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The Zebrafish Visual System: From Circuits to Behavior

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Abstract

Visual stimuli can evoke complex behavioral responses, but the underlying streams of neural activity in mammalian brains are difficult to follow because of their size. Here, I review the visual system of zebrafish larvae, highlighting where recent experimental evidence has localized the functional steps of visuomotor transformations to specific brain areas. The retina of a larva encodes behaviorally relevant visual information in neural activity distributed across feature-selective ganglion cells such that signals representing distinct stimulus properties arrive in different areas or layers of the brain. Motor centers in the hindbrain encode motor variables that are precisely tuned to behavioral needs within a given stimulus setting. Owing to rapid technological progress, larval zebrafish provide unique opportunities for obtaining a comprehensive understanding of the intermediate processing steps occurring between visual and motor centers, revealing how visuomotor transformations are implemented in a vertebrate brain.

1. INTRODUCTION

One of the most fundamental functions of brains across all species is the capacity to make behavioral choices, that is, in a broad sense, the distribution of neural activity in the brain can assume critical states that represent the commitment of an animal to perform one out of several possible actions on the basis of integrated sensory information. To do so, neural signals in sensory areas must evoke neural signals in motor areas that control the generation of precise movement patterns. In terms of vision, much detail is already known about how the retina encodes visual inputs, extracts visual features, and relays preprocessed information to retinorecipient brain areas. Likewise, much information has been obtained on how the specifics of a motor pattern are encoded in patterns of neural activity in motor-related areas in the brainstem and spinal cord. Arguably, the greatest challenge for understanding how brains generate behavior is to get a more comprehensive picture of how visual and motor areas communicate with each other, directly or indirectly via intermediate brain areas, in the intact brain.

Among vertebrate models for vision, the zebrafish at its larval stage provides unique opportunities for investigating the neural basis of behavior at the synaptic, cellular, circuit, and whole-brain levels. In the past three decades or so, this teleost species has emerged as a remarkably useful model for studying the development, structure, and function of neural circuits (Bilotta & Saszik 2001, Neuhauss 2003, Gahtan & Baier 2004, Friedrich et al. 2010) ranging from simple reflex pathways to distributed circuits that may represent an ancestral form of the subcortical pathways mediating selective attention in mammals (Krauzlis et al. 2018). Because of the small brain volume and translucent skin of zebrafish, genetic tools can be combined with whole-brain functional imaging approaches and targeted electrophysiological recordings in the intact nervous system, while the animal's behavior in response to complex visual stimuli can simultaneously be tracked. Moreover, substantial efforts have been made recently to merge genetic, anatomical, and functional data from different experiments in standardized atlases (Ronneberger et al. 2012, Marquart et al. 2015, Randlett et al. 2015, Kunst et al. 2019, Tabor et al. 2019).

From this work, the main areas that process input coming directly from the retina as well as the brainstem centers that encode motor variables at the output level have been described (**Figure 1**). The zebrafish retina, which is very similar to the mammalian retina in its cellular composition and laminar structure, projects to ten arborization fields (AFs) in the diencephalon and mesencephalon (**Figure 1**). Visually responsive populations primarily in the optic tectum, but also in the pretectum and thalamus, which are tuned to specific features of the visual stimulus, have been identified (**Figure 1**). Moreover, the main pathway relaying motor commands from the brain to the spinal cord is formed by reticulospinal (RS) neurons in the nucleus of the medial longitudinal fasciculus (nucMLF) and in the hindbrain (**Figure 1**), which activate motor neurons directly or via spinal interneurons. Many more areas in the larval brain are active during visually driven behaviors, such as the cerebellum and other structures in the rhombencephalon, as well as several, often genetically defined, populations in the diencephalon. They likely modify the parameters of the visuomotor transformation by generating signals important for motor learning or reporting the internal state of the organism, but their exact functions remain to be explored (**Figure 1**).

Here, I review what is known about the functional organization of the visual system in larval zebrafish in relation to its behavioral repertoire. I first consider the mechanisms involved in generating the multiple parallel representations of the visual world the zebrafish retina sends to the brain. In-depth discussion of the circuits downstream of the retina follows, focusing on their role in controlling specific visually guided behaviors and highlighting where recent technological advances have brought new levels of mechanistic understanding. The goal is to provide an overview of what is known about visuomotor function at the input and output levels, thereby

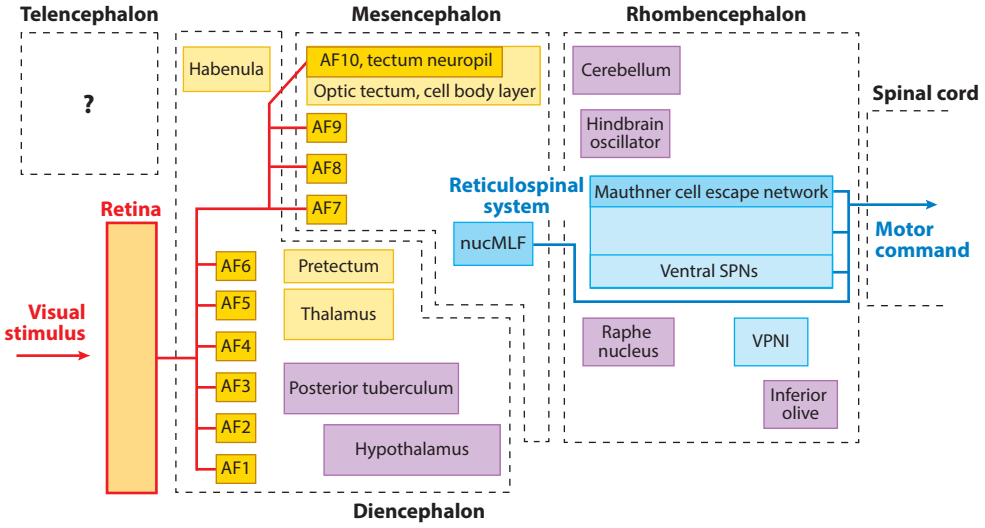

Figure 1

Organization of the zebrafish visual system in the brain of a week-old larva. The main areas (*yellow*) receiving direct or indirect projections from the retina and responding to visual input are located in the mesencephalon and diencephalon. Virtually all ganglion cells project to the optic tectum (AF10), but they often have collaterals with axon terminals in more ventral AFs. Spinal projection neurons in the midbrain nucMLF and hindbrain reticulospinal system encode motor variables, e.g., swim speed, duration, and turn amplitude (*blue*). VPNI neurons in the caudal hindbrain encode eye position. Other regions exhibit activity during visually driven behavior, likely changing the parameters of the visuomotor transformation (*purple*). Diagram does not indicate true anatomical positions. Abbreviations: AF, arborization field; nucMLF, nucleus of the medial longitudinal fasciculus; SPNs, spinal projection neurons; VPNI, velocity-to-position neural integrator.

revealing what is not known about the in-between steps but should in principle be resolvable in the zebrafish model.

2. THE RETINA: PROGRESS IN STRUCTURE, FUNCTION, AND DEVELOPMENT

2.1. Cell Types and Layers of the Zebrafish Retina

Like the retina of other vertebrates (Masland 2001, Wassle 2004), the retina of the zebrafish is a multilayered neuronal network composed of five canonical retinal neuron classes—photoreceptor, horizontal cell, bipolar cell, amacrine cell, and ganglion cell. The spatiotemporal distribution of light representing the visual surround of the fish is imaged through a spherical lens onto the outer retinal layer of rod and cone photoreceptors (Easter & Nicola 1996). The neural signal that results from phototransduction in the outer segments is relayed vertically from the photoreceptor via glutamatergic synapses to a layer of bipolar cells and then to retinal ganglion cells, the output layer of the retina. In between these layers, synaptic inputs from horizontal cells and amacrine cells in the outer plexiform layer and inner plexiform layer (IPL), respectively, shape the flow of signals (Diamond 2017, Franke & Baden 2017). As a consequence, image information is split into several parallel representations that are fed into different, interlaced subpopulations of bipolar and ganglion cells. Visual features such as luminance and contrast, object color and size, and visual motion direction, which critically affect an animal's behavior, are readily extracted in the retina and encoded in the spiking activity of different types of retinal ganglion cells (Masland 2012, Roska

& Meister 2014). After a brief overview of retinal development, aspects of retinal processing in the outer plexiform layer and IPL that have been elucidated in zebrafish larvae are described. A discussion of what is known about where functionally different ganglion cell types project to the brain follows.

2.2. Development: The First 7 Days

The visual system of zebrafish becomes functional approximately 3.5 days post fertilization (dpf), when the retinal circuitry and its projection to the brain have matured sufficiently to support the first visually evoked motor behaviors, such as visual startle and optokinetic responses (Stuermer 1988, Burrill & Easter 1994, Easter & Nicola 1996, Schmitt & Dowling 1999). Within this developmental time span, all retinal cell types have differentiated (**Figure 2*a***). In the outer plexiform layer and IPL, structural evidence for synaptic maturation is apparent and a basic sublayer-specific connectivity between retinal cell types, similar to that in the mammalian retina, begins to emerge (Schmitt & Dowling 1999, Godinho et al. 2005, Mumm et al. 2006). Functionally, synaptic currents in ganglion cells evoked by steps of light indicate that both ON-bipolar and OFF-bipolar cell connections with ganglion cells have already formed by 2.5 dpf (Zhang et al. 2010). Light-driven responses become more reliable within the following 3 days. Thus, ganglion cells can be functionally grouped into the classical transient-ON, sustained-ON, transient-OFF, sustained-OFF, and ON-OFF classes in response to steps of light (Emran et al. 2007), and moreover, direction-selective and orientation-selective ganglion cells can already be observed at this stage

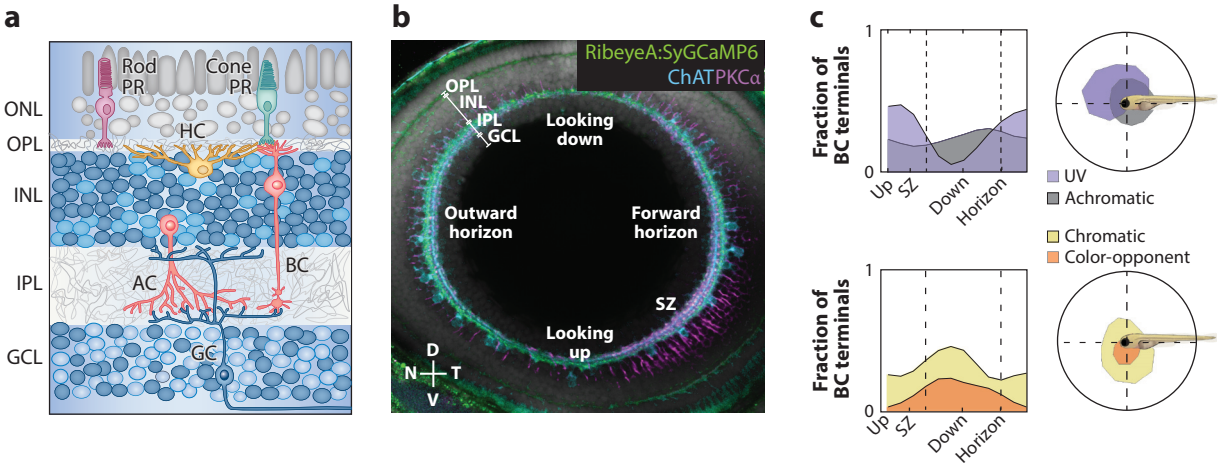

Figure 2

Retinal processing. (*a*) Retina of a 7-day-old larva. All five neural cell types have differentiated, and a functional synaptic network has formed, enabling feature extraction and transmission to the brain. (*b*) Immunostaining reveals nonuniform organization of the inner retina (*sagittal view*). Labels indicate where different regions of the visual field are projected on the retina. In a SZ in the upper and forward-looking visual field, corresponding to the region where prey is preferentially attacked, the IPL is thicker and more sublaminae have formed than elsewhere, suggesting different processing capabilities from those in other regions: (*green*) BC terminals, (*magenta*) PKCα-positive BCs, (*cyan*) cholinergic ACs. (*c*) Distributions of different functional types of bipolar terminals across the retina. UV–monochromatic bipolar terminals cluster in the SZ, whereas bipolar terminals processing color information (chromatic and color-opponent) are biased toward the lower visual field. Panels *b* and *c* adapted with permission from Zimmermann et al. (2018). Abbreviations: AC, amacrine cell; BC, bipolar cell; ChAT, choline acetyltransferase; D, dorsal; GC, ganglion cell; GCL, ganglion cell layer; HC, horizontal cell; INL, inner nuclear layer; IPL, inner plexiform layer; N, nasal; ONL, outer nuclear layer; OPL, outer plexiform layer; PKCα; protein kinase C alpha; PR, photoreceptor; SZ, strike zone; T, temporal; V, ventral.

