tuning properties	Orientation selectivity, spatial frequency (SF) preference, and response complexity covary; sharper orientation tuning with higher SF and complexity (Chen et al., 2020)	Similar covariation relationship: neurons with higher orientation selectivity tend to prefer higher spatial frequencies and exhibit greater response complexity (Tan et al., 2020)

Late is plastic: the interaction between the contralateral and ipsilateral eye cortical circuitries exemplifies a model of multimodal integration

The development of the binocular circuitry, particularly the delayed maturation of the ipsilateral eye cortical circuitry, cannot be explained by the model of activity-dependent competition between the two visual pathways that explains OD plasticity. In such a model, the stronger contralateral eye inputs would always overshadow the weaker ipsilateral eye inputs, ultimately leading to the absence of ipsilateral eye and binocular responses (Song et al., 2000; Espinosa and Stryker, 2012). The maturation of the binocular circuitry essentially exemplifies the "late is plastic" view regarding the sequential postnatal development of cortical circuits: the contralateral eye cortical circuitry is established early via intrinsic mechanisms and remains largely hardwired, whereas the ipsilateral eye circuitry emerges after the establishment of the contralateral eye circuitry and exhibits greater plasticity, with visual experience being essential for its formation, refinement, and integration into the preexisting contralateral eye circuitry.

An alternative model—multimodal integration—can explain the interaction between these two eye-specific cortical circuitries. The two eyes work as "separate channels", with each retina encoding the visual scene independently and transmitting it via distinct afferent projections, thus resembling a highly simplified version of separate modalities. Through protracted experience-dependent development of the ipsilateral eye circuitry, as we discussed earlier, the visual inputs of the binocular V1 from each eye become highly correlated with a shared representational space. Mechanistically, the heightened plasticity of the late-developing ipsilateral visual pathway constitutes a prerequisite for its integration into the early-developing contralateral visual pathway, by enabling its visual responses to be adaptively aligned with the preestablished contralateral eye circuitry by experience (Tan et al., 2021; Gorzek and Trachtenberg, 2025). This integration of eye-specific cortical circuitries, mediated by visual experience, progressively gives rise to a well-tuned binocular neuron ensemble that supports a unified visual representation of the external world, which is essential for depth perception and eye–forelimb coordination (Gorzek and Trachtenberg, 2025).

Multimodal integration, which occurs across the sensory, motor, and associative cortices, is a mechanism by which the brain comprehensively processes complex environmental information through multiple modalities, such as vision, audition, touch, olfaction, motor processes, and cognition. Multimodal integration enables adaptive perception–action loops that interface with complex, dynamic environmental statistics and task demands (Holmes et al., 2009; Mercier and Cappe, 2020). One example comes from the posterior parietal cortex in rats and a tacto–visual subregion in the mouse V1, where neurons driven by both visual and whisker-derived inputs facilitate accurate assessment of the ethological relevance of items that are simultaneously visualized and touched (Nikbakht et al., 2018; Weiler et al., 2024). Additionally, Velez-Fort et al. (2025) demonstrated that V1 in mice integrates motor, vestibular, and visual inputs to facilitate the separation of self-generated from externally generated visual motion. In addition to V1, a subset of neurons in the primary somatosensory cortex (S1) was recently revealed to integrate peripheral tactile input with value prediction error signals from the orbitofrontal cortex (OFC). This dynamic OFC–S1 interaction enabled context-dependent remapping of sensory representations, thereby supporting flexible and adaptive decision-making (Banerjee et al., 2020).

Notably, the capability for integrated processing of different modalities (multimodal integration) in a particular cortical area is typically gained through protracted experience-dependent postnatal development, with cortical responsiveness to different modalities emerging in a sequential order (Sydnor et al., 2021). Smith et al. (2017) reported that in mice, visual responses in dorsal stream higher visual areas involved in visually guided actions (Kravitz et al., 2011) emerge only after eye opening. The emergence of these responses coincides with the significantly increased motor activity in pups, after which they undergo ~2 weeks of vision-dependent development to reach full maturity. In contrast, ventral-stream visual areas associated with object perception (Kravitz et al., 2013) do not exhibit this delayed, vision-dependent development. In the cat anterior ectosylvian sulcus (AES), multisensory neurons integrate somatosensory, auditory, and visual inputs. Importantly, the emergence of these neuronal responses in this region follows a sequential order, with somatosensory neurons emerging and maturing first, followed by auditory neurons and, ultimately, visual neurons (Wallace et al., 2006). The earliest multisensory neurons are functionally immature and unable to synthesize information across sensory modalities. As unisensory neurons mature, however, multisensory neurons in the AES exhibit enhanced integrative capacity and progressively increase in number, reaching an adult-like incidence by 20 weeks. These observations are consistent with the notion inspired by the development of binocular circuitry that the early-maturing somatosensory neurons may provide a responsive scaffold for later-developing sensory modalities. During the experience-driven development, auditory and visual neurons may refine their tuning with reference to the scaffold, thus aligning with these preestablished somatosensory response patterns. As their responses become more closely aligned, this convergence could facilitate multisensory integration.

