Chapter 13
Functional Architecture of Lateral Line Afferent Neurons in Larval Zebrafish

James C. Liao

Abstract Fishes rely on the neuromasts of their lateral line system to detect water flow during behaviors such as predator avoidance and prey localization. While the pattern of neuromast development has been a topic of detailed research, we still do not understand the functional consequences of its organization. Previous work has demonstrated somatotopy in the posterior lateral line, whereby afferent neurons that contact more caudal neuromasts project more dorsally in the hindbrain than those that contact more rostral neuromasts. Recently, patch clamp recordings of posterior lateral line afferent neurons in larval zebrafish (*Danio rerio*) show that larger cells are born earlier, have a lower input resistance, a lower spontaneous firing rate, and tend to contact multiple neuromasts located closer to the tail than smaller neurons, which are born later, have a higher input resistance, a higher spontaneous firing rate, and tend to contact single neuromasts. These data indicate that early-born neurons are poised to detect large stimuli during the initial stages of development. Later-born neurons are more easily driven to fire and thus likely to be more sensitive to local, weaker flows. Afferent projections onto identified glutamatergic regions in the hindbrain suggest a novel mechanism for lateral line somatotopy, where afferent fibers associated with tail neuromasts respond to stronger stimuli and contact dorsal hindbrain regions associated with Mauthner-mediated escape responses and fast, avoidance swimming. The ability to process flow stimuli by circumventing higher order brain centers would ease the task of processing where speed is of critical importance.

Keywords Afferent neurons · Neuromast · Development · Electrophysiology · Flow sensing

J. C. Liao (✉)
The Whitney Laboratory for Marine Bioscience, Department of Biology,
University of Florida, 9505 Ocean Shore Boulevard, St. Augustine FL 32080, USA
e-mail: jliao@whitney.ufl.edu

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13.1 Introduction

The lateral line system consists of discrete clusters of hair cells and support cells that together make up the neuromasts, which in adult fishes either lie directly on the surface of the fish (superficial neuromasts), or associated with fluid-filled canals that are part of the scales (canal neuromasts). Fishes rely on their neuromasts to detect unsteady flows generated by predators, prey and physical obstacles (Coombs 1994; Montgomery et al. 2003; Chagnaud et al. 2006; Liao 2006; McHenry et al. 2009). Neuromasts are responsible for transmitting hydrodynamic information to afferent neurons, which in turn are relayed to the hindbrain (McCormick 1989; Montgomery et al. 1996; Coombs et al. 1998; Nicolson et al. 1998; Bleckmann 2008; Liao 2010). Experimental and modeling work has demonstrated that there are two main classes of lateral line sense organs, superficial and canal neuromasts, which respond to different aspects of the hydrodynamic stimulus, principally—flow velocity (i.e., shear stress) and flow acceleration (i.e., pressure gradients), respectively (Dijkgraaf 1963; Coombs et al. 1989; Montgomery et al. 2000; Engelmann et al. 2002; McHenry et al. 2008). Yet we still lack a framework to understand the overall *functional* organization of the lateral line system. For example, is there a functional significance to how neuromasts are organized along the body axis and how flow information is subsequently routed to the brain? Our ability to understand how this information is processed is greatly enhanced by knowing three things: (1) the number of neuromasts that an afferent fiber contacts, (2) how afferents vary in their response properties as a function of their age and the location of their contacted neuromast(s), and (3) how afferent projections are distributed to identified structures or processing areas in the hindbrain. This level of resolution is not possible in adult fishes, which can possess thousands of neuromasts. In contrast, the posterior lateral line of larval zebrafish (*Danio rerio*) (for which this chapter will focus on) has only a few dozen neuromasts and afferent neurons. Because of their optical transparency and the ease in which one can genetically label neurons with fluorescent proteins, larval zebrafish are emerging as a model system to study the organization of the lateral line during development (Alexandre and Ghysen 1999; Raible and Kruse 2000; Gompel et al. 2001; Ledent 2002; Nagiel et al. 2008; Faucherre et al. 2009; Sarrazin et al. 2010; Sato et al. 2010). The accessibility and tractability of the larval lateral line provides a unique opportunity to now look at a key aspect in lateral line processing that has never been possible with adult fishes; how do afferent physiology and their pattern of connectivity affect information transfer to the hindbrain?