(Nikolaou et al. 2012, Gabriel et al. 2012). Structurally, however, ganglion cells are much more diverse, yielding an estimated 14 types at this stage on the basis of dendritic stratification patterns (Robles et al. 2014). The number of types increases to more than 50 if axonal projection patterns are taken into account, which is similar to estimates in the mammalian retina (Sanes & Masland 2015).

Further increasing its complexity, the larval zebrafish retina also contains an estimated 28 morphological amacrine types (Jusuf & Harris 2009). Morphological classification of bipolar cells at this stage is difficult because their axons extend filopodia throughout the IPL and continue to undergo extensive laminar refinement until 14 dpf (Schroeter et al. 2006), resulting in a distinct sublaminar distribution of axon terminals in the adult retina (Connaughton et al. 2004). Classification based on the absorption spectra of their opsin variants indicates one rod and four cone photoreceptor types (Robinson et al. 1993, Chinen et al. 2003). Four cone types with absorption peaks at ∼550 nm (red), ∼470 nm (green), ∼410 nm (blue), and ∼360 nm (UV) form mosaics in the adult and larval retina, albeit with differences in their spatial organization (Robinson et al. 1993, Allison et al. 2010).

Finally, a morphological distinction among types of horizontal cells that connect to cones with distinct specificities in the adult retina (Song et al. 2008) can also be made in the larval retina (Yoshimatsu et al. 2014). In the latter study, the authors also showed how horizontal cells at larval stages selectively connect with spectrally different cone types by a process of early synapse elimination and subsequent cone-type-specific synaptogenesis, suggesting horizontal cells play a role in generating color-opponent signals in the nonmammalian outer retina in addition to their role in the generation of center-surround receptive fields. To summarize, although the retinal circuitry undergoes rapid development and ongoing refinement during the first week of development, it already possesses the processing power necessary to enable zebrafish larvae to perform sophisticated visually guided behaviors.

2.3. Visual Processing in the Inner Retina

A comprehensive overview of vertebrate retinal processing is beyond the scope of this review, and the reader is referred to recent reviews on this topic (for instance, see Masland 2012, Euler et al. 2014, Roska & Meister 2014, Demb & Singer 2015, Diamond 2017). Larval zebrafish, however, offer unique opportunities for the discovery of specific functional roles of retinal circuit components in vivo via the use of imaging and electrophysiological approaches in combination with powerful genetic tools for measuring neural activity and synaptic transmission.

2.3.1. Mapping functional diversity in the inner plexiform layer. In response to light, photoreceptors engage graded hyperpolarization. By contrast, the output signal of the retina is encoded by all-or-none action potentials generated in ganglion cells. It has been controversial where the transition from graded membrane potential changes to regenerative all-or-none voltage spikes occurs first. Along the vertical pathway in the intact zebrafish retina, this transition starts in the axon terminals of bipolar cells, many of which exhibit spiking activity that is phase-locked to the on- and offset of a step of light (Baden et al. 2011, Dreosti et al. 2011). The dynamic range to luminance changes is relatively narrow and highly nonlinear in many of these terminals, but across populations, their peak sensitivities are distributed widely and cover a luminance range of four to five log units (Odermatt et al. 2012). Further heterogeneity is apparent in the temporal response characteristics of bipolar cell axon terminals and in how they adapt to the modulation of temporal contrast (Nikolaev et al. 2013, Rosa et al. 2016). Because of the favorable imaging conditions in zebrafish retina, this heterogeneity can be compared across hundreds of simultaneously imaged

axon terminals and mapped onto the sublaminae of the IPL. In subsequent work, the functional diversity of bipolar cell axon terminals could be attributed in part to differences in the volume of individual terminals (Baden et al. 2014), dopaminergic modulation (Esposti et al. 2013), and crossover inhibition between ON and OFF pathways (Rosa et al. 2016).

2.3.2. Chromatic responses in larval retina. There is great diversity among the spectral responses of bipolar cell terminals, which may be grouped as achromatic, chromatic, color-opponent, or UV specific and whose distribution is highly nonuniform across the retina (Zimmermann et al. 2018) (**Figure 2*b*,*c***). Strikingly, the retinal distribution of color-specific bipolar cell signals and corresponding cone types corresponds to the behaviorally relevant chromatic content found in the natural habitat of zebrafish. At least in the adult retina, chromatic and color-opponent responses also occur in horizontal and amacrine cells (Connaughton & Nelson 2010, Torvund et al. 2017), and because cone-type-specific wiring of horizontal cells emerges at the early stages of development, horizontal cell signaling may shape color-specific and color-opponent signals in bipolar cells and also in larval retina (Yoshimatsu et al. 2014). More generally, given the differences in IPL organization along the dorsoventral and temporonasal dimensions (Zimmermann et al. 2018), it may be important to take retinal position into account when comparing results in future work.

2.3.3. Orientation and direction selectivity. As in most vertebrate species studied so far, the zebrafish retina contains ganglion cells with responses tuned to the orientation of an elongated stimulus or the direction of a moving stimulus, thereby giving rise to orientation-selective and direction-selective signals, respectively. The tuning properties of retinal ganglion cells have generally been determined using calcium imaging in their axon terminals outside the retina. Among direction-selective ganglion cells, three preferred directions are evident (Nikolaou et al. 2012, Gabriel et al. 2012, Lowe et al. 2013). Although mechanisms underlying direction-selective responses in mammalian ganglion cells have been elucidated in great detail (Euler et al. 2002, Briggman et al. 2011, Mauss et al. 2017), the combination of these mechanisms responsible for direction-selective responses in zebrafish retina is not known. A more direct approach using calcium imaging in the IPL was used to find orientation-selective signals in an amacrine cell type with an elongated dendritic tree, as well as in bipolar cell terminals. Functional orientation preference correlated with the orientation of these amacrine cell dendrites and vanished when these cells were ablated (Antinucci et al. 2016). Thus, the emergence of orientation selectivity in these cells can be traced back to a structural feature in the IPL—the orientation of an asymmetrical dendritic tree.

2.3.4. Size selectivity and looming responses. Some ganglion cells in larval retina exhibit pronounced size selectivity with a preference for small visual stimuli no larger than 5°–10° angular size (Preuss et al. 2014, Semmelhack et al. 2014), which corresponds to the size of ciliates actively hunted by zebrafish larvae. Larger stimuli evoke no response, suggesting an effective inhibitory surround circuitry shaping the receptive field of these ganglion cells. A comparison based on geometrical optics suggests a relatively narrow dendritic field diameter (~15 μm) (Preuss et al. 2014) that, together with their projection pattern to the superficial tectal neuropil and AF7, identifies them as narrow-field bistratified or diffuse ganglion cells (Robles et al. 2014, Semmelhack et al. 2014). Conversely, ganglion cell axons that respond strongly to dark expanding disks (looming stimuli) (Temizer et al. 2015, Dunn et al. 2016a), but not to an equivalent whole-field dimming stimulus, are also apparent in the tectum. However, little is known about their retinal origin, and further work is required to determine whether these signals arise from a genuine approach-sensitive ganglion cell type (Munch et al. 2009) or, alternatively, from ganglion

cells that respond mainly to large moving edges corresponding to lateral motion, as observed previously (Del Bene et al. 2010, Preuss et al. 2014).

2.4. The Emerging Functional Retinal Projectome

The distribution of retinal ganglion cells with different dendritic profiles and axonal projection patterns across the ten known AFs has been comprehensively studied by Robles et al. (2014). They found 14 distinct ganglion cell types based on dendritic morphology, almost all of which had an axon projecting to the optic tectum. Interestingly, 10 types also sent an axon collateral to one or more of the smaller AFs, suggesting that retinally processed visual features such as size, direction, or orientation are fed in parallel into multiple visual areas subserving different computational roles.

Owing to recent efforts in imaging visually driven activity in different AFs, components of a functional projectome are now emerging as well. AF7 is highly stimulus selective, responding exclusively to small moving objects (Semmelhack et al. 2014). In contrast, ganglion cell terminals in AF8 and AF6 are driven by dimming and looming stimuli (Temizer et al. 2015), suggesting they originate from ganglion cells with large dendritic fields in the OFF sublayer of the IPL, consistent with anatomical reconstructions (Robles et al. 2014). Interestingly, responses in the neuropil near AF6 also exhibit direction-selective responses to large-field moving stimuli (Naumann et al. 2016), raising the possibility that responses evoked by looming stimuli are from ganglion cells that detect large-field lateral motion. Axon terminals in AF9 respond to whole-field luminance changes, with a subdivision for ON and OFF responses in the dorsal and ventral AF9, respectively (Robles et al. 2014). Ganglion cell terminals in AF4 exhibit transient and sustained activity in response to luminance changes, consistent with their dendritic morphology (Cheng et al. 2017, Zhang et al. 2017). Because virtually all dendritic ganglion cell types also project to the tectum, all response categories (responses to whole-field luminance changes; looming responses; size-, direction-, and orientation-selective responses) can also be detected in various ganglion cell axons in the tectal neuropil (Gabriel et al. 2012, Nikolaou et al. 2012, Lowe et al. 2013, Preuss et al. 2014, Semmelhack et al. 2014, Temizer et al. 2015, Dunn et al. 2016a).

3. RETINOTECTAL PROJECTION: LAYERS, MAPS, AND CIRCUITS

The optic tectum, homologous to the mammalian superior colliculus, is the major retinorecipient brain area in nonmammalian vertebrates. It exhibits a highly laminar structure, with retinal ganglion cell axons forming well-defined sublayers in the tectal neuropil and a retinotopic distribution of ganglion cell axon terminals across its rostrocaudal and mediolateral dimensions. To date, the tectum has been a valuable model for studying the molecular and activity-dependent mechanisms underlying the development of the laminar network structure and topographic maps (Baier 2013, Kita et al. 2015). Here, I focus on aspects of functional topography of neural signals and lamina-specific processing of visual features such as visual motion and size processing in the larval visual system.

3.1. Topographic Maps and Functional Clusters

As a result of axon sorting and molecular guidance in the retinotectal projection, the temporonasal and dorsoventral axes of the retina are mapped onto the rostrocaudal and lateromedial axes of the tectum, respectively (Stuermer 1988). Small visual stimuli evoke activity in spatially clustered groups of neurons in the periventricular layer, indicating stimulus location is topographically

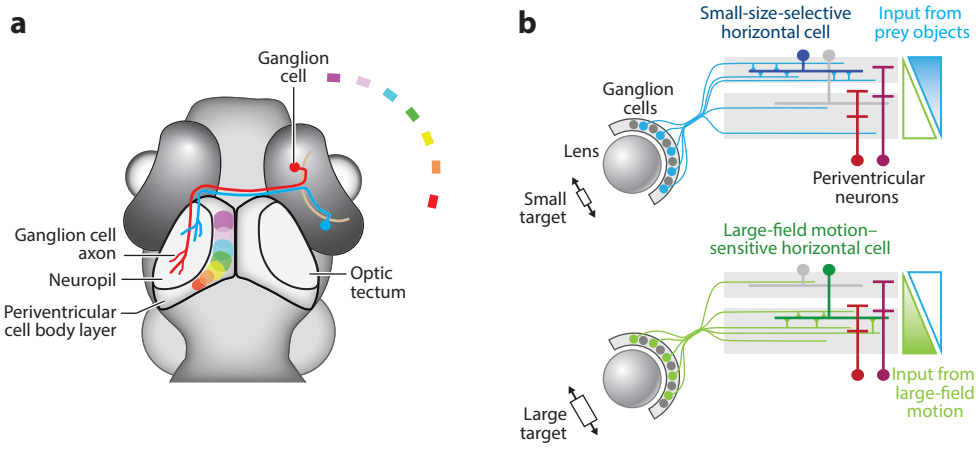

Figure 3

Layers and maps in the optic tectum. (*a*) Retinotopic mapping of axon terminals in the tectal neuropil occurs early on the basis of molecular guidance cues. Stimulus-evoked activity is clustered in topographically distributed cell assemblies that, nevertheless, overlap considerably. (*b*) Relay of feature-specific signals via layer-specific dendritic branching by tectal neurons. Tectal horizontal cells (also called superficial interneurons; Del Bene et al. 2010) exhibit dendritic branching in distinct sublayers: Large-field motion stimuli strongly modulate the activity of horizontal cells branching in deep layers, whereas mainly small prey-like objects drive the activity of horizontal cells branching in superficial neuropil. Panel *b* adapted with permission from Preuss et al. (2014).

represented where there is tectal population activity (Niell & Smith 2005, Romano et al. 2015) (**Figure 3*a***). However, owing to spatial imprecisions, mapping is coarse and unreliable, suggesting statistically more refined, experience-dependent decoding strategies may replace an early hard-wired topographic decoding mechanism (Avitan et al. 2016).