Language learning in humans offers another notable example of the experience-dependent multimodal integration. Infants begin language learning primarily as auditory learners, and by ~8 months of age, they start to exhibit sensitivity to visual prosodic signals that can be aligned with auditory prosody (Gervain, 2022). However, this integration remains immature at that stage (Gervain, 2022), with adult-like precision in audio–visual pairings typically attained at ~9 years of age (Han et al., 2022). Furthermore, audio–visual pairings have been demonstrated to depend on visual experience, as human patients with congenital binocular cataracts that undergo correction 5 months after birth exhibited impaired audio–visual integration despite their largely normal visual performance (Hornix et al., 2019).

Taken together, these developmental features of multimodal integration in different cortical areas, including the sequential emergence of cortical responsiveness to different modalities, the heightened plasticity of later-developing modalities, the experience-dependent integration of early- and late-established modalities, and the transition from poorly tuned to well-tuned integrative responsiveness, closely resemble those observed during the development of the binocular circuitry. While the precise mechanisms of multimodal integration in different cortical areas remain poorly understood, the development and integration of the contralateral and ipsilateral eye cortical circuitries may offer a highly accessible model system (see next section). On the basis of evidence from the binocular circuitry, it is possible that in other cortical areas, earlier-maturing modalities provide representational scaffolds onto which later-developing modalities are aligned. This framework is consistent with the "like-to-like" connectivity observed throughout the visual hierarchy, whereby neurons with similar receptive field tuning properties preferentially form connections (Ding et al., 2025). Such a cortical connectivity rule provides key insights into how late-developing modalities are aligned with and integrated into preestablished circuit scaffolds by experience (Fig. 4).

Conclusion and Outlook

In this review, we present the maturation of the binocular circuitry as a complex and integrative developmental process, wherein the nascent ipsilateral eye cortical circuitry undergoes protracted experience-dependent development following eye opening, capitalizing on the foundational reference frame established by the early-developing and mostly hardwired contralateral eye cortical circuitry. This orchestrated sequence of events ensures the precise alignment and integration of inputs from the two eyes, which is essential for the attainment of binocular vision.

Arcaro and Livingstone (2024) used the face recognition domain in primates as a case to elucidate the role of visual experience in the development of specialized functional circuits in the ventral visual cortex. They proposed that the interplay between innate mechanisms and experience-driven processes in shaping the cortical architecture extends beyond the ventral visual cortex, influencing cortical organization throughout the brain. Building on this proposal, we now posit, by conceptualizing the two eye-specific cortical circuitries as distinct modalities, that the binocular circuitry can similarly serve as a model for investigating and