13.2 Using Transgenic Fish to Reveal the Age of Afferent Neurons During Development

As illustrated in the timeline of Fig. 13.1, 5-day post fertilization (dpf) larvae have three distinct populations of neuromasts derived from two distinct placodes (Sarrazin et al. 2010). Placode I develop at 17 h post fertilization (hpf) and give

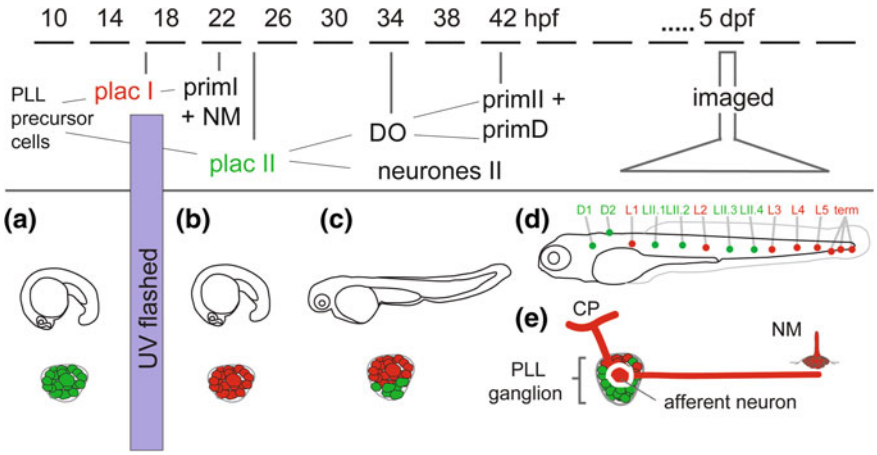

Fig. 13.1 Timeline of afferent neuron photoconversion in HuC:Kaede fish during the development of the posterior lateral line. **a** Initially all afferent neurons are *green* (e.g., at 10 h post fertilization, hpf). *Vertical gray bars* indicate approximate time of development. **b** When larvae are temporarily flashed with UV light at 17 hpf, all afferent neurons are converted to *red*. Neurons that subsequently develop after the UV flash are *green*. **c** When the lateral line ganglion is imaged at 5 days post fertilization (*dpf*), older cells are *red* and younger cells are *green*. **d** Neuromasts are not labeled by HuC:Kaede but are color-coded here to represent the age of the placode that they are derived from. L and terminal neuromasts are derived from placode I, while LII and D neuromasts are derived from placode II. **e** A single bipolar lateral line afferent neuron is highlighted to illustrate how information transduced by the neuromast hair cells are relayed to the hindbrain via central projections (*CP*). *plac* placode, *NM* neuromast, *prim* primordium, *D0* precursor cells. Adapted from Sarrazin et al. (2010)

rise to primordium I and its associated afferent neurons and L neuromasts (red neuromasts in Fig. 13.1d). Placode II develops around 24 hpf and gives rise to primordium II and primordium D, which in turn gives rise to more afferent neurons and the LII and D neuromast, respectively (green neuromast in Fig. 13.1d). In the transgenic line HuC:Kaede, larvae express a UV light-sensitive, photo-convertible protein under the control of a pan-neuronal promoter (Sato et al. 2006). This allows the ability to time-stamp afferent neurons to determine their relative stage of development. To do this, HuC:Kaede larvae are flashed with UV light for 10–20 s at 17 hpf. Under this protocol, all afferent neurons that are born at 17 hpf or before are imaged as red (older) and those that are born after 17 hpf are green (younger). Fish are then raised in the dark until they are imaged at 5 dpf. Note that while placodes give rise to both afferent neurons and neuromast hair cells, HuC:Kaede fish only label neurons and not hair cells. Because the larval lateral line system is experimentally accessible, single-cell labeling techniques can be used in combination with transgenic lines to reveal new information about afferent neurons. For example, old and young afferent cells can be targeted for electroporation and their projections down the body followed to confirm the number and location of neuromasts connected to that cell.