Of note, bouts of activity arising spontaneously in the absence of stimulation in small clusters of neurons also occur when small stimuli are presented in a retinotopically corresponding location, suggesting functional neuronal assemblies in the tectum that may facilitate motor responses to behaviorally relevant stimuli (Romano et al. 2015). These functional clusters are not abolished by eye removal, indicating they are the result of tectum-intrinsic connectivity. Removing the eye or rearing an animal in darkness from an early stage does not prevent the development of spontaneously active functional clusters, although their spatial and temporal properties are significantly affected (Avitan et al. 2017, Pietri et al. 2017). Similarly, the integration of newborn neurons in the tectal circuitry is strongly influenced by visual deprivation (Boulanger-Weill et al. 2017). Thus, visually driven activity, or activity from spontaneous retinal waves (Zhang et al. 2016), plays an important role in the maturation of visual circuit function during a critical window of early development.

3.2. Lamina-Specific Visual Processing

Virtually all retinal ganglion cells project to the tectum (Robles et al. 2014). Therefore, any retinal ganglion cell signal encoding specific stimulus properties should in principle be available to tectal cells. The high degree of laminar specificity with which retinal axons travel into and terminate in the tectal neuropil, forming distinct retinorecipient layers, has long been established, but how specific stimulus properties are represented in the tectal neuropil and processed in postsynaptic cells was addressed only recently. Functional calcium imaging at high spatial resolution in

genetically defined subpopulations and targeted patch-clamp recordings have provided strong evidence for lamina-specific relay of stimulus features to postsynaptic tectal cell types (Gabriel et al. 2012, Preuss et al. 2014, Nikolaou & Meyer 2015), which is also becoming increasingly evident for the mammalian superior colliculus (Dhande & Huberman 2014, Cang et al. 2018). Retinal ganglion cells with distinct directional tuning curves that send axons to particular adjacent sublayers in the tectal neuropil may be the clearest example of this process (Nikolaou et al. 2012, Gabriel et al. 2012). Postsynaptic tectal neurons with similar directional tuning have dendrites that stratify in the corresponding layer and receive directionally tuned excitatory inputs (Gabriel et al. 2012), suggesting they inherit their tuning properties directly from directionally tuned retinal ganglion cells. In addition, many directionally tuned tectal cells receive inhibitory synaptic input evoked by stimuli moving in the opposite direction (Gabriel et al. 2012, Grama & Engert 2012). This intratectal null-direction inhibition may explain how some cells in the periventricular cell body layer are tuned to motion in the rostrocaudal direction, which is not represented in direction-selective retinal ganglion cell signals in the tectal neuropil (Hunter et al. 2013). A potential source of null-direction inhibitory currents are horizontal cells with cell bodies located in the neuropil (Abbas et al. 2017), but other tectal cell types might also mediate null-direction inhibition (Gabriel et al. 2012).

The distribution of size-selective signals in the tectal network provides another example of how tectal neurons extract feature-specific synaptic input via lamina-specific dendritic branching. Ganglion cells tuned to small stimuli have axons with terminals frequently in the superficial neuropil, but they do not exhibit a strict laminar preference (Preuss et al. 2014). Preuss and colleagues (2014) found that tectal horizontal cells exhibit opposite size tuning depending on whether their dendrites stratify in the most superficial layer or in deeper layers of the tectal neuropil (**Figure 3*b***). The various excitatory synaptic currents these cells receive in different sublaminae may explain the differences in size tuning. Thus, size-selective horizontal cells may seek out their specific presynaptic partners from the multiple available retinal ganglion cell types.

Ganglion cell axons sensitive to other visual features such as orientation, whole-field luminance changes, and looming stimuli do not obey a strict laminar organization. Instead, they prefer central and deep layers in the tectal neuropil (Nikolaou et al. 2012, Temizer et al. 2015, Dunn et al. 2016a). Postsynaptic tectal neurons may inherit these stimulus sensitivities as well by guiding dendrites to particular input layers or regions and seeking out feature-specific ganglion cell axons, a process likely facilitated by molecular recognition (Antinucci et al. 2013, Nikolaou & Meyer 2015).

4. FOCUS ON CIRCUITS IN VISUAL BEHAVIORS

In recent years, the larval zebrafish brain has become an informative model for visual processing wherein the neuronal basis of visuomotor transformations and their modulations can be comprehensively elucidated throughout. With the development of new whole-brain imaging methods, optogenetic circuit perturbations, and genetic as well as physical ablations of circuit components, an increasingly detailed picture is emerging of how primary sensory and motor areas not only work, but also may communicate with each other and be influenced by modulatory areas. To investigate visual system function in response to stimuli that larvae are expected to encounter under natural conditions, a number of stimulus classes are commonly used. These include (*a*) large-field stimuli such as moving gratings and spatiotemporal steps or gradients in luminance that simultaneously evoke responses across the retina and (*b*) local stimuli such as flashing or moving spots that affect more restricted regions of the retina. Here, I first address several circuits and mechanisms implicated in the control of behaviors driven by large-field stimuli and then discuss behavioral patterns triggered by more local stimuli.

4.1. Responses to Spatiotemporal Illumination Patterns Affecting the Whole Retina

An animal experiences whole-field retinal image motion when it moves relative to the visual world, either because of self-motion or because of movement of the medium that it is situated in. These spatiotemporally correlated changes in illumination across the retina drive compensatory body and eye movements known as optomotor response (OMR) and optokinetic response (OKR). The OMR is an orienting swimming behavior wherein moving stripe patterns evoke discrete directed swim bouts in the direction of optic flow. The OKR consists of slow rotational eye movements in the direction of large drifting patterns, which stabilize the image of the visual surround on the retina. Under nonuniform illumination conditions, a third motor behavior, positive phototaxis, is observed, wherein larvae swim toward brighter areas.

4.1.1. Optomotor response. The OMR is a robust visual response in larval zebrafish, mediated by the red/green cone pathway (Neuhauss et al. 1999, Orger & Baier 2005). Studies using calcium imaging, ablations of identified neurons, and optogenetic manipulations clearly demonstrate that spinal projection neurons in the midbrain nucMLF and members of a well-defined set of descending projection neurons in the hindbrain reticular formation relay the commands for forward and turning components of directed swim bouts to motor circuits in the spinal cord (Kimmel et al. 1982, Orger et al. 2008, Huang et al. 2013, Thiele et al. 2014) (**Figure 4*a*,*b***). On

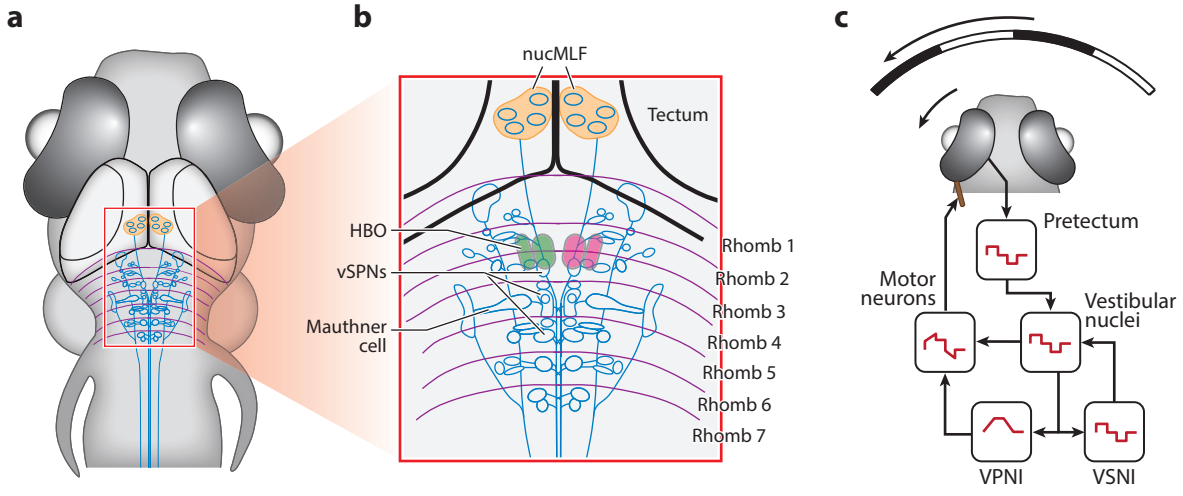

Figure 4

Large-field motion processing and motor command circuitry. (*a*) Descending motor control system in the midbrain and hindbrain. The RS system consists of several hundred symmetrically organized spinal projection neurons, many of which are morphologically identifiable (*blue*). Rhomb boarders in the hindbrain indicated by curves (*purple*). (*b*) Magnified view of the RS system. Activity in the nucMLF in the midbrain is correlated with forward motion. Activity in vSPNs is correlated with turning. Activity in the Mauthner cell and its homologues is strongly correlated with escape swims. Spontaneously occurring, left-right-alternating activity in the HBO region is correlated with gaze direction and turning bias during swimming. Array of RS neurons adapted with permission from Orger et al. (2008). (*c*) Model of signal flow during the optokinetic response evoked by steps in stimulus velocity. Stimulus velocity is represented in the pretectum and relayed to vestibular nuclei. Activity in these nuclei directly drives motor neurons and is concurrently fed into the VPNI, where it changes the level of persistent activity, which serves to provide tonic drive onto motor neurons to maintain eye position. Panel *c* adapted from Sylvester et al. (2017). Abbreviations: HBO, hindbrain oscillator; nucMLF, nucleus of the medial longitudinal fasciculus; rhomb, rhombomere; RS, reticulospinal; VPNI, velocity-to-position neural integrator; VSNI, velocity–storage neural integrator; vSPNs, ventromedial spinal projection neurons.

the sensory side, direction-selective ganglion cells signal the visual motion direction to discrete AFs, from where visually driven neurons in the pretectum integrate directional signals from both eyes (Kubo et al. 2014, Naumann et al. 2016). Researchers proposed a detailed organization based on a whole-brain imaging approach for how pretectal circuits connect to distinct motor areas in the hindbrain, assigning specific computational roles to circuit components downstream of the pretectum in refining OMR motor commands (Naumann et al. 2016). By contrast, more recent work found that the information necessary for driving the OMR (and OKR) is already represented in pretectal populations that unambiguously encode optic flow directions (Wang et al. 2019). Together, the proposed connectivity patterns in the pretectum (Kubo et al. 2014, Naumann et al. 2016) provide helpful hypotheses for experimental testing, but more work is required to elucidate how visual pretectal areas and the hindbrain circuitry are connected.

Notably, larvae exhibit a form of motor adaptation in changing the gain of their motor commands when they are confronted with changes in perceived swim velocity during closed-loop visual stimulation (Portugues & Engert 2011). Gain changes are associated with transient neural activity in the hindbrain inferior olive and the cerebellum, suggesting a role for the olivocerebellar pathway in larval adaptive motor control (Ahrens et al. 2012). After adapting to a new gain, larvae retain short-term memory of their last gain settings in the absence of visually evoked swimming, which has been associated with the buildup of persistent activity in the serotonergic dorsal raphe nucleus (Kawashima et al. 2016). The serotonergic system in larvae has also been implicated in the modulation of visual responsiveness during states of arousal (Yokogawa et al. 2012).