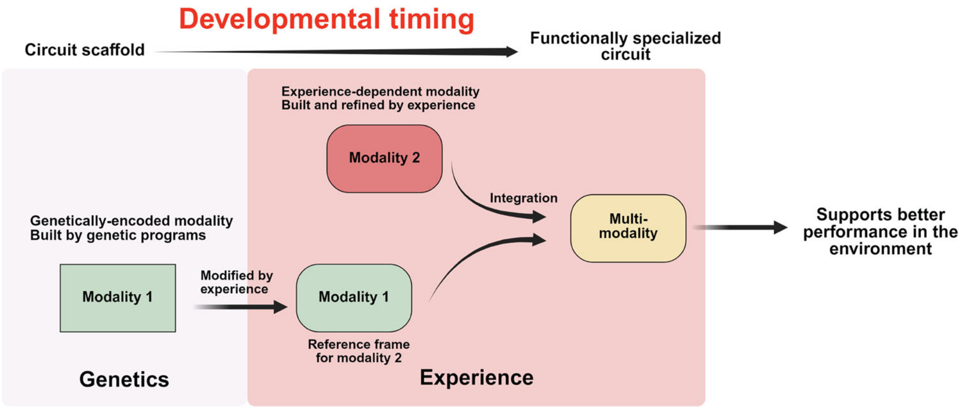

Figure 4. A conceptual framework that illustrates the role of experience in building a functionally specialized circuit. During development, the formation of a functionally specialized neural circuit is regulated by two key factors: genetics (pale purple block) and experience (blush pink block). Early in embryonic development, genetic programs (including spontaneous activity) lay down the native circuit that processes modality-specific information in a particular brain area (Modality 1, green rectangle; Guillamon-Vivancos et al., 2025). During postnatal development, the circuit for Modality 1 is modified by experience (green rounded rectangle) to improve the processing of environmental stimuli. The refined Modality 1 also functions as a responsive scaffold for experience to build and refine the late-emerging circuit that processes nonmodality-specific information in the brain area (Modality 2, red rounded rectangle). In parallel, experience also drives the integration of circuits underlying these two modalities, resulting in a new and functionally specialized circuit (multimodality, yellow rounded rectangle) that supports improved performance in the environment, ranging from sensory processing to cognition and complex behavior. In principle, this model can also apply to the integration of more than two modalities within a particular cortical area.

simulating how the genetically hardwired and experience-dependent modalities refine and integrate in response to environmental stimuli, ultimately leading to the maturation of specialized functional circuits across cortical areas.

Despite decades of progress, we still lack a clear understanding of how specialized functional circuits are assembled in the cortex. However, advancements in both conceptual understanding and experimental tools have provided new opportunities for revealing the molecular and cellular mechanisms underlying cortical circuit development. Among these opportunities, creative approaches combining cell taxonomy, spatial transcriptomics, cell type-specific drivers, patch-seq, calcium imaging, electron microscopy reconstruction, mesoscale single-neuron projectome mapping, high-density extracellular recording, protein interactome mapping, and artificial intelligence tools are expected to yield deeper insights and reveal unifying principles of cortical circuit organization and development (Gouwens et al., 2020; Wojtowicz et al., 2020; Siegle et al., 2021; Yao et al., 2023; Zhang et al., 2023; Qiu et al., 2024; Ben-Simon et al., 2025; Ding et al., 2025; MICrONS Consortium, 2025; Wang et al., 2025). Although such approaches have not yet been systematically implemented in the mouse cortex to reveal molecular mechanisms underlying circuit development, their successful application in the *Drosophila* visual system demonstrates both the feasibility and power of this framework (Takemura et al., 2013; Sanes and Zipursky, 2020; Dombrovski et al., 2025; Nern et al., 2025).

The MICrONS project, which combined in vivo calcium imaging and volumetric electron microscopy to an ∼1 mm^3 area of the mouse visual cortex (composed mostly of the “focea”/binocular region) with advanced artificial intelligence–based tools to reconstruct the functional and structural organization of the imaged cortex, represents a major step toward implementing such an integrative approach in mice (Ding et al., 2025; Schneider-Mizell et al., 2025). This project revealed general circuit-level wiring rules, including both pairwise and higher-order like-to-like connectivity patterns, and identified new organizing principles of cortical inhibition, providing a basis for linking multimodal neuronal atlases with the cortical wiring diagram. In parallel, newly developed enhancer-driven AAVs and transgenic mouse lines enable selective access to over 30 defined excitatory and inhibitory cortical cell types, greatly advancing the ability to manipulate circuit components with cell type specificity in vivo (Ben-Simon et al., 2025). These unprecedented studies are anticipated to inspire conceptual blueprints for disentangling the interplay between genetically hardwired mechanisms and experience-dependent plasticity in building specialized cortical circuits and for revealing how experience refines and integrates cortical networks at the molecular and cellular levels.

While current efforts have focused mainly on the visual cortex, the identified principles and methodologies will eventually inform mechanisms governing circuit assembly beyond the visual cortex and across broader cortical areas. Eventually, such progress in understanding cortical development will offer critical insights into its relevance to neuropsychiatric disorders (Paus et al., 2008; Yara and Khalil, 2023; McClellan et al., 2024), thereby enabling the precise design of experience-oriented intervention strategies for various neurodevelopmental disorders.

References

Arcaro M, Livingstone M (2024) A whole-brain topographic ontology. Annu Rev Neurosci 47:21–40.

Banerjee A, Parente G, Teutsch J, Lewis C, Voigt FF, Helmchen F (2020) Value-guided remapping of sensory cortex by lateral orbitofrontal cortex. Nature 585:245–250.