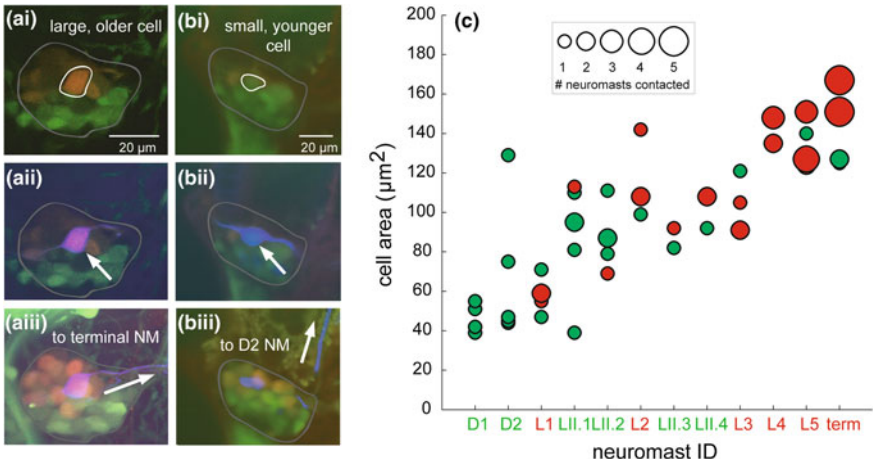

Fig. 13.2 Older and younger afferent neurons in HuC:Kaede larvae can be individually labeled to reveal the location and number of neuromasts contacted. **ai** A large, older cell (*red*) is targeted for labeling in the ganglion (*gray outline*). Dorsal is the *top of the image* and anterior is to the *left*. **aii** Upon successful electroporation the cell (*blue*) is double-labeled (*arrow*). **aiii** The merged image reveals a projection coursing down the body toward the terminal neuromasts of the tail (*arrow*). **bi** A small, younger cell (*green*) is targeted for labeling. **bii** The successfully electroporated cell is double-labeled. **biii** The merged image reveals a projection that rises sharply toward the D2 neuromast (*arrow*). **c** Plot of afferent somata size against the number and body location of the neuromast(s) that it contacts. The size of each data symbol represents the number of neuromasts contacted and the location of the data symbol along the *x*-axis indicates the caudal-most neuromast that the afferent cell contacts. Large, older afferents contact more neuromasts, of which the most caudal tend to be located closer to the tail compared to the neuromasts contacted by smaller, younger afferents. Neuromasts on the *x*-axis *label* are color-coded to symbolize the placode from which they were derived, as in Fig. 13.1e. *Red* indicates a neuromast derived from placode I while *green* indicates a neuromast derived from placode II. A discrepancy between afferent cell and neuromast color indicates that afferent cells are not restricted to contacting neuromasts derived from the same placode

13.3 Afferent Neuron Size and Connectivity is Related to Age

Older afferent neurons are found in the central and dorsal region of the posterior lateral line ganglion, while younger afferent neurons are located in the peripheral and ventral region (Liao 2010; Sato et al. 2010) (Fig. 13.1e). Older cells are significantly larger (Fig. 13.2a, 90.4 ± 13.7 µm^2) than younger cells (Fig. 13.2b, 63.5 ± 5.8 µm^2). More than half of afferent neurons (65 %) contact a single neuromast, and of these, the majority (79 %) consists of younger cells (Fig. 13.2c). Younger cells tend to contact neuromasts that are located closer to the head, although they may contact neuromasts located throughout the body. A smaller percentage of cells (21 %) contact two neuromasts, the majority (67 %) of which consists of older cells. It seems that only older cells contact three or more

