

REVIEW

Building a circuit through correlated spontaneous neuronal activity in the developing vertebrate and invertebrate visual systems

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During the development of the vertebrate nervous systems, genetic programs assemble an immature circuit that is subsequently refined by neuronal activity evoked by external stimuli. However, prior to sensory experience, the intrinsic property of the developing nervous system also triggers correlated network-level neuronal activity, with retinal waves in the developing vertebrate retina being the best documented example. Spontaneous activity has also been found in the visual system of *Drosophila*. Here, we compare the spontaneous activity of the developing visual system between mammalian and *Drosophila* and suggest that *Drosophila* is an emerging model for mechanistic and functional studies of correlated spontaneous activity.

How to build a functional nervous system is one of the most fundamental questions in developmental neuroscience. Establishing neuronal circuits that robustly respond to the external environment involves numerous challenging tasks, including the production of a diversity of neurons in the correct number, their assembly into circuits, and their maturation into functional neurons (Sporns et al. 2004; Sanes and Zipursky 2010; Perry et al. 2017; Price et al. 2018). Vertebrate circuits form through the interplay of genetic programs and environmental experience: Genetic programs assemble a hard-wired and immature neuronal network at early developmental stages, starting with neurogenesis, neuronal specification, axonal guidance, and synaptogenesis. During synaptogenesis, neuronal activity across neuronal networks shapes and refines the circuit to a more mature form that is optimized for various external sensory stimuli (Penn 2001; Ganguly and Poo 2013).

[*Keywords:* *Drosophila*; gap junctions; neural development; spontaneous activity; vertebrates versus invertebrates; visual system; wave of neural activity]

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Importantly, this network-level neuronal activity can be triggered not only by sensory experience but also by the intrinsic property of the developing nervous system. Prior to sensory stimuli, this early experience-independent, “spontaneous” neuronal activity initially occurs sporadically in individual cells but later becomes correlated in larger neuronal populations. Multiple studies in vertebrates have found this type of spontaneously emerging correlated activity in many developing neural tissues such as the retina, visual cortex, spinal cord, auditory cortex, cerebellum, and hippocampus, suggesting a role in proper circuit maturation and refinement (Katz and Shatz 1996; Friauf and Lohmann 1999; Zhang and Poo 2001; Moody and Bosma 2005; Huberman et al. 2008; Blankenship and Feller 2010; Kirkby et al. 2013; Wang and Bergles 2015; Arroyo and Feller 2016). This indicates that sensory stimulus-independent neuronal activity that is built in the genetically determined neuronal circuitry mediates an important developmental process. After the onset of sensory stimuli, the circuits are further optimized by experience-dependent neuronal activity (Hubel and Wiesel 1970; Ganguly and Poo 2013).

While correlated spontaneous activity has been found in most vertebrates, it was also recently discovered in invertebrates in the developing *Drosophila* visual system (Akin et al. 2019). It is widely believed that the invertebrate brain mostly forms in a highly stereotyped manner, leaving little space for experience-dependent development (Jefferis et al. 2001; Hiesinger et al. 2006). Naturally, it was also assumed that neuronal activity had a minimum role in building the simple brain of invertebrates. However, the new findings suggest that spontaneously emerging correlated neuronal activity could have a developmental function in the invertebrate nervous system.

We describe below the most extensively studied form of correlated spontaneous activity, the retinal waves in the

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developing mammalian visual system. We provide a general overview of the known cellular and molecular mechanisms of these retinal waves at different stages and present recent findings of how correlated spontaneous activity regulates circuit connectivity. Then, we focus on the recently discovered correlated spontaneous activity in the developing *Drosophila* visual system. We propose that these phenomena depend on neuronal features that are conceptually similar between vertebrates and invertebrates, opening up exciting avenues for a mechanistic understanding of correlated network activity. Finally, we illustrate the use of *Drosophila* to investigate how this spontaneously emerging neuronal activity contributes to the pattern refinement of a “hard-wired” brain.

Correlated spontaneous activity in the developing mammalian visual system

Correlated network activity is generally tightly coupled with sensory-input and/or motor output. It is an important feature of a mature nervous system (Draguhn et al. 2014; Yuste 2015). In contrast, the significance of the correlated network activity spontaneously occurring early in developing neuronal circuits has remained unclear (Hamburger and Balaban 1963; O'Donovan 1999; Kirkby et al. 2013). The best-documented example of such a developmental phenomenon comes from the vertebrate visual system (Huberman et al. 2008; Blankenship and Feller 2010; Kirkby et al. 2013). In *ex vivo* preparation of developing rabbit retina, spontaneous bursts of action potential in individual retinal ganglion cells (RGCs) were observed early, before the retina can respond to visual stimuli (Masland 1977). In the early 1990s, Shatz's group (Meister et al. 1991) discovered the correlated nature of the spontaneous activity in *ex vivo* preparation of developing ferret retina, taking advantage of the development of multiple electrode arrays that can measure the neural activity of ~100 neurons simultaneously. This correlated spontaneous activity, known as “retinal waves,” propagates as a wave-like form where neighboring RGCs exhibit correlated bursts of action potentials periodically across the ganglion cell layers of the retina (Wong 1999). Subsequently, using calcium influxes as a proxy for neuronal activity, both *ex vivo* and *in vivo* calcium imaging allowed the characterization of these waves at single-cell resolution (Wong et al. 1995). Subsequent pharmacological and genetic manipulations elucidated some of the underlying molecular and cellular mechanisms of retinal waves as well as their developmental role in the refinement of the visual system circuitry (Blankenship and Feller 2010; Kirkby et al. 2013; Arroyo and Feller 2016).

The stage II and III retinal waves also drive network activity over large domains of higher brain regions along the visual pathway, such as the lateral geniculate nucleus (dLGN) of the thalamus, the superior colliculus (SC), and the primary visual cortex (V1) areas (Hanganu et al. 2006; Ackman et al. 2012; Gribizis et al. 2019). However, correlated activity along the visual pathway can also have a central origin at later stages (Weliky and Katz 1999; Chiu

and Weliky 2002; Gribizis et al. 2019). The existence of early neuronal activity correlated between different parts of developing neuronal circuits suggests that the retinal waves have a role not just for refining local retinal circuitry but also for organizing the visual pathway at the global level prior to the onset of visual stimulation (Weliky and Katz 1999; Ackman and Crair 2014; Golding et al. 2014; Arroyo and Feller 2016; Gribizis et al. 2019).