Bauer J, Weiler S, Fernholz MHP, Laubender D, Scheuss V, Hubener M, Bonhoeffer T, Rose T (2021) Limited functional convergence of eye-specific inputs in the retinogeniculate pathway of the mouse. Neuron 109:2457–2468.e12.

Bear MF, Singer W (1986) Modulation of visual cortical plasticity by acetylcholine and noradrenaline. Nature 320:172–176.

Ben-Simon Y, et al. (2025) A suite of enhancer AAVs and transgenic mouse lines for genetic access to cortical cell types. Cell 188:3045–3064.e23.

Bonhoeffer T, Grinvald A (1991) Iso-orientation domains in cat visual cortex are arranged in pinwheel-like patterns. Nature 353:429–431.

Bonhoeffer T, Grinvald A (1993) The layout of iso-orientation domains in area 18 of cat visual cortex: optical imaging reveals a pinwheel-like organization. J Neurosci 13:4157–4180.

Boone HC, Samonds JM, Crouse EC, Barr C, Priebe NJ, McGee AW (2021) Natural binocular depth discrimination behavior in mice explained by visual cortical activity. Curr Biol 31:2191–2198.e3.

Broersen R, Thompson G, Thomas F, Stuart GJ (2025) Binocular processing facilitates escape behavior through multiple pathways to the superior colliculus. Curr Biol 35:1242–1257.e9.

Brown TC, McGee AW (2023) Monocular deprivation during the critical period alters neuronal tuning and the composition of visual circuitry. PLoS Biol 21:e3002096.

Callaway EM, Katz LC (1991) Effects of binocular deprivation on the development of clustered horizontal connections in cat striate cortex. Proc Natl Acad Sci U S A 88:745–749.

Cang J, Kaneko M, Yamada J, Woods G, Stryker MP, Feldheim DA (2005a) Ephrin-as guide the formation of functional maps in the visual cortex. Neuron 48:577–589.

Cang J, Renteria RC, Kaneko M, Liu X, Copenhagen DR, Stryker MP (2005b) Development of precise maps in visual cortex requires patterned spontaneous activity in the retina. Neuron 48:797–809.

Cang J, Feldheim DA (2013) Developmental mechanisms of topographic map formation and alignment. Annu Rev Neurosci 36:51–77.

Chang JT, Whitney D, Fitzpatrick D (2020) Experience-dependent reorganization drives development of a binocularly unified cortical representation of orientation. Neuron 107:338–350.e5.

Chapman B, Stryker MP, Bonhoeffer T (1996) Development of orientation preference maps in ferret primary visual cortex. J Neurosci 16:6443–6453.

Chapman B, Stryker MP (1993) Development of orientation selectivity in ferret visual cortex and effects of deprivation. J Neurosci 13:5251–5262.

Chattopadhyaya B, Di Cristo G, Higashiyama H, Knott GW, Kuhlman SJ, Welker E, Huang ZJ (2004) Experience and activity-dependent maturation of perisomatic GABAergic innervation in primary visual cortex during a postnatal critical period. J Neurosci 24:9598–9611.

Chen Y, Ko H, Zemelman BV, Seidemann E, Nauhaus I (2020) Uniform spatial pooling explains topographic organization and deviation from receptive-field scale invariance in primate V1. Nat Commun 11:6390.

Cheng S, Butrus S, Tan L, Xu R, Sagireddy S, Trachtenberg JT, Shekhar K, Zipursky SL (2022) Vision-dependent specification of cell types and function in the developing cortex. Cell 185:311–327.e24.

Cloherty SL, Hughes NJ, Hietanen MA, Bhagavatula PS, Goodhill GJ, Ibbotson MR (2016) Sensory experience modifies feature map relationships in visual cortex. Elife 5:e13911.

Crair MC, Ruthazer ES, Gillespie DC, Stryker MP (1997) Ocular dominance peaks at pinwheel center singularities of the orientation map in cat visual cortex. J Neurophysiol 77:3381–3385.

Crair MC, Gillespie DC, Stryker MP (1998) The role of visual experience in the development of columns in cat visual cortex. Science 279:566–570.

Crair MC, Horton JC, Antonini A, Stryker MP (2001) Emergence of ocular dominance columns in cat visual cortex by 2 weeks of age. J Comp Neurol 430:235–249.

Creel DJ (1971) Differences of ipsilateral and contralateral visually evoked responses in the cat: strains compared. J Comp Physiol Psychol 77:161–165.

Cumming BG, Parker AJ (1997) Responses of primary visual cortical neurons to binocular disparity without depth perception. Nature 389:280–283.