neuromasts, which often include a terminal neuromast that is located near the tail. Afferent neurons that contact one terminal neuromast typically contact other terminal neuromasts, but can also contact other neuromasts along the body. Interestingly, afferent neurons are not limited to contacting neuromasts derived from the same primordium. Thus, older cells derived from primordium I can contact a neuromast derived from primordium II (e.g., LII neuromasts), and younger cells derived from primordium II can contact a neuromast derived from primordium I. Afferent cell area also differs according to the body location of the neuromast that it contacts. Younger cells that innervate anterior neuromasts are generally smaller than afferents that innervate more posterior neuromasts. For example, an afferent cell that innervates D2 is typically smaller than an afferent cell that innervates terminal neuromasts. In addition, combining labeling experiments with transgenic lines allows cell age to be correlated to its projection patterns to post-synaptic structures in the hindbrain. For example, afferent neurons can be electroporated in Vglut GFP larvae, which mark glutamatergic neurons with GFP (Higashijima et al. 2004), to look at afferent projections in the hindbrain.

13.4 Exploring Hindbrain Targets of Afferent Neuron Projections

Once flow information from the neuromasts is transferred to afferent neurons, it is routed to the hindbrain for further processing. Most of our understanding of the post-synaptic targets of afferent neurons comes from tract-tracing experiments in adult fishes, where lateral line nerve projections were found in at least four different regions: (1) the medial octavolateralis nucleus, (2) the Mauthner neuron, (3) the caudal nucleus, and (4) the eminentia granularis in the cerebellum (McCormick 1989). However, whole-nerve labeling studies in adult fishes do not provide the single-cell resolution needed to reveal relationships between neuromasts, afferent neurons and hindbrain structures that living larval zebrafish provide (Alexandre and Ghysen 1999; Liao 2010; Liao and Haehnel 2012; Pujol-Marti et al. 2012). In 5 dpf larvae, the central projections of the posterior lateral line are likely located in at least three of the regions identified in adults (Mueller and Wullimann 2005). The establishment of these connections in the brain indicates that the lateral line system is a functional and important sensory modality at an early life history stage.

Transgenic zebrafish are poised to make exciting advances in revealing lateral line contacts in the brain. By using transgenic lines that mark neurons expressing difference neurotransmitter phenotypes, the location of putative contacts can be identified. For example, experiments using vglut GFP fish reveal that afferent projections terminate onto the lateral-most glutamatergic hindbrain stripe, contacting the eminentia granularis, medial octavolateralis nucleus (MON), the Mauthner neurons, and possibly the caudal nucleus. (Fig. 13.3a–c). While there seem to be direct contacts onto glutamatergic neuropil corresponding to the MON