Cellular and molecular mechanisms underlying the generation of retinal waves

Retinal waves appear to mainly propagate between RGCs, but there are distinct circuits and cellular players underlying retinal waves at different developmental stages (Fig. 1). Based on the molecular and cellular mechanisms of depolarization of RGCs, three different stages of retinal waves have been defined in mammals: Embryonic gap junction-mediated waves occur before birth (stage I), waves mediated by cholinergic synaptic transmission occur around the first postnatal week (stage II), and waves mediated by glutamatergic synaptic transmission occur around the second postnatal week, before eye opening (stage III) (Blankenship and Feller 2010; Kirkby et al. 2013; Kerschenshneider 2014; Arroyo and Feller 2016).

Stage I embryonic waves

The first stage of retinal waves occurs at the embryonic stage (approximately E17–P0 in mice) and lasts until birth, when the next stage of waves initiates. The onset of stage I waves coincides with the early development of RGC populations, including their neurogenesis, axonal guidance, and axonal arborization, but occurs prior to synaptic connection forming in the inner plexiform layer (IPL), where the major dendritic processes of RGC are located (Fig. 1A; Sernagor et al. 2001; D'Souza and Lang 2020). At this early stage of the mammalian retina, RGCs are coupled by gap junction channels like neurons in other brain areas (Penn et al. 1994; Singer et al. 2001; Montoro and Yuste 2004; Bloomfield and Völgyi 2009). Pharmacological experiments in rabbits and chicks have supported the model that stage I waves are mainly mediated by gap junction-dependent intercellular interactions (Catsicas et al. 1998; Wong et al. 1998; Syed et al. 2004). However, because monitoring this initial stage of waves in prenatal animals is more difficult, the underlying mechanisms of initiation and propagation of stage I waves between developing RGCs are significantly understudied compared with later stages (Huberman et al. 2008).

In the rabbit retina, where stage I embryonic waves have been most studied, the first waves are observed as soon as RGCs acquire the ability to generate action potentials and their axons reach their target area in the dLGN (Crabtree 1990; Syed et al. 2004). The pharmacological blockage of most neurotransmitter receptors, including acetylcholine, ionotropic glutamate, GABA_{A/C}, and glycine receptors, does not affect the propagation of stage I embryonic waves (Syed et al. 2004). Instead, these early retinal waves are

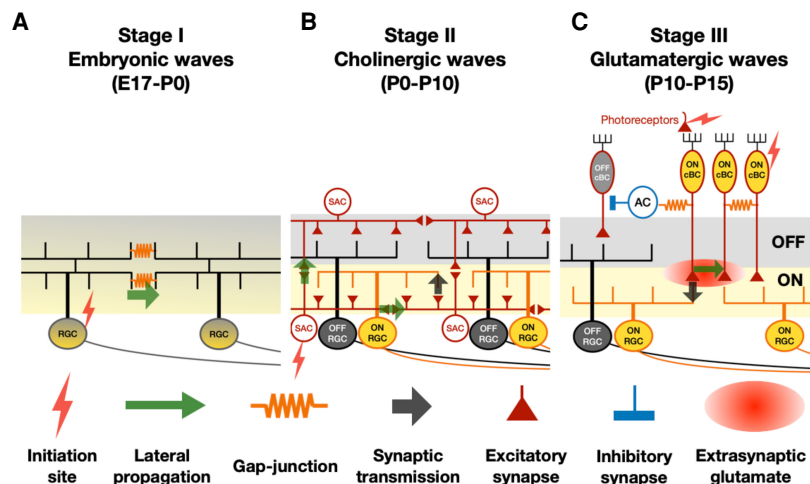


Figure 1. Transitions between mammalian retinal waves during development. Schematic diagram of the inner plexiform layer (IPL) in the mammalian retina. The developmental stages are based on mice. (A) During stage I, gap junctions mediate wave propagation between RGCs, where waves are thought to be initiated cell-autonomously. (B) During stage II, SAC circuits initiate the waves cell-autonomously and mediate their propagation when SACs activate both neighboring SACs and RGCs via cholinergic synaptic transmission. (C) Stage III waves are initiated either from photoreceptors stimulated by light through the closed eyelids, or cell-autonomously from cBCs. The waves propagate between cBCs via extrasynaptic spillover of glutamate that comes from the synaptic transmission between cBCs and RGCs. Gap junction coupling between cBCs further mediates lateral propagation of

waves. It also mediates the inhibitory input from On cBC to Off cBC via inhibitory AC. The On sublayer is colored in yellow and the Off sublayer is in gray. (RGC) Retinal ganglion cell, (SAC) starburst amacrine cell, (AC) amacrine cell, (cBC) cone bipolar cell.

inhibited by gap junction blockers (Fig. 1A; Syed et al. 2004). Interestingly, agonists for the GABA_B receptor as well as antagonists of the adenosine receptor also disrupt stage I retinal waves (Syed et al. 2004), suggesting that multiple pathways can modulate this activity prior to synaptogenesis. However, a detailed underlying mechanism awaits to be defined. Embryonic waves in mice have been less studied, and thus, a systematic pharmacological and genetic characterization of this activity is still lacking. For example, although rabbit and chick studies suggest that mice embryonic waves are mediated by gap junction coupling between RGCs (Catsicas et al. 1998; Syed et al. 2004), direct measurement of these waves in prenatal mice retina upon the inhibition of gap junction channel has never been reported. However, treatment of embryonic mice retina by antagonists of nicotinic acetylcholine receptor (nAChR) partially blocks the embryonic waves (Bansal et al. 2000). Because of the lack of canonical synaptic connections in the IPL at this stage, the nAChR might have a modulatory role similar to the GABA_B and adenosine receptors in the rabbit retina, but further studies will be required to confirm this model. Still, both rabbit and mice stage I embryonic waves have similar spatiotemporal properties, which are quite distinct from the waves at later stages as they are more than twice as fast and frequent and propagate to the entire retinal field without clear boundaries or refractory periods (Bansal et al. 2000; Syed et al. 2004).

Stage II cholinergic waves

The stage II cholinergic waves emerge around birth and last ~10 postnatal days (P0–P10 in mice) until stage III waves take over during the second postnatal week. Stage II waves appear as the synaptic connections between RGCs and amacrine cells in the IPL become mature (Fig. 1B; Fan et al. 2016; Nguyen-Ba-Charvet and Rebsam 2020). The pharmacological properties of stage II waves are almost identical between mice and rabbits (Syed

et al. 2004; Ford et al. 2012): They are mediated primarily through cholinergic (ACh) synaptic transmission as the application of antagonists of the nAChR and knockout mice of either the *nAChR* $\beta 2$ subunit or *ChAT* (choline acetyltransferase) have significantly disrupted stage II retinal waves (Feller et al. 1996; Bansal et al. 2000; Stacy et al. 2005; Sun et al. 2008). Stage II cholinergic waves initiate in random places across the retina and propagate to a larger area, at a slower speed and lower frequency than stage I waves. Importantly, they propagate homogeneously to the entire retina area in a nonoverlapping manner with clear boundaries that are determined by a refractory period of ~50 sec (Feller et al. 1997; Maccione et al. 2014). This nonoverlapping wave kinetic results in an even activation of the whole retina by the propagation of the waves (Feller et al. 1997).