4.1.2. Optokinetic response. Beginning at 3 dpf, larval zebrafish exhibit optokinetic behavior such as eye movements in response to whole-field motion (Brockerhoff et al. 1995, Easter & Nicola 1996). The velocity-to-position neural integrator (VPNI) located in the caudal hindbrain comprises neural populations that encode eye position via a population code of persistent activity (Miri et al. 2011a,b; Joshua & Lisberger 2015) (**Figure 4*c***). The symmetrically organized VPNI network integrates transient eye-velocity-encoding signals, likely via excitatory recurrent connectivity within each half-center, and coordinates activity between the left and the right half-centers via reciprocal inhibitory connections. Functional identification of VPNI neurons and comparison of their morphology with their location within the regularly organized scaffold of excitatory and inhibitory neurons in the hindbrain (Kinkhabwala et al. 2011) revealed corresponding cell types in support of this mechanism (Lee et al. 2015). More direct anatomical evidence for recurrent connectivity between VPNI neurons comes from an ultrastructural analysis using serial electron microscopy (Vishwanathan et al. 2017). Notably, whereas eye position is encoded in the overall magnitude of network activity, the context of how a given eye position is achieved (spontaneous versus visually driven) is reflected in differences in the distribution of activity within the VPNI population (Daie et al. 2015).

A neural representation of large-field motion is built into pretectal areas in many species (Masseck & Hoffmann 2009). The pathways driving the OKR and the OMR probably share components in the pretectum because the two behavioral responses are driven by similar large-field motion stimuli. The same direction-selective ganglion cell AFs and pretectal circuits may subserve the integration of binocular motion cues (Kubo et al. 2014, Naumann et al. 2016, Wang et al. 2019) that underlies the generation of input to the VPNI and oculomotor nuclei that drive the OKR, as well as of directional command signals in spinal projection neurons that drive the OMR.

Beyond the OKR circuitry, stimulus-driven and motor-associated activity can be observed throughout the zebrafish brain (Portugues et al. 2014). The tectum, for example, also exhibits strong stimulus-locked activity, and direction-selective tectal cells have recently been implicated

in modulating the OKR in a form of motion after effect (Perez-Schuster et al. 2016). More work, however, is needed to understand the role of the tectum in processing whole-field motion. In addition, cerebellar Purkinje cells and granule cells are activated during OKR and OMR behaviors, with a spatial bias depending on which behavior is performed (Matsui et al. 2014, Scalise et al. 2016, Knogler et al. 2017, Sylvester et al. 2017), and cerebellar output is fed back to visually responsive centers such as the optic tectum and thalamic areas (Heap et al. 2013). Finally, dopaminergic neurons in the posterior tuberculum are also active during the presentation of whole-field motion stimuli, potentially modulating the sensitivity of the visuomotor interface in the hindbrain and spinal cord (Reinig et al. 2017).

4.1.3. Phototaxis. When given a choice, larval zebrafish prefer illuminated areas over darker ones and swim toward sources of light, exhibiting positive phototaxis (Brockerhoff et al. 1995, Orger & Baier 2005, Burgess et al. 2010). This behavior can be explained by a mechanism wherein larvae detect spatial illumination gradients by comparing light levels between the two eyes and generating directed swim bouts on that basis. Alternatively, a larva may detect a spatial gradient by comparing light levels before and after a directed movement, which requires it to store information on earlier illumination levels and its own movement on a time scale of seconds (Chen & Engert 2014). To orient and swim toward sources of light, asymmetrically distributed activity upstream of tail motor circuits likely biases the direction of swim bouts, but where in the brain this activity is located was unclear. Not long ago, researchers discovered cell clusters in hindbrain rhombomeres 2 and 3, termed the hindbrain oscillator or anterior rhombencephalic turning region, that exhibit persistent activity alternating between the left and right side on a timescale of ∼10 s and that likely control the direction of spontaneous swim bouts during exploratory locomotion (Ahrens et al. 2013, Dunn et al. 2016b) (**Figure 4*b***). Using two-photon light-sheet imaging in combination with patterned visual stimulation, Wolf and colleagues (2017) recently showed that left-right alternating activity in these anterior hindbrain clusters is sensitive to visual stimulation in a phase-dependent manner. This hindbrain region may thus represent a neural substrate where information on spatiotemporal illumination gradients is integrated and thus provides the vision-dependent bias for directed eye and tail movements during phototaxis (Wolf et al. 2017).

The left habenula is one candidate region for the visual pathways contributing to phototaxis by relaying whole-field luminance changes to hindbrain circuits. The left habenula responds to ambient luminance changes (Dreosti et al. 2014) and receives input from ganglion cells with sustained responses in AF4 via relay neurons in the anterior thalamus (Cheng et al. 2017, Zhang et al. 2017). Because light-preference behavior depends on it, the left habenula may also form part of the circuit that interacts with the hindbrain oscillator circuitry, but the connectivity remains unclear.

Note that light-preference behavior can also result from increased nondirectional motor activity in dark areas, which is mediated by deep brain photoreceptors (Fernandes et al. 2012) and can be modulated by somatostatin signaling (Horstick et al. 2017).

4.2. Responses to Local Motion and Form

In addition to whole-field motion processing, the larval visual system is very sensitive to local object motion. Larvae respond to moving objects with different swim patterns, depending on the spatiotemporal properties of the stimulus on a small patch of the retina. Behaviors studied in depth regarding local object motion are prey capture behavior, avoidance of large moving objects, and looming-evoked escape responses.

4.2.1. Target-directed behaviors and prey capture sequences. At around 5 dpf, zebrafish larvae begin to feed by tracking and finally capturing small ciliates such as paramecia in a sequence of discrete swim bouts, which lasts no longer than 1 to 2 s (McElligott & O'Malley 2005, Trivedi & Bollmann 2013). A unique feature of prey capture behavior is that the eyes are held in a fully converged position until the behavior ends with a capture swim (Bianco et al. 2011). Importantly, the tail kinematics and the resultant amplitude of orienting turns are a smoothly varying function of the prey object's azimuth angle immediately preceding the swim bout, providing evidence for a continuous motor map in the visual system at this early stage (Patterson et al. 2013, Trivedi & Bollmann 2013) (**Figure 5*a*,*b***). The graded, target-directed turning response of larvae is consistent with the retinotopic organization of the tectum. Furthermore, it resembles that of target-directed eye, head, and trunk movements in mammals mediated by the superior colliculus (Gandhi & Katnani 2011). As a result, this larval behavior is a useful model for studying general mechanisms controlling target-directed saccades and orienting body movements at the cellular and circuit levels in vertebrate brains.

To gain experimental control over the input, researchers have developed stimulus projection methods that evoke individual steps of the behavior (Bianco et al. 2011, Semmelhack et al. 2014) as well as full prey capture sequences using a closed-loop virtual environment (Trivedi & Bollmann 2013). In the latter, the authors showed that symmetrical, fully converged eye position during prey capture is the result of two individual rotations of the contra- and ipsilateral eye during the first and second swim bout, respectively, suggesting that the position of each eye can be controlled independently. Furthermore, they found that the reaction time of a swim bout within a sequence depends on visual feedback that indicates the turning precision of the preceding swim.

4.2.2. Circuits in prey capture. Ablation studies searching for the circuit components that mediate prey capture showed that not only individual spinal projection neurons in the midbrain nucMLF are necessary (Gahtan et al. 2005), but also horizontal cells in the optic tectum (Del Bene et al. 2010, Yin et al. 2019). Subsequently, comparison between the behavioral sensitivity to stimulus size and the size tuning curves of neural populations in the visual pathway provided information on possible mechanisms. Target-directed orienting turns are evoked by small objects $\leq 5°$, but not large ones, both in freely moving (Bianco et al. 2011) and tethered larvae (Trivedi & Bollmann 2013). Ganglion cells with corresponding size tuning have axon terminals both in the superficial tectal neuropil, likely driving tectal neurons with similar size tuning (Preuss et al. 2014), and in AF7, from where relay neurons located in the pretectum project axons near spinal projection neurons (Semmelhack et al. 2014). Thus, these pathways provide two parallel conduits for processing prey-related signals (**Figure 5*c***). Owing to its retinotopic organization at its input (Stuermer 1988), global population (Romano et al. 2015), and output levels (Helmbrecht et al. 2018), the tectum most likely relays positional signals to the hindbrain that encode the amplitude of a turn. Although the role of the pretectal pathway remains less clear, this pathway might trigger or gate the actual swim event. Each of these pathways could therefore be responsible for controlling the asymmetric turning component and the symmetric, oscillatory forward component of an orienting turn, respectively, during prey capture (Trivedi & Bollmann 2013). However, more work is needed to understand the roles of these pathways and how they interact.

Further downstream in the tectal pathway, tectal cells exhibit large functional diversity to simple visual features (Niell & Smith 2005, Gabriel et al. 2012, Hunter et al. 2013, Preuss et al. 2014, Thompson et al. 2016), but more complex functional types with nonlinear mixed selectivities highly tuned to prey-like stimuli have also been found (Bianco & Engert 2015). Moreover, when tectal activity is correlated with eye convergence movements implicated in prey capture, tectal assemblies are observed that may represent a premotor signal initiating behavior (Bianco &