De Marco Garcia NV, Fishell G (2025) Interneuron diversity: how form becomes function. Cold Spring Harb Perspect Biol 17:a041513.

Di Cristo G, Wu C, Chattopadhyaya B, Ango F, Knott G, Welker E, Svoboda K, Huang ZJ (2004) Subcellular domain-restricted GABAergic innervation in primary visual cortex in the absence of sensory and thalamic inputs. Nat Neurosci 7:1184–1186.

Ding Z, et al. (2025) Functional connectomics reveals general wiring rule in mouse visual cortex. Nature 640:459–469.

Dombrovski M, et al. (2025) Molecular gradients shape synaptic specificity of a visuomotor transformation. Nature 644:453–462.

Dougherty K, Schmid MC, Maier A (2019) Binocular response modulation in the lateral geniculate nucleus. J Comp Neurol 527:522–534.

Espinosa JS, Stryker MP (2012) Development and plasticity of the primary visual cortex. Neuron 75:230–249.

Fagiolini M, Hensch TK (2000) Inhibitory threshold for critical-period activation in primary visual cortex. Nature 404:183–186.

Fahey PG, et al. (2019) A global map of orientation tuning in mouse visual cortex. bioRxiv 745323:745323.

Fu J, Tanabe S, Cang J (2023) Widespread and multifaceted binocular integration in the mouse primary visual cortex. J Neurosci 43:6495–6507.

Gervain J (2022) Development of speech perception. In: *Speech perception* (Holt LL, Peelle JE, Coffin AB, Popper AN, Fay RR, eds), pp 201–226. Switzerland: Springer.

Godat T, et al. (2022) In vivo chromatic and spatial tuning of foveolar retinal ganglion cells in Macaca fascicularis. PLoS One 17:e0278261.

Goltstein PM, Laubender D, Bonhoeffer T, Hubener M (2025) A column-like organization for ocular dominance in mouse visual cortex. Nat Commun 16:1926.

Gordon JA, Stryker MP (1996) Experience-dependent plasticity of binocular responses in the primary visual cortex of the mouse. J Neurosci 16:3274–3286.

Gorzek R, Trachtenberg JT (2025) A critical look at critical periods. Annu Rev Vis Sci 11:175–192.

Gouwens NW, et al. (2020) Integrated morphoelectric and transcriptomic classification of cortical GABAergic cells. Cell 183:935–953.e19.

Groen IIA, Dekker TM, Knapen T, Silson EH (2022) Visuospatial coding as ubiquitous scaffolding for human cognition. Trends Cogn Sci 26:81–96.

Gu Y, Cang J (2016) Binocular matching of thalamocortical and intracortical circuits in the mouse visual cortex. Elife 5:e22032.

Guan W, Cao JW, Liu LY, Zhao ZH, Fu Y, Yu YC (2017) Eye opening differentially modulates inhibitory synaptic transmission in the developing visual cortex. Elife 6:e32337.

Guido W (2018) Development, form, and function of the mouse visual thalamus. J Neurophysiol 120:211–225.

Guillamon-Vivancos T, Anibal-Martinez M, Puche-Aroca L, Martini FJ, Lopez-Bendito G (2025) Sensory modality-specific wiring of thalamocortical circuits. Nat Rev Neurosci 26:623–641.

Han S, Chen YC, Maurer D, Shore DI, Lewis TL, Stanley BM, Alais D (2022) The development of audio-visual temporal precision precedes its rapid recalibration. Sci Rep 12:21591.

Herrera E, Chedotal A, Mason C (2024) Development of the binocular circuit. Annu Rev Neurosci 47:303–322.

Holmes NP, Calvert GA, Spence C (2009) Multimodal integration. In: *Encyclopedia of neuroscience* (Binder MD, Hirokawa N, Windhorst U, eds), pp 2457–2461. Berlin, Heidelberg: Springer.

Hooks BM, Chen C (2020) Circuitry underlying experience-dependent plasticity in the mouse visual system. Neuron 107:986–987.

Hornix BE, Havekes R, Kas MJH (2019) Multisensory cortical processing and dysfunction across the neuropsychiatric spectrum. Neurosci Biobehav Rev 97:138–151.

Horton JC, Hocking DR (1998) Monocular core zones and binocular border strips in primate striate cortex revealed by the contrasting effects of enucleation, eyelid suture, and retinal laser lesions on cytochrome oxidase activity. J Neurosci 18:5433–5455.