The underlying circuit mechanism of stage II waves is well characterized. Starburst amacrine cells (SACs) in the inner nuclear layer and in the ganglion cell layer (Fig. 1B) are the main pacemakers that drive the initiation and propagation of the wave (Fig. 1B; Huberman et al. 2008; Balasubramanian and Gan 2014). SACs form homotypic synaptic connections with nearby SACs and heterotypic synaptic connections with RGCs. The SACs initiate cell-autonomous spontaneous firing that subsequently drives the activation of the neighboring SACs via cholinergic synaptic transmission, thereby laterally propagating waves across SAC circuits (Fig. 1B; Zheng et al. 2006; Huberman et al. 2008; Blankenship and Feller 2010). Along with this propagation across the SAC network, the SACs also activate their downstream RGCs via cholinergic transmission, allowing the synchronized firing of the neighboring RGC clusters (Fig. 1B). This SAC network governs the overall spatiotemporal structure of the waves with their refractory period (Zheng et al. 2006). Individual SACs cell-autonomously generate semiperiodic calcium spikes followed by after-hyperpolarizations (AHPs) and thus act as spontaneous oscillators. During waves, reciprocally excitatory interactions between these spontaneous oscillators

generate SAC network activity, and subsequently, the wave pattern (Zheng et al. 2006; Blankenship and Feller 2010; Ford et al. 2013).

Stage III glutamatergic waves

Stage III glutamatergic waves emerge in the second postnatal week (around P10 in mice) and last for the following three to four postnatal days. The waves then disappear around the time of eye opening (approximately P15), regardless of visual experience (Demas et al. 2003; Kerschensteiner 2016). The onset of stage III waves coincides with the emergence of the bipolar cell (BC) circuit, as BCs are generated during stage II waves and begin to form synapses with upstream photoreceptors and with downstream RGCs (Fig. 1C; Fan et al. 2016; Nguyen-Ba-Charvet and Rebsam 2020). The mechanism by which the waves terminate around eye opening is still unknown (Demas et al. 2003; Kerschensteiner 2016). Like stage II, the pharmacological features of stage III waves are comparable between mice and rabbits (Syed et al. 2004; Kerschensteiner 2016). The hallmark of stage III waves is its underlying glutamatergic drive. In mice, glutamate receptor antagonists or mutants of *vglut1* (the vesicular glutamate transporter) disrupt stage III waves after approximately P10, when the waves become insensitive to nAChR antagonists (Blankenship et al. 2009). During the transition between stage II and III waves, the cholinergic drive disappears as the SACs stop expressing nAChR, preventing cholinergic drive within the network (Zheng et al. 2004), while the glutamatergic drive increases as the synaptic connections of glutamatergic BCs gradually form and mature (Huberman et al. 2008; Kerschensteiner 2016).

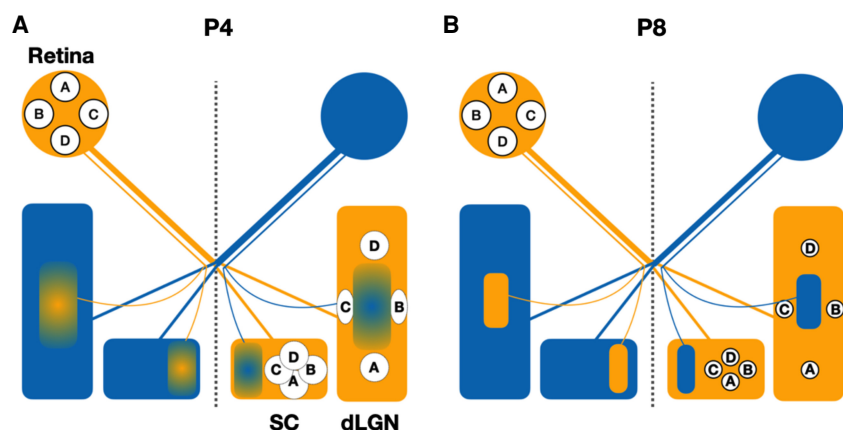
In addition to the distinct neurotransmitters they use, stage III waves have dramatically different initiation and propagating features compared with previous stages (Fig. 1C). While stage II waves are triggered by the spontaneous firing of SACs, stage III waves can be triggered not only by the cell-autonomous firing of BCs (Zhang et al. 2016) but also by ambient light through the closed eyelids (Tiriac et al. 2018) via newly emerging photoreceptor connections at this stage (Fig. 1C). However, despite their distinct initiation mechanisms, the spatiotemporal properties of both light-triggered and spontaneously emerging waves are indistinguishable from each other, suggesting that they use a common underlying circuit mechanism (Tiriac et al. 2018). Thus, this visual stimulus through close eyelids increases the occurrence of glutamatergic waves (Tiriac et al. 2018). The spatiotemporal propagation of glutamatergic waves is faster, nonrandom, and more repetitive within a smaller area than stage II waves, although both waves have clear boundaries with a refractory period (Maccione et al. 2014).

In contrast to stage II waves, which indiscriminately propagate to the SACs and RGCs in the proximity of the initiation point via the SAC circuit, stage III waves occur preferentially between specific neuronal subtypes via the BC circuit (Fig. 1C). In the adult visual system, cone BCs relay signals from cone photoreceptors to RGCs, while rod BCs do not directly connect to RGCs. Cone BCs and