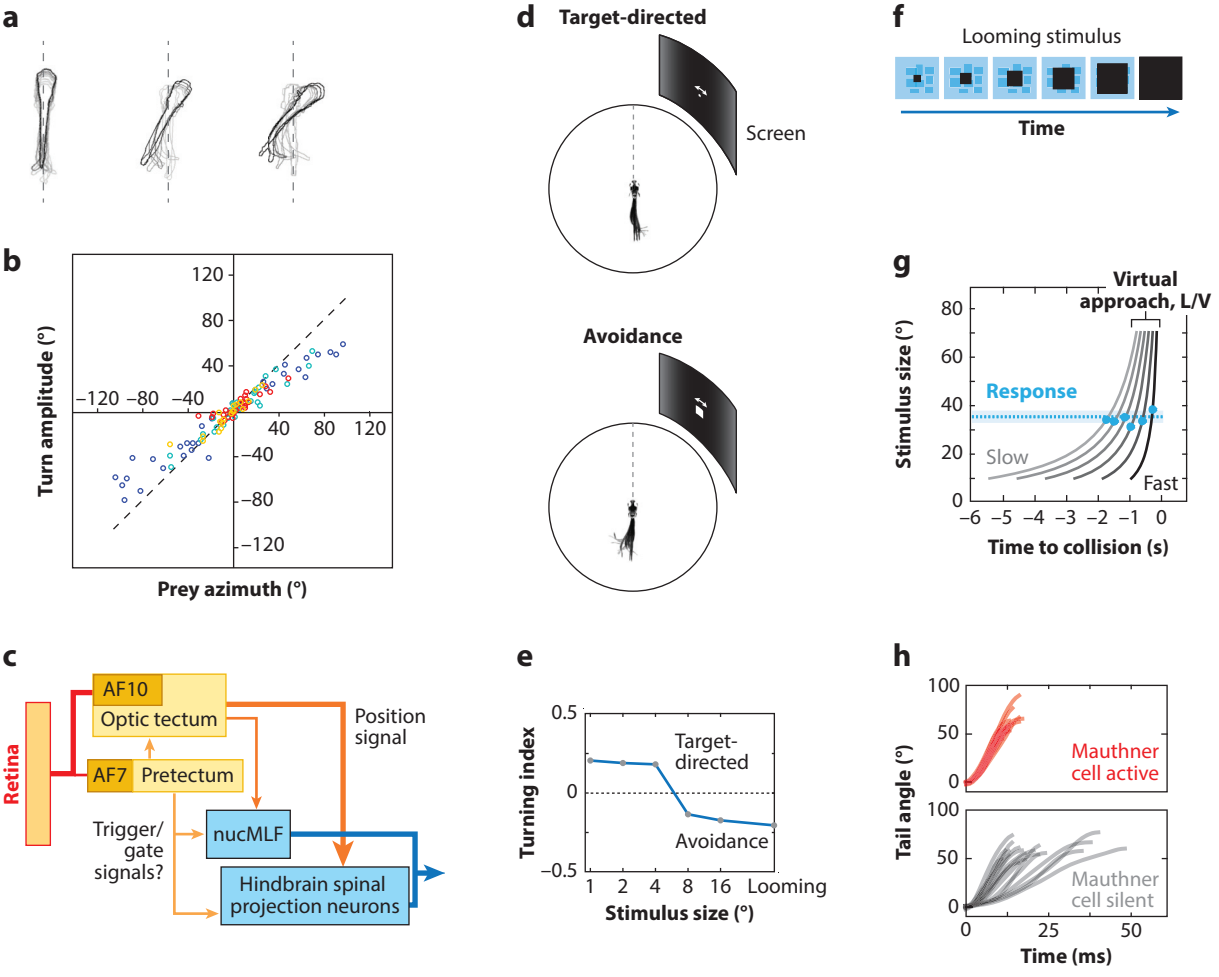

Figure 5

Prey capture, looming, and behavioral choice. (*a*) Three examples of a larva turning toward prey. (*b*) Turn amplitudes when larvae hunt prey as a function of the angle between heading direction of an animal and direction at which prey appears (azimuth). Note the graded, continuous distribution of turning angles. (*c*) Pathways implicated in prey capture behavior: Regions in retinorecipient areas AF10 (tectum) and AF7 exhibit selectivity for prey-like stimuli. Tectal projection neurons relay a position signal to the hindbrain, controlling the turning amplitude. By contrast, a pretectal pathway from AF7 to nucMLF and the hindbrain could trigger or gate the actual swim event. Arrows indicate putative connectivity based on anatomical reconstructions. (*d*) Schematic of behavioral choice experiment in response to laterally moving objects of different sizes. Small spots evoke target-directed turns, whereas larger spots evoke avoidance turns. (*e*) Behavioral tuning curve. The critical size threshold where turning reverses is between 4° and 8°. (*f*) An expanding rectangle as a looming stimulus. (*g*) The looming-evoked escape response occurs at a critical angular size of the object (*blue horizontal line*) for all approach speeds. Fast, stereotyped escape responses involving Mauthner cell activation are more often evoked by fast-approaching stimuli (*darker curves*) than by slowly approaching ones. (*h*) When the Mauthner cell is active during a looming response, escape kinematics are fast and invariant. By contrast, escape trials without Mauthner cell activation are more variable, during both quickly and slowly approaching stimuli. Panels *a*, *b*, and *d* adapted from Trivedi & Bollmann (2013). Panels *f–h* adapted with permission from Bhattacharyya et al. (2017). Abbreviations: AF, arborization field; nucMLF, nucleus of the medial longitudinal fasciculus.

Engert 2015). As further evidence, optogenetic stimulation of the anterior-ventral tectum suffices to evoke eye and tail movements resembling those during prey capture (Fajardo et al. 2013). Of note, researchers have found a new pathway component formed by pretectal neurons responsive to prey-like stimuli that project to a feeding center in the hypothalamus and possibly play a motivational role (Muto et al. 2017), but this pathway awaits further structural and functional dissection.

4.2.3. Behavioral choice. Zebrafish larvae not only initiate hunting behavior in response to small objects, but also exhibit behavioral choice by orienting away from laterally moving objects larger than approximately 5° visual angle under various conditions (Bianco et al. 2011, Trivedi & Bollmann 2013) (**Figure 5*d*,*e***). A neural correlate of this behavioral threshold size has been found in the activity of certain ganglion cells (Preuss et al. 2014, Semmelhack et al. 2014), suggesting that behaviorally relevant size classification begins in the retina. Further downstream, object size is represented in different populations of tectal neurons in the periventricular layer, suggesting a central role for the tectum in object size–dependent behavioral choice (Preuss et al. 2014). Furthermore, the size threshold for orienting behavior in another discrimination assay that uses approaching objects appears to be under modulatory control from serotonergic neurons projecting from the raphe nucleus to the tectum, potentially biasing the tectally mediated choice toward avoidance behavior during states of satiety (Barker & Baier 2015, Filosa et al. 2016).

4.2.4. Escape responses to looming stimuli. Perhaps the most effective visual stimulus for driving avoidance responses in zebrafish is a dark expanding shape such as a disc or rectangle resembling a looming object on a collision path that may activate a pathway for visually evoked fear conserved from fish to mammals (Carr 2015). Looming-evoked escape has long been known in adult zebrafish (Dill 1974), but in recent efforts that address the behavior in the larval model (Temizer et al. 2015, Dunn et al. 2016a, Bhattacharyya et al. 2017, Nair et al. 2017), the underlying pathways have come under closer scrutiny (**Figure 5*f–h***). Imaging activity in retinal ganglion cell axons suggests that the processing of looming-evoked activity occurs predominantly in the deeper layers of the tectal neuropil (Temizer et al. 2015), and models of the timing of tectal cell responses indicate that defined population activity shaped by tectal horizontal cells is involved in triggering the response (Dunn et al. 2016a).

In addition to a direct retinotectal pathway, an indirect pathway involving tectum-projecting neurons in the thalamus may modulate looming responses (Heap et al. 2018). As in other model systems, the looming response is relatively independent from approach speed and occurs when stimulus size reaches a fixed threshold that, curiously, appears to depend on whether the stimulus comes from the bottom or from the side (Temizer et al. 2015, Dunn et al. 2016a, Bhattacharyya et al. 2017). Notably, however, the approach speed of the object has an effect on the variability of the escape trajectory, as slower approaches trigger more variable escape paths and faster approaches trigger more stereotypical, fast escapes (Bhattacharyya et al. 2017). Using light field imaging in the hindbrain, Bhattacharyya and colleagues (2017) compared behavioral variability with neural activity measured simultaneously in a larger set of identifiable spinal projection neurons, including the Mauthner cell, from which distinct roles could be inferred in controlling the timing and kinematic variability of the behavior.

Another circuit motif implicated in the selection of looming responses is a dopaminergic hypothalamus-to-hindbrain connection that may enable escape responses through looming-evoked disinhibition of spinal projection neurons (Yao et al. 2016). Of note, Lovett-Barron et al. (2017) recently used the larval looming response to assess the modulation of alertness levels. The authors identified several peptidergic, monoaminergic, and cholinergic populations implicated in

behavior modulation, thus adding new layers of complexity to a seemingly simple visuomotor transformation (Lovett-Barron et al. 2017).

5. TRANSFORMING THE BRAIN'S DECISIONS INTO ACTIONS: DESCENDING CONTROL OF SPINAL MOTOR CIRCUITS

Taken together, the emerging picture is that the variables of an impending movement pattern are computed using the available visual input and encoded in specific activity patterns that are distributed across multiple areas, while the actual movement is triggered when a critical threshold of activity is reached. Eventually, these activity patterns are translated at the time of movement into motor patterns via spinal cord circuitry. The mechanisms of this circuitry have already been elucidated in considerable detail thanks to comprehensive approaches relating structure to function at the light and electronmicroscopical levels (Hale et al. 2001; Higashijima et al. 2004; McLean et al. 2007, 2008; Bagnall & McLean 2014; Berg et al. 2018; Svara et al. 2018). Patterns of activity that signal the decision to move and the variables of the intended movement are routed to the spinal cord via projection neurons in the RS system. This system comprises several hundreds of descending projection neurons, among which a large subset of segmentally organized neurons in the mid- and hindbrain, including the two Mauthner cells and their segmental homologues, stands out because of their highly stereotyped morphologies (Kimmel et al. 1982, Metcalfe et al. 1986, Gahtan & O'Malley 2003). The roles of the Mauthner cell and its homologues MiD2cm and MiD3cm in controlling the kinematics of fast escape responses are firmly established (O'Malley et al. 1996, Liu & Fetcho 1999, Kohashi & Oda 2008).

In addition, recent work shows that, during looming-evoked escapes, activity in several other, more ventral projection neurons correlates with the kinematic variability of the responses; thus, the signals encoding the respective motor variables are distributed across a larger subset of the RS system (Bhattacharyya et al. 2017), similar to those encoding nonvisually evoked escapes (Gahtan et al. 2002). This seems also to apply to how neural activity in RS neurons is organized when a larva swims more slowly, as occurs during OMR, phototaxis, and spontaneous swimming. For example, some projection neurons in the midbrain nucMLF probably relay the symmetrically descending drive for forward swimming, whereas ventromedial spinal projection neurons in the hindbrain signal an asymmetric command component about the intended turning amplitude (Orger et al. 2008, Huang et al. 2013). Furthermore, some nucMLF neurons may be involved in asymmetrical tail movements for steering (Thiele et al. 2014). With recent development and application of combined 3D optogenetic activation and functional imaging approaches in the larval mid- and hindbrain, the causal role of small sets of nucMLF neurons in controlling motor variables can now be further dissected (Dal Maschio et al. 2017).

The time at which a motor pattern is executed depends on when neural activity exceeds a certain threshold, but where in the visuomotor pathway this threshold is implemented is still poorly understood. A possibility is that the central pattern generators in the spinal cord represent a threshold by requiring a certain level of descending activity before motoneurons are recruited (Wang & McLean 2014). However, at least for the Mauthner cell, and perhaps also in nucMLF neurons active during OMR, suprathreshold activity always correlates with motor output (O'Malley et al. 1996, Severi et al. 2014, Thiele et al. 2014, Bhattacharyya et al. 2017). As such, a threshold mechanism may be located further upstream, which could be implemented in multiple thresholds operating as a logical AND gate. This raises the question of how visually responsive centers in the midbrain and diencephalon are synaptically connected with spinal projection neurons in the RS system, about which little is known. For escapes evoked by somatosensory or auditory/vestibular stimulation, circuit motifs within the local hindbrain network that shape the behavioral response

have been discovered (Koyama et al. 2011, 2016; Lacoste et al. 2015). However, the way in which neural activity encoding visual features is relayed and integrated in RS neurons is poorly understood. There are several possibilities, including direct connections from the tectum (Sato et al. 2007, Helmbrecht et al. 2018), from the pretectum (Semmelhack et al. 2014), or from visually responsive dopaminergic neurons in the hypothalamus and posterior tuberculum (McLean & Fetcho 2004, Tay et al. 2011, Reinig et al. 2017) as well as potential tonic turning bias from the hindbrain oscillator (Dunn et al. 2016b, Wolf et al. 2017). Determining the synaptic organization of the network layers between visual centers and the RS system is the next important step for obtaining a comprehensive understanding of visuomotor transformation in this vertebrate model.

6. CONCLUSIONS AND FUTURE DIRECTIONS

In summary, we now know where in the brain of young larvae, down to the cellular level, steps within visuomotor transformations take place. For example, we know where feature extraction and stimulus classification occur at the input level and where motor variables are encoded at the output level. What are the next major challenges?

In the longer term, the first challenge is to improve and extend the methods currently used to study circuits in the brain of 5- to 9-day-old larvae so they can be used to elucidate what has changed in older larvae and juvenile fish as a consequence of circuit development. The promise of such methodological efforts is the identification of new circuit components in the intact brain whose functional refinement correlates with new categories of behavior that emerge in the first 3 to 4 weeks of development. Among those behaviors is the preference for the presence of conspecifics, which is a form of visually mediated social behavior (Dreosti et al. 2015, Hinz & de Polavieja 2017, Stowers et al. 2017, Larsch & Baier 2018). Another is visually mediated associative learning, in the form of classical or operant conditioning, which becomes increasingly robust over the course of the first 4 weeks (Aizenberg & Schuman 2011, Valente et al. 2012, Hinz et al. 2013, Roberts et al. 2013, Matsuda et al. 2017). Functional imaging approaches with cellular resolution in the intact brain have now been extended to ~3-week-old fish (Vendrell-Llopis & Yaksi 2015, Matsuda et al. 2017, Bergmann et al. 2018), indicating that functional analysis of circuits underlying more complex behaviors should become possible. Of note, owing to its small size and transparent skin even during adulthood, the teleost species *Danionella translucida* may provide complementary opportunities for studying visual circuit function in the adult brain (Schulze et al. 2018).