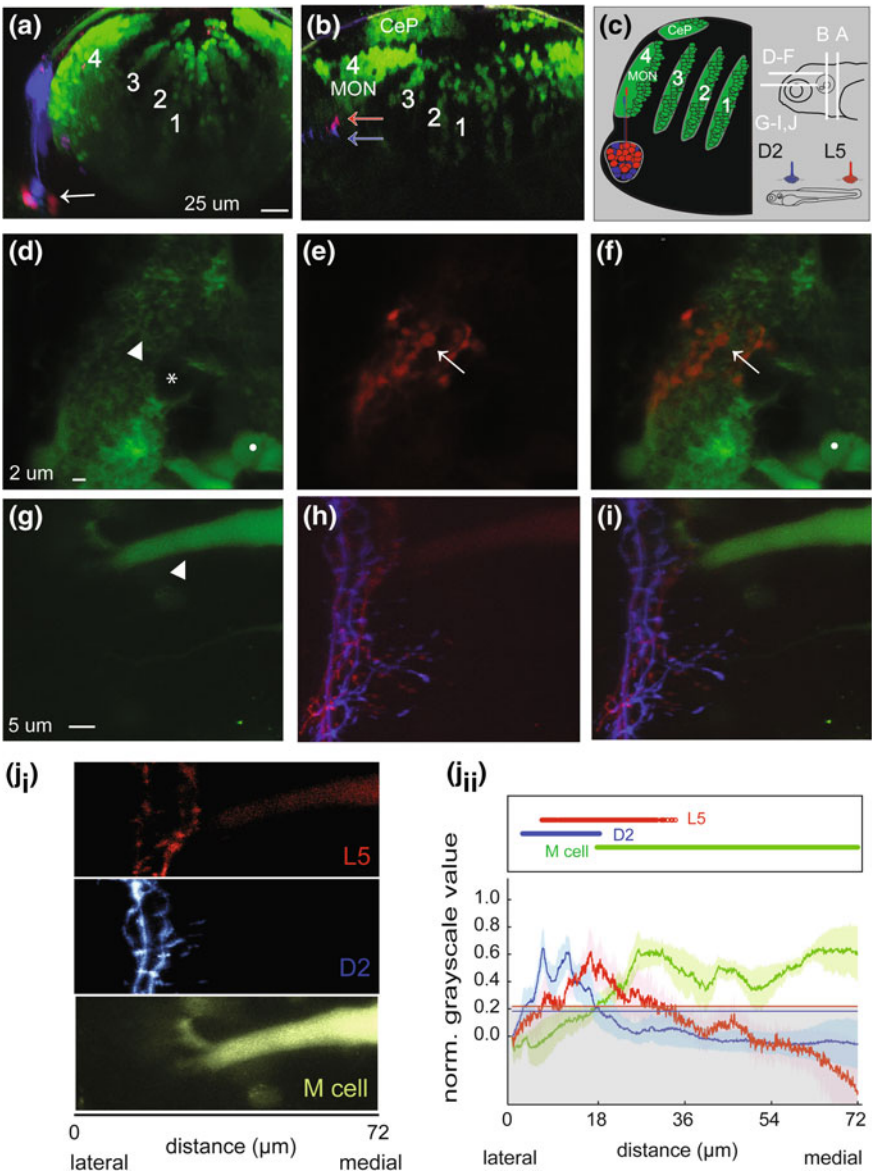

Fig. 13.3 Posterior lateral line afferent neurons contact identified post-synaptic targets in the hindbrain. **a** Afferent soma (*arrow*) labeled by backfilling at the site of a neuromast (D2 *blue*, L5 *red*) in a vglut GFP transgenic fish showing four glutamatergic stripes in one-half of the hindbrain seen in cross-section. **b** A more rostral hindbrain cross-section shows that afferent projections (*arrow*) of the L5 neuromast (*red*) projects more dorsally onto the neuropil of the fourth, lateral-most glutamatergic stripe than afferents associated with the D2 neuromast (*blue*). This region corresponds to the medial octavolateralis nucleus (*MON*) and lies ventral to the cerebellar plate (*CeP*). **c** Schematic of an image stack of (**a**) and (**b**) Medial-lateral position of. Diagram of the