Hubel DH, Wiesel TN (1962) Receptive fields, binocular interaction and functional architecture in the cat's visual cortex. J Physiol 160:106–154.

Hubel DH, Wiesel TN (1968) Receptive fields and functional architecture of monkey striate cortex. J Physiol 195:215–243.

Hubel DH, Wiesel TN (1969) Anatomical demonstration of columns in the monkey striate cortex. Nature 221:747–750.

Huberman AD, Feller MB, Chapman B (2008) Mechanisms underlying development of visual maps and receptive fields. Annu Rev Neurosci 31:479–509.

Huh CYL, Abdelaal K, Salinas KJ, Gu D, Zeitoun J, Figueroa Velez DX, Peach JP, Fowlkes CC, Gandhi SP (2020) Long-term monocular deprivation during juvenile critical period disrupts binocular integration in mouse visual thalamus. J Neurosci 40:585–604.

Inan M, Welagen J, Anderson SA (2012) Spatial and temporal bias in the mitotic origins of somatostatin- and parvalbumin-expressing interneuron subgroups and the chandelier subtype in the medial ganglionic eminence. Cereb Cortex 22:820–827.

Issa NP, Trachtenberg JT, Chapman B, Zahs KR, Stryker MP (1999) The critical period for ocular dominance plasticity in the Ferret's visual cortex. J Neurosci 19:6965–6978.

Iwai Y, Fagiolini M, Obata K, Hensch TK (2003) Rapid critical period induction by tonic inhibition in visual cortex. J Neurosci 23:6695–6702.

Jenks KR, Shepherd JD (2020) Experience-dependent development and maintenance of binocular neurons in the mouse visual cortex. Cell Rep 30:1982–1994.e4.

Johnson KP, Fitzpatrick MJ, Zhao L, Wang B, McCracken S, Williams PR, Kerschensteiner D (2021) Cell-type-specific binocular vision guides predation in mice. Neuron 109:1527–1539.e4.

Koulakov AA, Chklovskii DB (2001) Orientation preference patterns in mammalian visual cortex: a wire length minimization approach. Neuron 29:519–527.

Kravitz DJ, Saleem KS, Baker CI, Mishkin M (2011) A new neural framework for visuospatial processing. Nat Rev Neurosci 12:217–230.

Kravitz DJ, Saleem KS, Baker CI, Ungerleider LG, Mishkin M (2013) The ventral visual pathway: an expanded neural framework for the processing of object quality. Trends Cogn Sci 17:26–49.

Kuhlman SJ, Olivas ND, Tring E, Ikrar T, Xu X, Trachtenberg JT (2013) A disinhibitory microcircuit initiates critical-period plasticity in the visual cortex. Nature 501:543–546.

La Chioma A, Hubener M (2021) Visual cortex: binocular matchmaking. Curr Biol 31:R197–R199.

Lazarus MS, Huang ZJ (2011) Distinct maturation profiles of perisomatic and dendritic targeting GABAergic interneurons in the mouse primary visual cortex during the critical period of ocular dominance plasticity. J Neurophysiol 106:775–787.

Leamey CA, Merlin S, Lattouf P, Sawatari A, Zhou X, Demel N, Glendining KA, Oohashi T, Sur M, Fassler R (2007) Ten_m3 regulates eye-specific patterning in the mammalian visual pathway and is required for binocular vision. PLoS Biol 5:e241.

Lee SH, et al. (2012) Activation of specific interneurons improves V1 feature selectivity and visual perception. Nature 488:379–383.

Lempel AA, Trägenap S, Tepohl C, Kaschube M, Fitzpatrick D (2024) Coherent cortical representations develop after experience via feedforward-recurrent circuit alignment. bioRxiv 547747.

Levelt CN, Hubener M (2012) Critical-period plasticity in the visual cortex. Annu Rev Neurosci 35:309–330.

Lien AD, Scanziani M (2018) Cortical direction selectivity emerges at convergence of thalamic synapses. Nature 558:80–86.

Luongo FJ, Liu L, Ho CLA, Hesse JK, Wekselblatt JB, Lanfranchi FF, Huber D, Tsao DY (2023) Mice and primates use distinct strategies for visual segmentation. Elife 12:e74394.

Mazziotti R, et al. (2017) Mir-132/212 is required for maturation of binocular matching of orientation preference and depth perception. Nat Commun 8:15488.

McClellan JM, et al. (2024) An evolutionary perspective on complex neuropsychiatric disease. Neuron 112:7–24.