their downstream RGCs are further categorized as On if they depolarize in response to light increments or Off if they hyperpolarize to light (Euler et al. 2014; Kerschensteiner 2016). Among these subtypes, action potential firing patterns during stage III waves are more synchronized within the population of On or of Off RGCs, but are anticorrelated between On and Off subtypes (Kerschensteiner and Wong 2008; Kerschensteiner 2016). This alternative firing pattern between On and Off RGCs originates from the BC network: Once BCs fire, either cell-autonomously or by light stimulus via photoreceptors, they subsequently activate RGCs using glutamatergic synaptic transmission (Fig. 1C). BC activation also propagates laterally across neighboring BCs via two nonsynaptic mechanisms (Fig. 1C): (1) Glutamate that is spilled over during synaptic transmission from On BC to On RGC diffuses extrasynaptically and activates the neighboring On BC subpopulation that expresses the ionotropic glutamate receptor (iGluR) (Blankenship et al. 2009; Akrouh and Kerschensteiner 2013; Firl et al. 2013; Rosa et al. 2015). The diffusion of glutamate is limited to the On sublayer of IPL by Müller glial cells (MGCs) that express the glutamate transporter (EAAT1) and prevent the cross-activation of Off BC (Akrouh and Kerschensteiner 2013). (2) Gap junction coupling also mediates lateral propagation of the waves from iGluR-positive On BCs to iGluR-negative On BCs as well as to adjacent inhibitory amacrine cells (Fig. 1C; Akrouh and Kerschensteiner 2013; Kerschensteiner 2016). While this lateral propagation of activity across the On-type BC circuit generates synchronized activation of On RGCs, gap junction-coupled GABAergic and glycinergic amacrine cells with the On BC circuit generate inhibitory inputs to the Off BC circuit (Fig. 1C). This hyperpolarizes Off BCs when On BCs and RGCs are depolarized. Once this inhibition of Off BCs is relieved after the On wave has passed, they can activate Off RGCs and generate a wave in the Off circuit (Matthews and Fuchs 2010; Kerschensteiner 2016). Thus, inhibitory amacrine cells are responsible for anticorrelated activation between On/Off pathways and shape the spatiotemporal properties of stage III waves.

Role of correlated spontaneous activity in the refinement of retinotopic maps

The developmental role of retinal waves is best characterized in the connectivity of RGCs, the main output neurons in the retina (Kirkby et al. 2013; Arroyo and Feller 2016). To appropriately process visual input, RGCs send projections to several main target regions in the brain, including the dLGN and SC (Dhande and Huberman 2014; Dhande et al. 2015; Guido 2018). Processing spatial information of visual input requires retinotopic axonal projections of RGCs, which refers to the topographic distribution of RGC axons receiving input from neighboring neurons in the retina projecting to neighboring locations of the dLGN and SC (Fig. 2). Another feature of the spatial arrangement of RGC axons in binocular animals is the eye-specific map: RGC axons show either ipsilateral or



other in the dLGN and SC. (B) At the P8 stage, the retinotopic maps of RGCs are established, and the axonal arborizations from both eyes have become segregated depending on which eye they came from. (SC) Superior colliculus, (dLGN) lateral geniculate nucleus.

contralateral projections to dLGN and SC (Fig. 2; Dhande and Huberman 2014; Dhande et al. 2015; Guido 2018). Ipsilateral axons project to the center of the dLGN, while contralateral axons project to the surrounding regions. In mice, at P0, ipsilateral and contralateral axons are initially intermingled with each other in the dLGN. From P4 to P8, prior to the onset of visual input, they start to segregate in an eye-specific manner (Fig. 2). While these circuitries are eventually refined and matured by sensory input-dependent activity during the critical period (Hubel and Wiesel 1970; Katz 1999), the refinement of both retinotopic and eye-specific maps requires the retinal waves prior to visual input, making the developing retina a unique model to study the functional role of correlated spontaneous activity in shaping visual circuit development (Huberman et al. 2008; Blankenship and Feller 2010; Kirkby et al. 2013; Kerschensteiner 2014; Arroyo and Feller 2016).

The topographic organization of RGC axons is determined both by cell surface repulsive guidance molecules (Ephrins and their Eph receptors) and by spontaneous activity. Members of the Eph and Ephrin families are expressed in complementary gradients in the retina (Eph) and the target brain regions (Ephrins) to regulate positional information in different axes: EphA and Ephrin-As are important for the nasal–temporal axis, and EphB and Ephrin-Bs for the dorso–ventral axis of the retina (McLaughlin et al. 2003a; McLaughlin and O’Leary 2005; O’Leary and McLaughlin 2005; Triplett and Feldheim 2012). These guidance molecules establish an early coarse map of RGC axonal projection.

The eye-specific segregation of the RGC projections is further refined by the retinal waves that appear to play an instructive (i.e., correlated patterns are important) role in driving map formation (Crair 1999; Chalupa 2009; Feller 2009), as supported by various pharmacological and genetic alterations of retinal activity or manipulations of specific spatiotemporal features of retinal waves (Chandrasekaran et al. 2005; Xu et al. 2011; Zhang et al. 2012; Burbridge et al. 2014; Arroyo and Feller 2016). In this regard, stage II cholinergic waves are the most studied, as

they are temporally correlated with the stage of axonal refinement of RGCs (Fig. 2). Two features of retinal waves are thought to be important instructive signals. During stage II waves, the activity of neighboring RGCs is more synchronized than that of distant RGCs within the same retina, suggesting these patterns of local intraretinal waves convey retinotopic information (Eglen et al. 2003). On the contrary, the firing patterns of RGCs from different eyes are not synchronized, allowing eye-specific segregation. In *nAChR* $\beta 2$ knocked-out mice, which inhibit stage II waves, both intraretinal and interretinal patterns of waves are severely disrupted, leading to disrupted retinotopic connection and eye-specific segregation of RGCs (Rossi et al. 2001; Muir-Robinson et al. 2002; McLaughlin et al. 2003b; Sun et al. 2008). To disrupt a specific pattern of waves, several genetic and optogenetic manipulations are used (Xu et al. 2011, 2015; Zhang et al. 2012). For example, in mice in which *nAChR* $\beta 2$ is exclusively knocked out in the retina from early development, the amplitude of retinal waves is lowered with variable interwave intervals. The reduced activity limits the propagating distance of the waves, which are unable to trigger large-scale asynchronous activity between the two eyes. In contrast, the short-range intraretinal waves still promote locally synchronized activation of RGCs (Xu et al. 2015). As a consequence, the eye-specific segregation of RGC axons of these mutants is specifically defective, while retinotopic connectivity is normal (Xu et al. 2015). This model is further supported by optogenetics, where artificially synchronized activity between eyes induces defective eye-specific segregation, while induced anticorrelated activity between eyes not only preserves eye-specific segregation but also partially rescues the segregation defects of *nAChR* $\beta 2$ knocked-out mice (Zhang et al. 2012). Altogether, the correlation of retinal waves instructs different features of visual maps, although the effects may differ between the target brain regions and species examined. However, the molecular and cellular signaling underlying retinal activity that drives the rearrangements of axons for map refinement remains incomplete (Kirkby et al. 2013; Arroyo and Feller 2016).