◀ head where cross-sectional images were taken. **d** Glutamatergic neuropil (*arrowhead*) and soma (*dot*) in the MON of a vglut GFP transgenic fish. A cell that is not labeled with GFP is presumably not glutamatergic (*asterisk*). **e** Central projection terminals (*arrow*) of an afferent neuron connected to the L5 neuromast. **f** The merged image illustrates contacts onto glutamatergic neuropil, but not soma. **g** The lateral dendrite of the Mauthner cell. **h** Red projections of afferent neurons connected to the L5 neuromast lie medial to the blue projections associated with the D2 neuromast. **i** The merged image shows putative contacts of L5-associated afferent neurons with the lateral dendrite of the Mauthner cell. $\mathbf{j_i}$ Medial-lateral position of L5 and D2 afferent terminals relative to the Mauthner cell lateral dendrite. $\mathbf{j_{ii}}$ To quantify the spatial distribution for each of the three structures in J_i, grayscale pixel intensity was collapsed into a single mean value for each image column of pixels and plotted, along with the standard error, relative to a reference point in the hindbrain. The standard deviation of the intensity distribution was taken as a cut-off value to exclude background noise. Values above the cut-off are plotted in the top panel, which show that L5 hindbrain terminals start and end more medially than D2 terminals and possess more overlap with the Mauthner cell. Note that the cutoff line for the Mauthner cell is obscured by the cutoff line for the L5 projection

(Fig. 13.3d–f), there are no obvious contacts onto cell bodies, similar to general findings in adult fishes (McCormick 1989; Montgomery et al. 1996; New et al. 1996). Furthermore, afferents innervating neuromasts closer to the tail (i.e., L5) contact dorsal glutamatergic neuropil in the MON, while afferents innervating neuromasts closer to the head (i.e., D2) contact ventral neuropil (Fig. 13.3b)(Alexandre and Ghysen 1999; Liao and Haehnel 2012). In addition, afferent projections from L5 neuromasts project more medially than D2 neuromasts, making contact with the lateral dendrite of the Mauthner neuron (Fig. 13.3g–j_{ii}).

13.5 Intracellular Recordings of Lateral Line Afferent Neurons

Another strength of the zebrafish system is the ability to perform intracellular recordings in an undissected, behaving preparation, where the physiology is likely the closest to natural as possible. Recordings from afferent neurons show spontaneous spiking activity ranging from 5 to 50 Hz due to the constant release of glutamate from the hair cells of the neuromasts (Trapani and Nicolson 2011; Liao and Haehnel 2012). Whole-cell patch clamp recordings (Fig. 13.4a, b) reveal that afferent neurons possess excitable soma which can generate tonic firing in response to depolarizing current steps, both in the presence of spontaneous activity as well as when the cell is quieted by hyperpolarization (Fig. 13.4c, d).

The same recordings show differences in the intrinsic properties of afferent neurons residing in the same ganglion, suggesting that the sensory information transmitted from the neuromasts is functionally differentiated before it reaches the hindbrain (Liao and Haehnel 2012). Although cells display a continuum of sizes, cells which have an area smaller than $\sim 50\ \mu m^2$ tend to have a higher spontaneous firing frequency and are more excitable (e.g., have a higher input resistance) than cells larger than $\sim 100\ \mu m^2$ (Fig. 13.4e–h).