McLaughlin T, Torborg CL, Feller MB, O'Leary DD (2003) Retinotopic map refinement requires spontaneous retinal waves during a brief critical period of development. Neuron 40:1147–1160.

Mercier MR, Cappe C (2020) The interplay between multisensory integration and perceptual decision making. Neuroimage 222:116970.

Michalski A, Wimborne BM, Henry GH (1994) The role of ipsilateral and contralateral inputs from primary cortex in responses of area 21a neurons in cats. Vis Neurosci 11:839–849.

MICrONS Consortium (2025) Functional connectomics spanning multiple areas of mouse visual cortex. Nature 640:435–447.

Min KW, et al. (2023) Visuomotor anomalies in achiasmatic mice expressing a transfer-defective Vax1 mutant. Exp Mol Med 55:385–400.

Nern A, et al. (2025) Connectome-driven neural inventory of a complete visual system. Nature 641:1225–1237.

Nikbakht N, Tafreshiha A, Zoccolan D, Diamond ME (2018) Supralinear and supramodal integration of visual and tactile signals in rats: psychophysics and neuronal mechanisms. Neuron 97:626–639.e8.

Paus T, Keshavan M, Giedd JN (2008) Why do many psychiatric disorders emerge during adolescence? Nat Rev Neurosci 9:947–957.

Pfeffer CK, Xue M, He M, Huang ZJ, Scanziani M (2013) Inhibition of inhibition in visual cortex: the logic of connections between molecularly distinct interneurons. Nat Neurosci 16:1068–1076.

Qin X, Tape CJ (2024) Functional analysis of cell plasticity using single-cell technologies. Trends Cell Biol 34:854–864.

Qiu S, et al. (2024) Whole-brain spatial organization of hippocampal single-neuron projectomes. Science 383:eadj9198.

Ramot A, et al. (2025) Motor learning refines thalamic influence on motor cortex. Nature 643:725–734.

Ringach DL, Mineault PJ, Tring E, Olivas ND, Garcia-Junco-Clemente P, Trachtenberg JT (2016) Spatial clustering of tuning in mouse primary visual cortex. Nat Commun 7:12270.

Rossi LF, Harris KD, Carandini M (2020) Spatial connectivity matches direction selectivity in visual cortex. Nature 588:648–652.

Sanes JR, Zipursky SL (2020) Synaptic specificity, recognition molecules, and assembly of neural circuits. Cell 181:536–556.

Schneider-Mizell CM, et al. (2025) Inhibitory specificity from a connectomic census of mouse visual cortex. Nature 640:448–458.

Scholl B, Burge J, Priebe NJ (2013) Binocular integration and disparity selectivity in mouse primary visual cortex. J Neurophysiol 109:3013–3024.

Seabrook TA, Burbridge TJ, Crair MC, Huberman AD (2017) Architecture, function, and assembly of the mouse visual system. Annu Rev Neurosci 40:499–538.

Severin D, et al. (2021) All-or-none disconnection of pyramidal inputs onto parvalbumin-positive interneurons gates ocular dominance plasticity. Proc Natl Acad Sci U S A 118:e2105388118.

Siegle JH, et al. (2021) Survey of spiking in the mouse visual system reveals functional hierarchy. Nature 592:86–92.

Smith IT, Townsend LB, Huh R, Zhu H, Smith SL (2017) Stream-dependent development of higher visual cortical areas. Nat Neurosci 20:200–208.

Smith SL, Trachtenberg JT (2007) Experience-dependent binocular competition in the visual cortex begins at eye opening. Nat Neurosci 10:370–375.

Sommeijer JP, Ahmadlou M, Saiepour MH, Seignette K, Min R, Heimel JA, Levelt CN (2017) Thalamic inhibition regulates critical-period plasticity in visual cortex and thalamus. Nat Neurosci 20:1715–1721.

Song S, Miller KD, Abbott LF (2000) Competitive Hebbian learning through spike-timing-dependent synaptic plasticity. Nat Neurosci 3:919–926.

Sydnor VJ, et al. (2021) Neurodevelopment of the association cortices: patterns, mechanisms, and implications for psychopathology. Neuron 109: 2820–2846.

Takemura SY, et al. (2013) A visual motion detection circuit suggested by *Drosophila* connectomics. Nature 500:175–181.

Tan L, Tring E, Ringach DL, Zipursky SL, Trachtenberg JT (2020) Vision changes the cellular composition of binocular circuitry during the critical period. Neuron 108:735–747.e6.