The second challenge arising directly from studying visuomotor transformation in young larvae is completeness: There is a gap between input and output levels in the system (**Figure 1**) where the precise connectivity is largely unknown. To close this gap, several steps have already been taken. For example, the full locomotor repertoire has been broken down into elementary components using an unsupervised clustering approach to obtain context- and stimulus-dependent ethograms (Marques et al. 2018). This knowledge should help clarify whether specific intermediate circuit components independently control distinct motor components. Progress is also being made in the analysis of whole-brain imaging data that allows one to better distinguish at the single-cell level between visually driven and motor-related activity and to identify intermediate cellular clusters where activity evoked by different stimulus types appears to converge (Chen et al. 2018).

The third challenge is to image distributed neural activity at high spatiotemporal resolution in freely moving larvae. Recent improvements in the methodology (Muto et al. 2013, Cong et al. 2017, Kim et al. 2017, Symvoulidis et al. 2017) should eventually enable investigations, for example, of how somatosensory and vestibular feedback during swimming affect visuomotor transformation. Future work may also benefit from using more naturalistic stimulus conditions, which have varied in earlier work such that, frequently, limited bands of the visible spectrum were

used and different regions of the visual field were stimulated, making some results difficult to compare. Beyond improvements in imaging technology, it will also be important to determine the functional properties of synapses within and between processing centers using electrophysiological recordings, which are indispensable for resolving how synaptic properties shape the function of a circuit—think of decades of electrophysiological recordings in the retina, without which our current unparalleled understanding of retinal processing would not have been possible. Ultimately, the combination of functional imaging, electrophysiology, optogenetic manipulations, pharmacology, and morphological reconstructions at light and electronmicroscopical levels that is possible only in the larval zebrafish brain should enable research to close the gap between input and output and build a comprehensive understanding of visuomotor transformation in the vertebrate brain.

SUMMARY POINTS

1. Larval zebrafish provide unique opportunities for studying the neural basis of visual behaviors in an intact vertebrate nervous system, where the merits of state-of-the-art genetic, functional, and anatomical analyses can be combined.
2. Similar to the mammalian retina, the retina of larval zebrafish extracts information about different features of the visual scene, such as contrast, color, object size, motion direction, and whole-field optic flow, and encodes it in patterns of activity in different types of ganglion cells.
3. Where in the brain the axons of retinal ganglion cells terminate is known in anatomical detail. Imaging neural activity in vivo reveals how these feature-sensitive inputs from the retina form functional topographic maps and feature-specific layers or subregions in retinorecipient areas.
4. Circuits controlling stabilizing behaviors in response to whole-field optic flow (OMR, OKR) are localized in the pretectum, where they integrate signals from both eyes as an early step for generating appropriate motor commands in downstream oculomotor circuits and reticulospinal command neurons. The connectivity between visual and motor centers remains to be established.
5. Larvae robustly respond to external object motion with directed turning behavior, depending on stimulus properties such as size, speed, or rate of expansion. Some of the early processing steps are likely mediated by distinct cell types with corresponding feature selectivities and specific synaptic connectivity in the optic tectum.
6. Whole-brain imaging suggests new roles for intermediate regions to modulate visuomotor transformations in the larval brain. For example, activity in the olivo-cerebellar pathway and the serotonergic raphe nucleus correlates with gain changes in optomotor behavior, and rhythmic activity in an anterior hindbrain population is associated with state transitions in directed motor behaviors.
7. Different variables of a visually evoked motor pattern, such as swim speed, frequency, and turning direction, are encoded in different sets of reticulospinal projection neurons. How these components of a composite motor command are programmed by upstream visual circuits is not well understood.
8. Key challenges now lie in identifying the anatomical and functional connectivity between visual and motor centers with cellular- and synaptic-level detail.

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LITERATURE CITED

Abbas F, Triplett MA, Goodhill GJ, Meyer MP. 2017. A three-layer network model of direction selective circuits in the optic tectum. *Front. Neural Circuits* 11:88

Ahrens MB, Li JM, Orger MB, Robson DN, Schier AF, et al. 2012. Brain-wide neuronal dynamics during motor adaptation in zebrafish. *Nature* 485:471–77

Ahrens MB, Orger MB, Robson DN, Li JM, Keller PJ. 2013. Whole-brain functional imaging at cellular resolution using light-sheet microscopy. *Nat. Methods* 10:413–20

Aizenberg M, Schuman EM. 2011. Cerebellar-dependent learning in larval zebrafish. *J. Neurosci.* 31:8708–12

Allison WT, Barthel LK, Skebo KM, Takechi M, Kawamura S, Raymond PA. 2010. Ontogeny of cone photoreceptor mosaics in zebrafish. *J. Comp. Neurol.* 518:4182–95

Antinucci P, Nikolaou N, Meyer MP, Hindges R. 2013. Teneurin-3 specifies morphological and functional connectivity of retinal ganglion cells in the vertebrate visual system. *Cell Rep.* 5:582–92

Antinucci P, Suleyman O, Monfries C, Hindges R. 2016. Neural mechanisms generating orientation selectivity in the retina. *Curr. Biol.* 26:1802–15

Avitan L, Pujic Z, Hughes NJ, Scott EK, Goodhill GJ. 2016. Limitations of neural map topography for decoding spatial information. *J. Neurosci.* 36:5385–96

Avitan L, Pujic Z, Molter J, Van De Poll M, Sun B, et al. 2017. Spontaneous activity in the zebrafish tectum reorganizes over development and is influenced by visual experience. *Curr. Biol.* 27:2407–19.e4

Baden T, Esposti F, Nikolaev A, Lagnado L. 2011. Spikes in retinal bipolar cells phase-lock to visual stimuli with millisecond precision. *Curr. Biol.* 21:1859–69

Baden T, Nikolaev A, Esposti F, Dreosti E, Odermatt B, Lagnado L. 2014. A synaptic mechanism for temporal filtering of visual signals. *PLOS Biol.* 12:e1001972

Bagnall MW, McLean DL. 2014. Modular organization of axial microcircuits in zebrafish. *Science* 343:197–200

Baier H. 2013. Synaptic laminae in the visual system: molecular mechanisms forming layers of perception. *Annu. Rev. Cell Dev. Biol.* 29:385–416

Barker AJ, Baier H. 2015. Sensorimotor decision making in the zebrafish tectum. *Curr. Biol.* 25:2804–14

Berg EM, Bjornfors ER, Pallucchi I, Picton LD, El Manira A. 2018. Principles governing locomotion in vertebrates: lessons from zebrafish. *Front. Neural Circuits* 12:73

Bergmann K, Meza Santoscoy P, Lygdas K, Nikolaeva Y, MacDonald RB, et al. 2018. Imaging neuronal activity in the optic tectum of late stage larval zebrafish. *J. Dev. Biol.* 6:6

Bhattacharyya K, McLean DL, MacIver MA. 2017. Visual threat assessment and reticulospinal encoding of calibrated responses in larval zebrafish. *Curr. Biol.* 27:2751–62.e6

Bianco IH, Engert F. 2015. Visuomotor transformations underlying hunting behavior in zebrafish. *Curr. Biol.* 25:831–46

Bianco IH, Kampff AR, Engert F. 2011. Prey capture behavior evoked by simple visual stimuli in larval zebrafish. *Front. Syst. Neurosci.* 5:101

Bilotta J, Saszik S. 2001. The zebrafish as a model visual system. *Int. J. Dev. Neurosci.* 19:621–29

Boulanger-Weill J, Candat V, Jouary A, Romano SA, Perez-Schuster V, Sumbre G. 2017. Functional interactions between newborn and mature neurons leading to integration into established neuronal circuits. *Curr. Biol.* 27:1707–20.e5

Briggman KL, Helmstaedter M, Denk W. 2011. Wiring specificity in the direction-selectivity circuit of the retina. *Nature* 471:183–88

Brockerhoff SE, Hurley JB, Janssen-Bienhold U, Neuhauss SC, Driever W, Dowling JE. 1995. A behavioral screen for isolating zebrafish mutants with visual system defects. *PNAS* 92:10545–49

Burgess HA, Schoch H, Granato M. 2010. Distinct retinal pathways drive spatial orientation behaviors in zebrafish navigation. *Curr. Biol.* 20:381–86

Burrill JD, Easter SS Jr.. 1994. Development of the retinofugal projections in the embryonic and larval zebrafish (*Brachydanio rerio*). *J. Comp. Neurol.* 346:583–600

Cang J, Savier E, Barchini J, Liu X. 2018. Visual function, organization, and development of the mouse superior colliculus. *Annu. Rev. Vis. Sci.* 4:239–62

Carr JA. 2015. I'll take the low road: the evolutionary underpinnings of visually triggered fear. *Front. Neurosci.* 9:414

Chen X, Engert F. 2014. Navigational strategies underlying phototaxis in larval zebrafish. *Front. Syst. Neurosci.* 8:39

Chen X, Mu Y, Hu Y, Kuan AT, Nikitchenko M, et al. 2018. Brain-wide organization of neuronal activity and convergent sensorimotor transformations in larval zebrafish. *Neuron* 100:876–90.e5

Cheng RK, Krishnan S, Lin Q, Kibat C, Jesuthasan S. 2017. Characterization of a thalamic nucleus mediating habenula responses to changes in ambient illumination. *BMC Biol.* 15:104

Chinen A, Hamaoka T, Yamada Y, Kawamura S. 2003. Gene duplication and spectral diversification of cone visual pigments of zebrafish. *Genetics* 163:663–75

Cong L, Wang Z, Chai Y, Hang W, Shang C, et al. 2017. Rapid whole brain imaging of neural activity in freely behaving larval zebrafish (*Danio rerio*). *eLife* 6:e28158

Connaughton VP, Graham D, Nelson R. 2004. Identification and morphological classification of horizontal, bipolar, and amacrine cells within the zebrafish retina. *J. Comp. Neurol.* 477:371–85

Connaughton VP, Nelson R. 2010. Spectral responses in zebrafish horizontal cells include a tetraphasic response and a novel UV-dominated triphasic response. *J. Neurophysiol.* 104:2407–22

Daie K, Goldman MS, Aksay ER. 2015. Spatial patterns of persistent neural activity vary with the behavioral context of short-term memory. *Neuron* 85:847–60

Dal Maschio M, Donovan JC, Helmbrecht TO, Baier H. 2017. Linking neurons to network function and behavior by two-photon holographic optogenetics and volumetric imaging. *Neuron* 94:774–89.e5

Del Bene F, Wyart C, Robles E, Tran A, Looger L, et al. 2010. Filtering of visual information in the tectum by an identified neural circuit. *Science* 330:669–73

Demb JB, Singer JH. 2015. Functional circuitry of the retina. *Annu. Rev. Vis. Sci.* 1:263–89

Dhande OS, Huberman AD. 2014. Retinal ganglion cell maps in the brain: implications for visual processing. *Curr. Opin. Neurobiol.* 24:133–42

Diamond JS. 2017. Inhibitory interneurons in the retina: types, circuitry, and function. *Annu. Rev. Vis. Sci.* 3:1–24

Dill LM. 1974. The escape response of the zebra danio (*Brachydanio rerio*) I. The stimulus for escape. *Anim. Behav.* 22:711–22

Dreosti E, Esposti F, Baden T, Lagnado L. 2011. In vivo evidence that retinal bipolar cells generate spikes modulated by light. *Nat. Neurosci.* 14:951–52

Dreosti E, Lopes G, Kampff AR, Wilson SW. 2015. Development of social behavior in young zebrafish. *Front. Neural Circuits* 9:39

Dreosti E, Vendrell Llopis N, Carl M, Yaksi E, Wilson SW. 2014. Left-right asymmetry is required for the habenulae to respond to both visual and olfactory stimuli. *Curr. Biol.* 24:440–45

Dunn TW, Gebhardt C, Naumann EA, Riegler C, Ahrens MB, et al. 2016a. Neural circuits underlying visually evoked escapes in larval zebrafish. *Neuron* 89:613–28