Correlated spontaneous activity during development in invertebrates

The invertebrate central nervous system (CNS) is believed to be built in a genetically deterministic and hard-wired manner (Jefferis et al. 2001; Scott et al. 2003; Berdnik et al. 2006; Hiesinger et al. 2006), although activity-dependent developmental plasticity of the *Drosophila* peripheral nervous system (PNS) has been extensively studied in the larval neuromuscular junction (Choi et al. 2014; Vonhoff and Keshishian 2017; Bai and Suzuki 2020). This notion is based on the observation that brain development in invertebrates is largely normal under several genetic manipulations that disrupt canonical mechanisms required for sensory input, neuronal activity, or synaptic transmission (Jefferis et al. 2001; Scott et al. 2003; Berdnik et al. 2006; Hiesinger et al. 2006). These earlier studies have focused on gross morphological phenotypes, without measuring neuronal activity during development, partially owing to the technical challenge of recording in the tiny invertebrate brain.

However, recent studies with more advanced tools suggest that neuronal activity is still required for building a larval motor and sensory CNS circuit in flies, prior to sensory input (Suster and Bate 2002; Giachello and Baines 2015; see Akin and Zipursky 2020; Valdes-Aleman et al. 2021). For example, genetic tools with a higher temporal and spatial resolution have been developed for stage-specific activation or inhibition of neuronal activity with single cell type resolution and advanced in vivo imaging technology (Kleinlogel et al. 2011; Chen et al. 2013, 2014; Özel et al. 2015; Akin and Zipursky 2016; Simpson and Looger 2018). These observations raise the question of how neuronal activity actually occurs during development. More recently, the improvement of genetically encoded optical sensors and in vivo imaging platforms have allowed versatile functional imaging of neuronal activity at a population level in the developing invertebrate CNS (Chen et al. 2013; Özel et al. 2015; Akin and Zipursky 2016; Simpson and Looger 2018; Dana et al. 2019). This improved imaging platform has revealed the occurrence of correlated spontaneous activity in the developing invertebrate nervous system (Akin et al. 2019), reminiscent of vertebrates. We describe below correlated spontaneous activity in the developing *Drosophila* visual system and compare it with its vertebrate counterpart, the retinal waves.

Correlated spontaneous activity in the developing *Drosophila* visual system

Akin et al. (2019) recently discovered correlated spontaneous activity—called patterned, stimulus-independent neuronal activity (PSINA) in the developing *Drosophila* CNS—using cutting-edge intravital two-photon imaging of intact pupae and the genetically encoded calcium indicator GCaMP6 (Chen et al. 2013). They found robust and correlated neuronal activity throughout the developing pupal brain, starting ~50 h after puparium formation

(APF), the onset of synaptogenesis (Sanes and Zipursky 2010). Almost all neuronal populations participate in this highly structured and stereotypic network activity throughout the developing brain. In the visual system, they showed that the patterned activity has three distinct stages based on the temporal pattern: a periodic stage (55–65 h APF), a turbulent stage (from 70 h APF to eclosion), and a young adult stage (until they are 5 d old), when visual input-independent activity occurs alongside visual stimulus-evoked activity. This neuronal activity is sensitive to tetrodotoxin (a blocker of voltage-gated sodium channels) and is correlated with neurotransmitter (glutamate) release as shown with a genetically encoded optical sensor for glutamate (Dürst et al. 2019; Leopold et al. 2019). This suggests that this spontaneously emerging neuronal activity is mediated by action potential and neurotransmitter release like the adult visual stimulus-evoked activity.

The investigators then focused on 15 different neuronal types from all distinct neuropiles (retina, lamina, medulla, and lobula complex) of the visual system and discovered that each cell type shows its own unique pattern of spontaneous activity (Fig. 3). The *Drosophila* retina, lamina, and medulla areas are equivalent structures to the vertebrate retinal circuit, while the lobula complex is comparable with the dLGN and SC areas (Sanes and Zipursky 2010). Importantly, two orthogonal axes of correlations have been found during PSINA in these areas (Fig. 3). The fly visual system is composed of ~800 repeated topographically matched modules, where all 15 neuronal types tested are evenly distributed (Fig. 3). Although there is no direct synaptic connection between neurons of the same type in the adult, their spontaneous activity during PSINA is correlated. Interestingly, while these cell type-specific correlations are stereotypic and quantifiable, only some of them are qualitatively similar to the wave-like pattern seen in the vertebrate retina, suggesting diverse underlying propagating mechanisms.

Meanwhile, the pattern of activity between different cell types that are synaptically connected along the visual processing pathway in the adult is also more correlated (see below) (Fig. 3). Preventing synaptic transmission with genetically encoded tetanus toxin in the presynaptic cell population weakens this correlation, suggesting that this vertical correlation depends on functional synaptic coupling that must therefore already exist during synaptogenesis. Still, a potential specific developmental role has not yet been demonstrated.

Comparison of correlated spontaneous activity between vertebrates and invertebrates

Using simpler model systems allows a deeper understanding of complex biological phenomena (Venken et al. 2011; Ugur et al. 2016; Holguera and Desplan 2018; Zheng et al. 2018; Baenas and Wagner 2019; Mirzoyan et al. 2019). However, correlated spontaneous activity was until recently thought to be a unique feature of vertebrates. With the recently described PSINA in the *Drosophila*