Tan L, Ringach DL, Zipursky SL, Trachtenberg JT (2021) Vision is required for the formation of binocular neurons prior to the classical critical period. Curr Biol 31:4305–4313.e5.

Tan L, Ringach DL, Trachtenberg JT (2022) The development of receptive field tuning properties in mouse binocular primary visual cortex. J Neurosci 42:3546–3556.

Trachtenberg JT, Trepel C, Stryker MP (2000) Rapid extragranular plasticity in the absence of thalamocortical plasticity in the developing primary visual cortex. Science 287:2029–2032.

Tsimring K, Jenks KR, Cusseddu C, Heller GR, Ip JPK, Gjorgjieva J, Sur M (2025) Large-scale synaptic dynamics drive the reconstruction of binocular circuits in mouse visual cortex. Nat Commun 16:5810.

Urban-Ciecko J, Barth AL (2016) Somatostatin-expressing neurons in cortical networks. Nat Rev Neurosci 17:401–409.

van Beest EH, et al. (2021) Mouse visual cortex contains a region of enhanced spatial resolution. Nat Commun 12:4029.

Velez-Fort M, Cossell L, Porta L, Clopath C, Margrie TW (2025) Motor and vestibular signals in the visual cortex permit the separation of self versus externally generated visual motion. Cell 188:2175–2189.e15.

Wallace MT, Carriere BN, Perrault TJ Jr, Vaughan JW, Stein BE (2006) The development of cortical multisensory integration. J Neurosci 26:11844–11849.

Wamsley B, Fishell G (2017) Genetic and activity-dependent mechanisms underlying interneuron diversity. Nat Rev Neurosci 18:299–309.

Wang BS, Feng L, Liu M, Liu X, Cang J (2013) Environmental enrichment rescues binocular matching of orientation preference in mice that have a precocious critical period. Neuron 80:198–209.

Wang EY, et al. (2025) Foundation model of neural activity predicts response to new stimulus types. Nature 640:470–477.

Wang H, et al. (2019) Scalable volumetric imaging for ultrahigh-speed brain mapping at synaptic resolution. Natl Sci Rev 6:982–992.

Weiler S, Guggiana Nilo D, Bonhoeffer T, Hübener M, Rose T, Scheuss V (2023) Functional and structural features of L2/3 pyramidal cells continuously covary with pial depth in mouse visual cortex. Cereb Cortex 33: 3715–3733.

Weiler S, et al. (2024) A primary sensory cortical interareal feedforward inhibitory circuit for tacto-visual integration. Nat Commun 15:3081.

White LE, Coppola DM, Fitzpatrick D (2001) The contribution of sensory experience to the maturation of orientation selectivity in ferret visual cortex. Nature 411:1049–1052.

Wojtowicz WM, et al. (2020) A human IgSF cell-surface interactome reveals a complex network of protein-protein interactions. Cell 182:1027–1043.e17.

Woo J, et al. (2013) The adhesion protein IgSF9b is coupled to neuroligin 2 via *S*-SCAM to promote inhibitory synapse development. J Cell Biol 201:929–944.

Xu X, Cang J, Riecke H (2020) Development and binocular matching of orientation selectivity in visual cortex: a computational model. J Neurophysiol 123:1305–1319.

Yaeger CE, Ringach DL, Trachtenberg JT (2019) Neuromodulatory control of localized dendritic spiking in critical period cortex. Nature 567:100–104.

Yao Z, et al. (2023) A high-resolution transcriptomic and spatial atlas of cell types in the whole mouse brain. Nature 624:317–332.

Yara F, Khalil R (2023) The effects of abnormal visual experience on neurodevelopmental disorders. Dev Psychobiol 65:e22408.

Zeater N, Cheong SK, Solomon SG, Dreher B, Martin PR (2015) Binocular visual responses in the primate lateral geniculate nucleus. Curr Biol 25: 3190–3195.

Zhang M, Eichhorn SW, Zingg B, Yao Z, Cotter K, Zeng H, Dong H, Zhuang X (2021) Spatially resolved cell atlas of the mouse primary motor cortex by MERFISH. Nature 598:137–143.

Zhang M, et al. (2023) Molecularly defined and spatially resolved cell atlas of the whole mouse brain. Nature 624:343–354.

Zhao X, Liu M, Cang J (2013) Sublinear binocular integration preserves orientation selectivity in mouse visual cortex. Nat Commun 4:2088.

Zhu Y, Qiao W, Liu K, Zhong H, Yao H (2015) Control of response reliability by parvalbumin-expressing interneurons in visual cortex. Nat Commun 6:6802.