Dunn TW, Mu Y, Narayan S, Randlett O, Naumann EA, et al. 2016b. Brain-wide mapping of neural activity controlling zebrafish exploratory locomotion. *eLife* 5:e12741
Easter SS Jr., Nicola GN. 1996. The development of vision in the zebrafish (*Danio rerio*). *Dev. Biol.* 180:646–63
Emran F, Rihel J, Adolph AR, Wong KY, Kraves S, Dowling JE. 2007. OFF ganglion cells cannot drive the optokinetic reflex in zebrafish. *PNAS* 104:19126–31
Esposti F, Johnston J, Rosa JM, Leung KM, Lagnado L. 2013. Olfactory stimulation selectively modulates the OFF pathway in the retina of zebrafish. *Neuron* 79:97–110
Euler T, Detwiler PB, Denk W. 2002. Directionally selective calcium signals in dendrites of starburst amacrine cells. *Nature* 418:845–52
Euler T, Haverkamp S, Schubert T, Baden T. 2014. Retinal bipolar cells: elementary building blocks of vision. *Nat. Rev. Neurosci.* 15:507–19
Fajardo O, Zhu P, Friedrich RW. 2013. Control of a specific motor program by a small brain area in zebrafish. *Front. Neural Circuits* 7:67
Fernandes AM, Fero K, Arrenberg AB, Bergeron SA, Driever W, Burgess HA. 2012. Deep brain photoreceptors control light-seeking behavior in zebrafish larvae. *Curr. Biol.* 22:2042–47
Filosa A, Barker AJ, Dal Maschio M, Baier H. 2016. Feeding state modulates behavioral choice and processing of prey stimuli in the zebrafish tectum. *Neuron* 90:596–608
Franke K, Baden T. 2017. General features of inhibition in the inner retina. *J. Physiol.* 595:5507–15
Friedrich RW, Jacobson GA, Zhu P. 2010. Circuit neuroscience in zebrafish. *Curr. Biol.* 20:R371–81
Gabriel JP, Trivedi CA, Maurer CM, Ryu S, Bollmann JH. 2012. Layer-specific targeting of direction-selective neurons in the zebrafish optic tectum. *Neuron* 76:1147–60
Gahtan E, Baier H. 2004. Of lasers, mutants, and see-through brains: functional neuroanatomy in zebrafish. *J. Neurobiol.* 59:147–61
Gahtan E, O'Malley DM. 2003. Visually guided injection of identified reticulospinal neurons in zebrafish: a survey of spinal arborization patterns. *J. Comp. Neurol.* 459:186–200
Gahtan E, Sankrithi N, Campos JB, O'Malley DM. 2002. Evidence for a widespread brain stem escape network in larval zebrafish. *J. Neurophysiol.* 87:608–14
Gahtan E, Tanger P, Baier H. 2005. Visual prey capture in larval zebrafish is controlled by identified reticulospinal neurons downstream of the tectum. *J. Neurosci.* 25:9294–303
Gandhi NJ, Katnani HA. 2011. Motor functions of the superior colliculus. *Annu. Rev. Neurosci.* 34:205–31
Godinho L, Mumm JS, Williams PR, Schroeter EH, Koerber A, et al. 2005. Targeting of amacrine cell neurites to appropriate synaptic laminae in the developing zebrafish retina. *Development* 132:5069–79
Grama A, Engert F. 2012. Direction selectivity in the larval zebrafish tectum is mediated by asymmetric inhibition. *Front. Neural Circuits* 6:59
Hale ME, Ritter DA, Fetcho JR. 2001. A confocal study of spinal interneurons in living larval zebrafish. *J. Comp. Neurol.* 437:1–16
Heap LA, Goh CC, Kassahn KS, Scott EK. 2013. Cerebellar output in zebrafish: an analysis of spatial patterns and topography in eurydendroid cell projections. *Front. Neural Circuits* 7:53
Heap LAL, Vanwalleghem G, Thompson AW, Favre-Bulle IA, Scott EK. 2018. Luminance changes drive directional startle through a thalamic pathway. *Neuron* 99:293–301.e4
Helmbrecht TO, Dal Maschio M, Donovan JC, Koutsouli S, Baier H. 2018. Topography of a visuomotor transformation. *Neuron* 100:1429–45.e4
Higashijima S, Schaefer M, Fetcho JR. 2004. Neurotransmitter properties of spinal interneurons in embryonic and larval zebrafish. *J. Comp. Neurol.* 480:19–37
Hinz FI, Aizenberg M, Tushev G, Schuman EM. 2013. Protein synthesis-dependent associative long-term memory in larval zebrafish. *J. Neurosci.* 33:15382–87
Hinz RC, de Polavieja GG. 2017. Ontogeny of collective behavior reveals a simple attraction rule. *PNAS* 114:2295–300
Horstick EJ, Bayleyen Y, Sinclair JL, Burgess HA. 2017. Search strategy is regulated by somatostatin signaling and deep brain photoreceptors in zebrafish. *BMC Biol.* 15:4
Huang KH, Ahrens MB, Dunn TW, Engert F. 2013. Spinal projection neurons control turning behaviors in zebrafish. *Curr. Biol.* 23:1566–73

Hunter PR, Lowe AS, Thompson ID, Meyer MP. 2013. Emergent properties of the optic tectum revealed by population analysis of direction and orientation selectivity. *J. Neurosci.* 33:13940–45

Joshua M, Lisberger SG. 2015. A tale of two species: neural integration in zebrafish and monkeys. *Neuroscience* 296:80–91

Jusuf PR, Harris WA. 2009. Ptf1a is expressed transiently in all types of amacrine cells in the embryonic zebrafish retina. *Neural Dev.* 4:34

Kawashima T, Zwart MF, Yang CT, Mensh BD, Ahrens MB. 2016. The serotonergic system tracks the outcomes of actions to mediate short-term motor learning. *Cell* 167:933–46.e20

Kim DH, Kim J, Marques JC, Grama A, Hildebrand DGC, et al. 2017. Pan-neuronal calcium imaging with cellular resolution in freely swimming zebrafish. *Nat. Methods* 14:1107–14

Kimmel CB, Powell SL, Metcalfe WK. 1982. Brain neurons which project to the spinal cord in young larvae of the zebrafish. *J. Comp. Neurol.* 205:112–27

Kinkhabwala A, Riley M, Koyama M, Monen J, Satou C, et al. 2011. A structural and functional ground plan for neurons in the hindbrain of zebrafish. *PNAS* 108:1164–69

Kita EM, Scott EK, Goodhill GJ. 2015. Topographic wiring of the retinotectal connection in zebrafish. *Dev. Neurobiol.* 75:542–56

Knogler LD, Markov DA, Dragomir EI, Stih V, Portugues R. 2017. Sensorimotor representations in cerebellar granule cells in larval zebrafish are dense, spatially organized, and non-temporally patterned. *Curr. Biol.* 27:1288–302

Kohashi T, Oda Y. 2008. Initiation of Mauthner- or non-Mauthner-mediated fast escape evoked by different modes of sensory input. *J. Neurosci.* 28:10641–53

Koyama M, Kinkhabwala A, Satou C, Higashijima S, Fetcho J. 2011. Mapping a sensory-motor network onto a structural and functional ground plan in the hindbrain. *PNAS* 108:1170–75

Koyama M, Minale F, Shum J, Nishimura N, Schaffer CB, Fetcho JR. 2016. A circuit motif in the zebrafish hindbrain for a two alternative behavioral choice to turn left or right. *eLife* 5:e16808

Krauzlis RJ, Bogadhi AR, Herman JP, Bollimunta A. 2018. Selective attention without a neocortex. *Cortex* 102:161–75

Kubo F, Hablitzel B, Dal Maschio M, Driever W, Baier H, Arrenberg AB. 2014. Functional architecture of an optic flow-responsive area that drives horizontal eye movements in zebrafish. *Neuron* 81:1344–59

Kunst M, Laurell E, Mokayes N, Kramer A, Kubo F, et al. 2019. A cellular-resolution atlas of the larval zebrafish brain. *Neuron* 103:21–38.e5

Lacoste AM, Schoppik D, Robson DN, Haesemeyer M, Portugues R, et al. 2015. A convergent and essential interneuron pathway for Mauthner-cell-mediated escapes. *Curr. Biol.* 25:1526–34

Larsch J, Baier H. 2018. Biological motion as an innate perceptual mechanism driving social affiliation. *Curr. Biol.* 28:3523–32.e4

Lee MM, Arrenberg AB, Aksay ER. 2015. A structural and genotypic scaffold underlying temporal integration. *J. Neurosci.* 35:7903–20

Liu KS, Fetcho JR. 1999. Laser ablations reveal functional relationships of segmental hindbrain neurons in zebrafish. *Neuron* 23:325–35

Lovett-Barron M, Andalman AS, Allen WE, Vesuna S, Kauvar I, et al. 2017. Ancestral circuits for the coordinated modulation of brain state. *Cell* 171:1411–23.e17

Lowe AS, Nikolaou N, Hunter PR, Thompson ID, Meyer MP. 2013. A systems-based dissection of retinal inputs to the zebrafish tectum reveals different rules for different functional classes during development. *J. Neurosci.* 33:13946–56

Marquart GD, Tabor KM, Brown M, Strykowski JL, Varshney GK, et al. 2015. A 3D searchable database of transgenic zebrafish Gal4 and Cre lines for functional neuroanatomy studies. *Front. Neural Circuits* 9:78

Marques JC, Lackner S, Felix R, Orger MB. 2018. Structure of the zebrafish locomotor repertoire revealed with unsupervised behavioral clustering. *Curr. Biol.* 28:181–95.e5

Masland RH. 2001. The fundamental plan of the retina. *Nat. Neurosci.* 4:877–86

Masland RH. 2012. The neuronal organization of the retina. *Neuron* 76:266–80

Masseck OA, Hoffmann KP. 2009. Comparative neurobiology of the optokinetic reflex. *Ann. N.Y. Acad. Sci.* 1164:430–39

Matsuda K, Yoshida M, Kawakami K, Hibi M, Shimizu T. 2017. Granule cells control recovery from classical conditioned fear responses in the zebrafish cerebellum. *Sci. Rep.* 7:11865

Matsui H, Namikawa K, Babaryka A, Koster RW. 2014. Functional regionalization of the teleost cerebellum analyzed in vivo. *PNAS* 111:11846–51

Mauss AS, Vlasits A, Borst A, Feller M. 2017. Visual circuits for direction selectivity. *Annu. Rev. Neurosci.* 40:211–30

McElligott MB, O'Malley DM. 2005. Prey tracking by larval zebrafish: axial kinematics and visual control. *Brain Behav. Evol.* 66:177–96

McLean DL, Fan J, Higashijima S, Hale ME, Fetcho JR. 2007. A topographic map of recruitment in spinal cord. *Nature* 446:71–75

McLean DL, Fetcho JR. 2004. Relationship of tyrosine hydroxylase and serotonin immunoreactivity to sensorimotor circuitry in larval zebrafish. *J. Comp. Neurol.* 480:57–71

McLean DL, Masino MA, Koh IY, Lindquist WB, Fetcho JR. 2008. Continuous shifts in the active set of spinal interneurons during changes in locomotor speed. *Nat. Neurosci.* 11:1419–29

Metcalfe WK, Mendelson B, Kimmel CB. 1986. Segmental homologies among reticulospinal neurons in the hindbrain of the zebrafish larva. *J. Comp. Neurol.* 251:147–59

Miri A, Daie K, Arrenberg AB, Baier H, Aksay E, Tank DW. 2011a. Spatial gradients and multidimensional dynamics in a neural integrator circuit. *Nat. Neurosci.* 14:1150–59

Miri A, Daie K, Burdine RD, Aksay E, Tank DW. 2011b. Regression-based identification of behavior-encoding neurons during large-scale optical imaging of neural activity at cellular resolution. *J. Neurophysiol.* 105:964–80

Mumm JS, Williams PR, Godinho L, Koerber A, Pittman AJ, et al. 2006. In vivo imaging reveals dendritic targeting of laminated afferents by zebrafish retinal ganglion cells. *Neuron* 52:609–21

Munch TA, da Silveira RA, Siegert S, Viney TJ, Awatramani GB, Roska B. 2009. Approach sensitivity in the retina processed by a multifunctional neural circuit. *Nat. Neurosci.* 12:1308–16

Muto A, Lal P, Ailani D, Abe G, Itoh M, Kawakami K. 2017. Activation of the hypothalamic feeding centre upon visual prey detection. *Nat. Commun.* 8:15029

Muto A, Ohkura M, Abe G, Nakai J, Kawakami K. 2013. Real-time visualization of neuronal activity during perception. *Curr. Biol.* 23:307–11