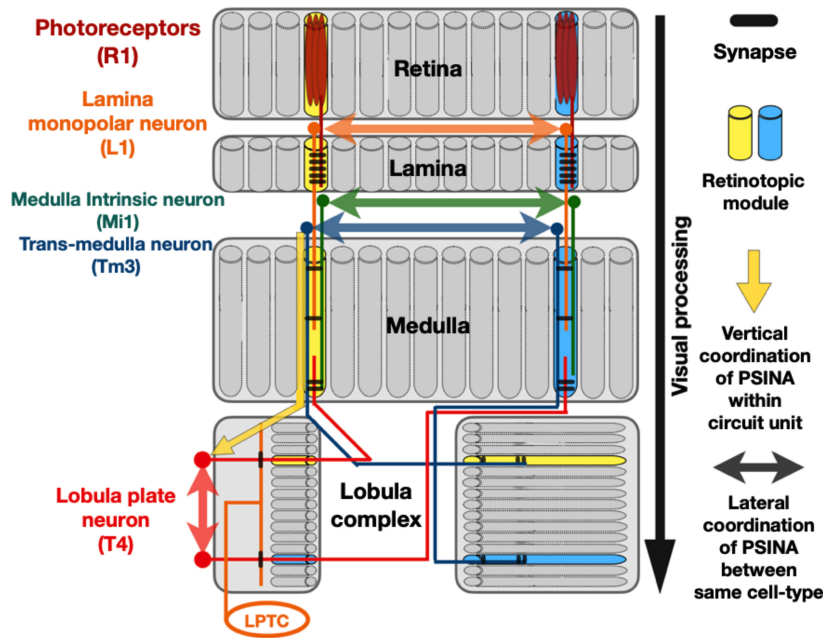


Figure 3. Retinotopically organized visual input channels in the *Drosophila* visual system. Schematic diagram of the fly optic lobe. Yellow and blue represent two retinotopically organized parallel and independent input channels that process visual information. Representative unicolunar neuronal types from each neuropile and their connectivity are shown: photoreceptor neurons from the retina, a L1 lamina monopolar neuron from the lamina, a Tm3 *trans*-medulla neurons, an Mi1 medulla intrinsic neuron from the medulla, and a T4 lobula plate neuron from the lobula complex. During visual processing in the adult, visual information flows via synaptic connection down the vertical axis while preserving retinotopic information before the LPTCs. In contrast, during development, PSINA occurs between the same neuronal type, suggesting transient excitatory coupling (shown in double-headed arrows) along the lateral axis of the visual system. (LPTC) Lobula plate tangential cell, (PSINA) patterned, stimulus-independent neuronal activity.

visual system, where circuit analogy can be made to the vertebrate system (Sanes and Zipursky 2010), and our deep knowledge about its development (Sanes and Zipursky 2010; N eriec and Desplan 2016; Perry et al. 2017; Holguera and Desplan 2018; Chen and Desplan 2020), it is now possible to compare this developmental process between vertebrate and invertebrate systems. There are intriguing conceptual similarities between the spontaneous activity in the mammalian and fly visual systems, suggesting that this phenomenon may be evolutionarily conserved. We discuss these similarities below and posit how a simpler genetic model system can answer the remaining outstanding questions in the field. Notably, while our comparison uses mammalian retinal waves and *Drosophila* PSINA in the visual system as specific examples, their properties are often generalizable to those seen with spontaneous emerging patterned activity in other nervous systems (Blankenship and Feller 2010; Kirkby et al. 2013).

Correlated activity in developmentally transient neuronal circuits

The correlation of neuronal stimulus-induced activity in adult circuits is different from the correlation of spontaneous activity during development (Blankenship and Feller 2010). In the mammalian visual system, the adult circuit is organized as iterative structures in a retinotopic manner (Arcaro et al. 2009; Arcaro and Livingstone 2017; Seabrook et al. 2017). Thus, neuronal activity evoked by sensory input propagates to higher brain areas through multiple parallel channels, while lateral excitatory synaptic transmission between these channels is limited in order to preserve spatial information of visual cues (W assle 2004; Demb and Singer 2015). In contrast, retinal waves in the developing visual system propagate laterally between the same cell types (RGCs), therefore activating RGC clusters

covering very large visual receptive fields (Blankenship and Feller 2010). This excitatory lateral coupling is mediated by developmentally transient circuit mechanisms (Fig. 1). For example, the SACs only express the nAChR subunit during stage II waves, thereby allowing temporary cholinergic transmission between SAC circuits via their lateral synaptic connections (Fig. 1B; Masland 2005; Blankenship and Feller 2010; Ford et al. 2012). In stage III waves, SACs no longer express nAChR while maturing bipolar cells express iGluR, which mediates lateral coupling between the same On or Off types of bipolar cells via extrasynaptic glutamate spillover (Fig. 1C; Kerschensteiner 2016).

Similar phenomena are also observed for PSINA in the developing *Drosophila* visual system. The adult *Drosophila* visual circuit is also retinotopically organized as ~800 repeated topographically matched modules (i.e., ommatidia in the retina, cartridges in the lamina, and columns in the medulla) (Fig. 3; Morante and Desplan 2008; Sanes and Zipursky 2010; Meinertzhagen and Lee 2012; N eriec and Desplan 2016). These individual modules act as parallel input channels to propagate visual information vertically through three distinct neuropils: lamina, medulla, and lobula complex. Since retinotopic information is preserved until it is integrated in the lobula plate tangential cells (LPTCs) (Fig. 3; Borst et al. 2020; Wei et al. 2020), their upstream neuronal pathway presumably has minimum lateral excitatory coupling between parallel channels. Each individual module is formed by ~200 distinct neuronal types. Some of these cell types are unicolunar neurons as they mainly project within a single module (lamina monopolar, medulla intrinsic, and *trans*-medullar neurons in Fig. 3; Morante and Desplan 2008; N eriec and Desplan 2016; Erlik et al. 2017). However, during PSINA, all unicolunar neurons tested show cell type-specific correlation of activity across multiple modules (Fig. 3; Akin et al. 2019), indicating a temporary lateral

excitatory coupling during development. While the exact cellular and molecular mechanisms of this lateral correlation of PSINA are not known, it is tempting to speculate that the multicolumnar neurons that innervate multiple columns could be one of the substrates involved in this transient excitatory lateral communication (Morante and Desplan 2008; Néric and Desplan 2016; Erclik et al. 2017) between individual modules, like the SAC circuits for mammalian retinal waves (Blankenship and Feller 2010; Ford et al. 2012).

Developmental timing of correlated spontaneous activity during synaptogenesis

In vertebrates, retinal waves occur just after initial synaptic contact and last through complete synaptogenesis (Blankenship and Feller 2010; Kirkby et al. 2013; Kerschenshneider 2014). This is the developmental window when a rough connectome is established by a genetically hard-wired process, including axon guidance, but further refinement and maturation of synaptic coupling are required for generating a fully functional adult circuit. Multiple studies in vertebrates have suggested that the spontaneously emerging correlated activity triggered by the intrinsic properties of this immature and developing circuit mediates this synaptic maturation process. At each developmental stage, a transient circuit like the SAC network during stage II waves is mediated by still-developing synaptic coupling and drives the specific correlation of network activity, which feeds back into refining the developing circuit to advance the next maturation stage (Blankenship and Feller 2010; Kirkby et al. 2013; Kerschenshneider 2014; Arroyo and Feller 2016).

In *Drosophila*, the occurrence time window of PSINA is closely reminiscent of this vertebrate model. PSINA initiates at ~50 h APF when initial circuit assembly is complete in response to secreted signals and contact-dependent signaling (Perry et al. 2017; Akin et al. 2019; Sanes and Zipursky 2020). Then, the pattern of PSINA changes in a stereotypic manner through the entire synaptogenesis process, potentially depending on a transient circuitry via immature synaptic coupling. Whether and how the fly PSINA has a developmental role for refining circuitry, as it does in vertebrates, still remain to be determined.

Long-distance correlation of spontaneous activity between distinct brain areas

In the mouse visual system, retinal waves are not confined to the retina but also propagate to higher brain areas such as the dLGN, SC, and V1. While neuronal activity can occur and be correlated autonomously in higher brain areas such as SC and V1 of the visual cortex without retinal activity (Weliky and Katz 1999), during stages II and III, retinal waves instruct the pattern of network activity in these higher regions through synaptic transmission (Ackman and Crair 2014; Gribizis et al. 2019). This correlation between distinct brain areas that are synaptically connected suggests a potential developmental role of this activity as long-distance signaling at the global circuit level.

In the developing fly visual system, PSINA is also correlated between multiple cell types from distinct neuropils that are synaptically connected in adults along the visual processing pathway (Akin et al. 2019). For example, along the On motion detection circuit between the medulla and lobula complex, which are comparable with the inner retina and dLGN/SC area, respectively, PSINA in Tm3 transmedullary neurons is closely correlated with the activity patterns of the lobula plate T4 neurons that are synaptically downstream from Tm3 neurons (Sanes and Zipursky 2010; Silies et al. 2014). The expression of tetanus toxin, which disrupts evoked synaptic vesicle release (Venken et al. 2011) in the presynaptic side (Tm3) but not in the postsynaptic side (T4), weakens the correlation of PSINA between Tm3 and T4, suggesting that this coupling is mediated by synaptic transmission. As a negative control, lobula plate T5 neurons that are not connected to Tm3 but are developmentally and spatially closely related to T4 neurons do not exhibit a high correlation of PSINA with Tm3, demonstrating circuit specificity. Whether and how spontaneous activity patterns from potentially presynaptic neurons instruct the pattern of their downstream partners and how they propagate during synaptogenesis remain unknown.

Neuron–glia interaction during correlated activity

In vertebrate, recent studies have found that stage II and III retinal waves propagate not just to neuronal population but also to Müller glial cells (MGCs), the sole astroglia cell type in the inner plexiform layer that contacts most neuronal types in the retina (Rosa et al. 2015; Zhang et al. 2019). In mice, this neuron–glia correlation is mediated by neurotransmitter spillover (Rosa et al. 2015). Interestingly, MGCs express multiple neurotransmitter receptors during this stage, allowing them to respond to both cholinergic and glutamatergic drives. During stage II cholinergic waves, extrasynaptic acetylcholine release from SACs on RGCs also diffuses to activate muscarinic AChRs in MGCs, thus inducing calcium activity in these glia cells. During stage III glutamatergic waves, extrasynaptically released glutamate between BCs on RGCs activates MGCs via AMPA-type iGluRs. This neuronal–glial wave propagation decreases at later stages (from P9 to P11) when MGCs express higher levels of the glutamate transporter (EAAT1), which limits extrasynaptic glutamate (Rosa et al. 2015). While astrocytes like MGCs have been shown to have an essential role in the synaptogenesis process (Clarke and Barres 2013; Chung et al. 2015), the functional significance of these neuronal–MGC interactions remains to be determined.

During fly PSINA, the astrocyte glial population also shows calcium activity correlated with the neuronal population (Akin et al. 2019). This correlation is initially weak but becomes more obvious throughout the periodic stage of PSINA as neuronal and glial activity patterns are phased-shifted with each other. *Drosophila* astrocytes also play a critical role in synaptogenesis (Muthukumar et al. 2014; Richier et al. 2017), but both the propagating

mechanism and developmental function of this glial calcium activity remain unanswered.

Using an invertebrate model to study correlated spontaneous activity

With these intriguing conceptual similarities between mammalian retinal waves and fly PSINA, could the fly model system strengthen decades of previous studies and provide solutions to the remaining questions in the field? Compared with the vertebrate model systems commonly used to study correlated spontaneous activity such as mice, ferrets, rabbits, chickens, and zebrafish, which often depend on electrophysiology, functional imaging, and pharmacology (Chiu and Weliky 2001; Blankenship and Feller 2010; Momose-Sato and Sato 2016; Marachlian et al. 2018), *Drosophila* has unparalleled genetic and anatomical accessibility with its tiny brain size (Bellen et al. 2010). Through the manipulation of specific cellular functions using quickly-evolving genetic and optogenetic tools, this simple invertebrate model will greatly facilitate future studies of this important developmental phenomenon (Simpson and Looger 2018). Below, we present several examples illustrating the power of the fly model to address the remaining outstanding questions.

The role of gap junction coupling during correlated spontaneous activity.

The intercellular signaling mediated by gap junction is important but often understudied during correlated spontaneous activity. From the early days, the study of correlated spontaneous activity has been considered as a subset of activity-dependent developmental plasticity (Kirkby et al. 2013; Pan and Monje 2020). Naturally, investigations of the developmental role of spontaneous activity have focused on neuronal circuits (Kirkby et al. 2013). This neuron-centric approach often ignored nonneuronal aspects of development in guiding the correlation of spontaneous activity. Specifically, most studies focused on canonical synaptic transmission as the major intercellular signaling mechanism (Blankenship and Feller 2010; Kirkby et al. 2013; Kerschensteiner 2014; Arroyo and Feller 2016). However, throughout species, the very first correlation of activity emerges prior to synaptogenesis, like stage I embryonic retinal waves of mammals, when gap junction coupling is the major intercellular pathway (Cook and Becker 2009; Nagy et al. 2018). Furthermore, robust gap junction networks exist between various retinal cell types throughout development and in the adult retina, where they have important functions such as in motion sensitivity and in injury response (Bloomfield and Völgyi 2009; Völgyi et al. 2013). Indeed, gap junction coupling exists during all three stages of retinal waves (Cook and Becker 2009). In addition to mediating lateral wave propagation along the BC circuit during stage III waves (Fig. 1C), recent studies also have shown that the retinal gap junction network is important for homeostatic mechanism in response to the disruption of retinal waves (Stacy et al. 2005; Blan-

kenship and Feller 2010; Arroyo et al. 2016). In both *ChAT* and *nAChR β 2* mutants where stage II cholinergic waves are severely disrupted, the residual waves are sensitive to a gap junction blocker, although stage II waves in wild-type retina are not inhibited by the same gap junction blocker (Stacy et al. 2005; Sun et al. 2008). These gap junction-mediated waves are thought to be the homeostatic compensatory response to the disruption of the cholinergic waves (Stacy et al. 2005; Blankenship and Feller 2010). When cholinergic waves are inhibited, the emergence of these compensatory waves appears to be mediated by strengthening the gap junction network between a subtype of RGCs, the intrinsically photosensitive retinal ganglion cells (Kirkby and Feller 2013; Arroyo et al. 2016). These findings suggest that gap junction coupling not only mediates the embryonic retinal waves but also plays a significant role at all stages of retinal waves.