Nair A, Changsing K, Stewart WJ, McHenry MJ. 2017. Fish prey change strategy with the direction of a threat. *Proc. R. Soc. B* 284:2017.0393

Naumann EA, Fitzgerald JE, Dunn TW, Rihel J, Sompolinsky H, Engert F. 2016. From whole-brain data to functional circuit models: the zebrafish optomotor response. *Cell* 167:947–60.e20

Neuhauss SC. 2003. Behavioral genetic approaches to visual system development and function in zebrafish. *J. Neurobiol.* 54:148–60

Neuhauss SC, Biehlmaier O, Seeliger MW, Das T, Kohler K, et al. 1999. Genetic disorders of vision revealed by a behavioral screen of 400 essential loci in zebrafish. *J. Neurosci.* 19:8603–15

Niell CM, Smith SJ. 2005. Functional imaging reveals rapid development of visual response properties in the zebrafish tectum. *Neuron* 45:941–51

Nikolaev A, Leung KM, Odermatt B, Lagnado L. 2013. Synaptic mechanisms of adaptation and sensitization in the retina. *Nat. Neurosci.* 16:934–41

Nikolaou N, Lowe AS, Walker AS, Abbas F, Hunter PR, et al. 2012. Parametric functional maps of visual inputs to the tectum. *Neuron* 76:317–24

Nikolaou N, Meyer MP. 2015. Lamination speeds the functional development of visual circuits. *Neuron* 88:999–1013

Odermatt B, Nikolaev A, Lagnado L. 2012. Encoding of luminance and contrast by linear and nonlinear synapses in the retina. *Neuron* 73:758–73

O'Malley DM, Kao YH, Fetcho JR. 1996. Imaging the functional organization of zebrafish hindbrain segments during escape behaviors. *Neuron* 17:1145–55

Orger MB, Baier H. 2005. Channeling of red and green cone inputs to the zebrafish optomotor response. *Vis. Neurosci.* 22:275–81

Orger MB, Kampff AR, Severi KE, Bollmann JH, Engert F. 2008. Control of visually guided behavior by distinct populations of spinal projection neurons. *Nat. Neurosci.* 11:327–33

Patterson BW, Abraham AO, MacIver MA, McLean DL. 2013. Visually guided gradation of prey capture movements in larval zebrafish. *J. Exp. Biol.* 216:3071–83

Perez-Schuster V, Kulkarni A, Nouvian M, Romano SA, Lygdas K, et al. 2016. Sustained rhythmic brain activity underlies visual motion perception in zebrafish. *Cell Rep*. 17:1098–112

Pietri T, Romano SA, Perez-Schuster V, Boulanger-Weill J, Candat V, Sumbre G. 2017. The emergence of the spatial structure of tectal spontaneous activity is independent of visual inputs. *Cell Rep*. 19:939–48

Portugues R, Engert F. 2011. Adaptive locomotor behavior in larval zebrafish. *Front. Syst. Neurosci.* 5:72

Portugues R, Feierstein CE, Engert F, Orger MB. 2014. Whole-brain activity maps reveal stereotyped, distributed networks for visuomotor behavior. *Neuron* 81:1328–43

Preuss SJ, Trivedi CA, vom Berg-Maurer CM, Ryu S, Bollmann JH. 2014. Classification of object size in retinotectal microcircuits. *Curr. Biol.* 24:2376–85

Randlett O, Wee CL, Naumann EA, Nnaemeka O, Schoppik D, et al. 2015. Whole-brain activity mapping onto a zebrafish brain atlas. *Nat. Methods* 12:1039–46

Reinig S, Driever W, Arrenberg AB. 2017. The descending diencephalic dopamine system is tuned to sensory stimuli. *Curr. Biol.* 27:318–33

Roberts AC, Bill BR, Glanzman DL. 2013. Learning and memory in zebrafish larvae. *Front. Neural Circuits* 7:126

Robinson J, Schmitt EA, Harosi FI, Reece RJ, Dowling JE. 1993. Zebrafish ultraviolet visual pigment: absorption spectrum, sequence, and localization. *PNAS* 90:6009–12

Robles E, Laurell E, Baier H. 2014. The retinal projectome reveals brain-area-specific visual representations generated by ganglion cell diversity. *Curr. Biol.* 24:2085–96

Romano SA, Pietri T, Perez-Schuster V, Jouary A, Haudrechy M, Sumbre G. 2015. Spontaneous neuronal network dynamics reveal circuit's functional adaptations for behavior. *Neuron* 85:1070–85

Ronneberger O, Liu K, Rath M, Ruebeta D, Mueller T, et al. 2012. ViBE-Z: a framework for 3D virtual colocalization analysis in zebrafish larval brains. *Nat. Methods* 9:735–42

Rosa JM, Ruehle S, Ding H, Lagnado L. 2016. Crossover inhibition generates sustained visual responses in the inner retina. *Neuron* 90:308–19

Roska B, Meister M. 2014. The retina dissects the visual scene into distinct features. In *The New Visual Neurosciences*, ed. JS Werner, LM Chalupa, pp. 163–82. Cambridge, MA: MIT Press

Sanes JR, Masland RH. 2015. The types of retinal ganglion cells: current status and implications for neuronal classification. *Annu. Rev. Neurosci.* 38:221–46

Sato T, Hamaoka T, Aizawa H, Hosoya T, Okamoto H. 2007. Genetic single-cell mosaic analysis implicates ephrinB2 reverse signaling in projections from the posterior tectum to the hindbrain in zebrafish. *J. Neurosci.* 27:5271–79

Scalise K, Shimizu T, Hibi M, Sawtell NB. 2016. Responses of cerebellar Purkinje cells during fictive optomotor behavior in larval zebrafish. *J. Neurophysiol.* 116:2067–80

Schmitt EA, Dowling JE. 1999. Early retinal development in the zebrafish, *Danio rerio*: light and electron microscopic analyses. *J. Comp. Neurol.* 404:515–36

Schroeter EH, Wong RO, Gregg RG. 2006. *In vivo* development of retinal ON-bipolar cell axonal terminals visualized in *nyx::MYFP* transgenic zebrafish. *Vis. Neurosci.* 23:833–43

Schulze L, Henninger J, Kadobianskyi M, Chaigne T, Faustino AI, et al. 2018. Transparent *Danionella translucida* as a genetically tractable vertebrate brain model. *Nat. Methods* 15:977–83

Semmelhack JL, Donovan JC, Thiele TR, Kuehn E, Laurell E, Baier H. 2014. A dedicated visual pathway for prey detection in larval zebrafish. *eLife* 3:e04878

Severi KE, Portugues R, Marques JC, O'Malley DM, Orger MB, Engert F. 2014. Neural control and modulation of swimming speed in the larval zebrafish. *Neuron* 83:692–707

Song PI, Matsui JI, Dowling JE. 2008. Morphological types and connectivity of horizontal cells found in the adult zebrafish (*Danio rerio*) retina. *J. Comp. Neurol.* 506:328–38

Stowers JR, Hofbauer M, Bastien R, Griessner J, Higgins P, et al. 2017. Virtual reality for freely moving animals. *Nat. Methods* 14:995–1002

Stuermer CA. 1988. Retinotopic organization of the developing retinotectal projection in the zebrafish embryo. *J. Neurosci.* 8:4513–30
Svara FN, Kornfeld J, Denk W, Bollmann JH. 2018. Volume EM reconstruction of spinal cord reveals wiring specificity in speed-related motor circuits. *Cell Rep*. 23:2942–54
Sylvester SJG, Lee MM, Ramirez AD, Lim S, Goldman MS, Aksay ERF. 2017. Population-scale organization of cerebellar granule neuron signaling during a visuomotor behavior. *Sci. Rep.* 7:16240
Symvoulidis P, Lauri A, Stefanoiu A, Cappetta M, Schneider S, et al. 2017. NeuBtracker—imaging neurobehavioral dynamics in freely behaving fish. *Nat. Methods* 14:1079
Tabor KM, Marquart GD, Hurt C, Smith TS, Geoca AK, et al. 2019. Brain-wide cellular resolution imaging of Cre transgenic zebrafish lines for functional circuit-mapping. *eLife* 8:e42687
Tay TL, Ronneberger O, Ryu S, Nitschke R, Driever W. 2011. Comprehensive catecholaminergic projectome analysis reveals single-neuron integration of zebrafish ascending and descending dopaminergic systems. *Nat. Commun.* 2:171
Temizer I, Donovan JC, Baier H, Semmelhack JL. 2015. A visual pathway for looming-evoked escape in larval zebrafish. *Curr. Biol.* 25:1823–34
Thiele TR, Donovan JC, Baier H. 2014. Descending control of swim posture by a midbrain nucleus in zebrafish. *Neuron* 83:679–91
Thompson AW, Vanwalleghem GC, Heap LA, Scott EK. 2016. Functional profiles of visual-, auditory-, and water flow-responsive neurons in the zebrafish tectum. *Curr. Biol.* 26:743–54
Torvund MM, Ma TS, Connaughton VP, Ono F, Nelson RF. 2017. Cone signals in monostratified and bistratified amacrine cells of adult zebrafish retina. *J. Comp. Neurol.* 525:1532–57
Trivedi CA, Bollmann JH. 2013. Visually driven chaining of elementary swim patterns into a goal-directed motor sequence: a virtual reality study of zebrafish prey capture. *Front. Neural Circuits* 7:86
Valente A, Huang KH, Portugues R, Engert F. 2012. Ontogeny of classical and operant learning behaviors in zebrafish. *Learn. Mem.* 19:170–77
Vendrell-Llopis N, Yaksi E. 2015. Evolutionary conserved brainstem circuits encode category, concentration and mixtures of taste. *Sci. Rep.* 5:17825
Vishwanathan A, Daie K, Ramirez AD, Lichtman JW, Aksay ERF, Seung HS. 2017. Electron microscopic reconstruction of functionally identified cells in a neural integrator. *Curr. Biol.* 27:2137–47.e3
Wang K, Hinz J, Haikala V, Reiff DF, Arrenberg AB. 2019. Selective processing of all rotational and translational optic flow directions in the zebrafish pretectum and tectum. *BMC Biol*. 17:29
Wang WC, McLean DL. 2014. Selective responses to tonic descending commands by temporal summation in a spinal motor pool. *Neuron* 83:708–21
Wassle H. 2004. Parallel processing in the mammalian retina. *Nat. Rev. Neurosci.* 5:747–57
Wolf S, Dubreuil AM, Bertoni T, Bohm UL, Bormuth V, et al. 2017. Sensorimotor computation underlying phototaxis in zebrafish. *Nat. Commun.* 8:651
Yao Y, Li X, Zhang B, Yin C, Liu Y, et al. 2016. Visual cue-discriminative dopaminergic control of visuomotor transformation and behavior selection. *Neuron* 89:598–612
Yin C, Li X, Du J. 2019. Optic tectal superficial interneurons detect motion in larval zebrafish. *Protein Cell* 10:238–48
Yokogawa T, Hannan MC, Burgess HA. 2012. The dorsal raphe modulates sensory responsiveness during arousal in zebrafish. *J. Neurosci.* 32:15205–15
Yoshimatsu T, Williams PR, D'Orazi FD, Suzuki SC, Fadool JM, et al. 2014. Transmission from the dominant input shapes the stereotypic ratio of photoreceptor inputs onto horizontal cells. *Nat. Commun.* 5:3699
Zhang BB, Yao YY, Zhang HF, Kawakami K, Du JL. 2017. Left habenula mediates light-preference behavior in zebrafish via an asymmetrical visual pathway. *Neuron* 93:914–28.e4
Zhang RW, Li XQ, Kawakami K, Du JL. 2016. Stereotyped initiation of retinal waves by bipolar cells via presynaptic NMDA autoreceptors. *Nat. Commun.* 7:12650
Zhang RW, Wei HP, Xia YM, Du JL. 2010. Development of light response and GABAergic excitation-to-inhibition switch in zebrafish retinal ganglion cells. *J. Physiol.* 588:2557–69
Zimmermann MJY, Nevala NE, Yoshimatsu T, Osorio D, Nilsson DE, et al. 2018. Zebrafish differentially process color across visual space to match natural scenes. *Curr. Biol.* 28:2018–32.e5

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