However, the retinal gap junction network during the waves is not well understood due to several technical challenges in vertebrate systems. For example, a robust genetic model system for gap junction is missing (Bansal et al. 2000; Syed et al. 2004; Sun et al. 2008; Blankenship et al. 2011). In contrast to chemical synaptic transmission where *nAChR- β 2*, *chat*, or *vglut* mouse mutants are specific for retinal waves and extensively characterized, mammalian gap junctions have multiple paralogs (20 connexins and three pannexins in mice) (Cook and Becker 1995; Söhl et al. 2005; Burnstock 2018), which are usually essential for early development. Cells express multiple combinations of connexins, hindering the use of versatile loss-of-function strategies. We also lack specific pharmacological antagonists (Swayne and Bennett 2016; Wörsdörfer et al. 2018). Furthermore, despite the growing evidence of the functional significance, complexity, and potential plasticity of gap junction coupling, conventional approaches for investigating chemical synaptic connection might not be suited to study the gap junction network (Bloomfield and Völgyi 2009; Nagy et al. 2018). For example, unlike chemical synapses that can be well characterized by electron micrograph, gap junction coupling is very challenging to visualize (Nagy et al. 2018), and the electrical connectome in vertebrate systems is generally unknown.

The *Drosophila* model has powerful advantages for addressing these challenges. The fly has eight gap junction genes (eight innexins), six of which are expressed in the developing visual system (Stebbing et al. 2002; Dolezelova et al. 2007). While these genes are dynamically expressed with unique temporal and spatial patterns throughout pupal development, the peak expression of *inx8* (also called *ShakB*), a major gap junction gene in most neuronal populations (Crompton et al. 1995; Stebbings et al. 2002), occurs at ~50 h APF (Kurmangaliyev et al. 2020), just prior to synaptogenesis, suggesting a potential role in generating initial stages of correlated activity similar to the embryonic retinal waves in mammals. As the developing fly neurons, glia, and epithelial accessory cell types each expresses a cell type-specific combination of the six innexins just prior to PSINA (Stebbing et al. 2002; BJ Choi and C Desplan, unpubl.), this makes the developing

fly visual system an ideal model system to study the specific role of these genes during PSINA. The robust genetic accessibility of *Drosophila* can greatly facilitate the characterization of the gap junction coupling during PSINA and could lead to a systematic mapping of the gap junction network as has been done in *C. elegans* (Bhattacharya et al. 2019; Jin et al. 2020). In vivo functional assays in specific populations of neurons by genetically encoded optical sensors are also easily performed in flies (Wu et al. 2019).

Cell type-specific role for generating correlated spontaneous activity

A comprehensive determination of cellular diversity in the developing vertebrate nervous system is still technically challenging (Sanes and Masland 2015). For example, the vertebrate retina is composed of six main neuronal classes, rod and cone photoreceptors, amacrine, horizontal, bipolar interneurons, and RGCs (Cepko 2014). However, RGCs alone can be further classified into at least 30 distinct cell types (Sanes and Masland 2015), while there are at least 63 amacrine cell types (Yan et al. 2020). These diverse cell types are critical for the correlation of spontaneous activity. During stage III waves, although they have similar morphologies, On BCs can be subdivided into at least two groups depending on their expression of iGluR. During the lateral propagation of stage III waves in the BC circuit, iGluR-positive On BCs can be activated by extrasynaptic glutamate diffused from neighboring BCs, while iGluR-negative On BCs can participate in wave propagation through gap junction coupling (Fig. 1C; Kerschensteiner 2016). However, despite the recent development of advanced genetic and genomic tools, the determination of retinal cell types is still far from complete (Sanes and Masland 2015), making it difficult to understand whether they have specific contributions to the waves and are affected by them.

Meanwhile, the cellular diversity of the *Drosophila* visual system has been rigorously determined by taking advantage of the powerful genetic tools as well as the smaller brain size that allows for the completion of a detailed EM-level connectome (Venken et al. 2011; Takekura et al. 2013; Zheng et al. 2018; Scheffer et al. 2020). Through multiple systematic screening studies, tools are available for robust cell type-specific genetic manipulation at multiple developmental stages (Nern et al. 2015; Luan et al. 2020), making the fly an ideal model system to study how individual cell types participate in the correlation of spontaneous activity.

Furthermore, recent advances in genomics, such as single-cell mRNA sequencing (scRNA-seq), enable a robust and systematic determination of cellular diversity and its transcriptome throughout development. A combination of the large-scale use of scRNAseq during development and machine-learning algorithms has described the transcriptome of nearly all major optic lobe neuronal and glial cell types at different developmental stages (Kurmangaliyev et al. 2020; Özel et al. 2021), from the time the neurons are specified to the periods of axonal projection,

synaptogenesis, and adult function. Intriguingly, initial analysis of these data shows that well-studied presynaptic genes critical for membrane depolarization (*para*) and synaptic vesicle release (*brp* and *cac*) have peak expression levels in pan-neuronal population ~60 h APF (Kittel and Heckmann 2016; Kurmangaliyev et al. 2020), which roughly coincides with the onset of PSINA and is consistent with the requirement of synaptic coupling for this process. Similarly, the *hr38* (hormone receptor-like in 38), the best-characterized activity-dependent immediate early gene in insects (Fujita et al. 2013), is highly expressed in all neuronal types during the second half of pupal development when PSINA actively occurs and well before the start of sensory-evoked activity (Kurmangaliyev et al. 2020). This suggests not just that both spontaneous and sensory-evoked activity activate similar downstream signaling pathways but also that *hr38* can be used as an activity marker for correlated spontaneous activity. By taking advantage of these comprehensive resources, it is now possible to systematically identify how individual cell types engage in the PSINA process through single-cell sequencing of the transcriptional profiles of flies where PSINA has been specifically disrupted.

Concluding remarks

Since the first discovery of retinal waves ~30 yr ago, correlated spontaneous activity has been a fascinating and general phenomenon of vertebrate neurodevelopment with its striking visual spectacle. However, its transient nature and delicate phenotype have made it challenging to obtain a comprehensive understanding of this process. Recent advances in *Drosophila* suggest that spontaneously emerging correlated activity is an evolutionarily conserved developmental process. With an ever-advancing field of genetic and genomic tools, this new avenue of investigation using a simpler and genetically accessible model system will greatly promote our understanding of this fundamental feature of the nervous system.

Competing interest statement

The authors declare no competing interests.

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