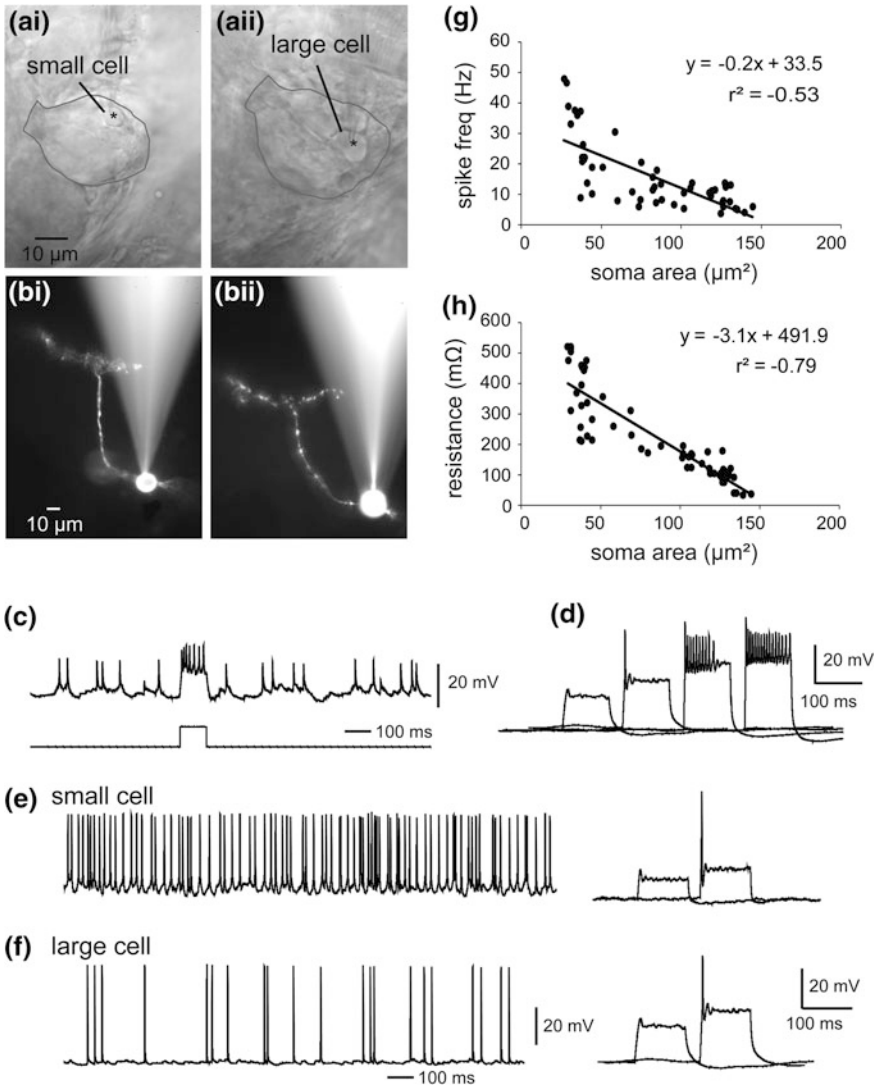

Fig. 13.4 Whole-cell patch clamp recordings of afferent neurons reveal differences in physiology with cell size. **ai–ii** Both small and large cells in the posterior lateral line ganglion can be targeted for recording with standard Nomarski optics. **bi–ii** Dye in the patch pipette labels the cell body and its projections to the neuromasts and hindbrain. **c** Afferent neurons are spontaneously active and increase their firing rate upon depolarization by current injection. **d** Increasing current injection step size elicits tonic firing. **e–f** Smaller cells have a higher spontaneous spike frequency and lower rheobase than larger cells. **g–h** There is an inverse relationship between soma area and spontaneous spike frequency, as well as between soma area and input resistance

The ability to record from single afferent neurons is an important technique that has allowed the first functional interpretation of lateral line somatotopy (Alexandre and Ghysen 1999; Gompel et al. 2001; Fame et al. 2006; Liao and Haehnel 2012). When these data are taken together with other work (Gompel et al. 2001; Pujol-Marti et al. 2010), it is clear that the intrinsic properties and projection patterns of afferent neurons match their birth date. Less excitable, older afferent neurons associated with caudal neuromasts project more dorsally into the hindbrain. These neurons have the largest soma, likely the largest axon diameters (Schellart and Kroese 2002), and have long projections that branch onto multiple neuromasts, resulting in a lower input resistance than later-born neurons. These older neurons are in a unique position to register stronger flow stimuli such as those generated from a predator (McHenry et al. 2009). In contrast, later-developing afferent neurons have smaller diameters, higher spontaneous firing rates, and lower thresholds for firing and are more inclined to contact single neuromasts (Nagiel et al. 2008). Younger afferents are therefore more excitable and may be better suited for detecting weaker flow stimuli in localized regions of the body, maturing perhaps to coincide with the onset of feeding and prey detection. A picture is emerging which suggests that a broad sensory scaffold is initially established by afferents and neuromasts derived from placode I to detect coarse flow, followed by a second wave of cells derived from placode II that would confer the ability to detect flow with greater sensitivity and finer spatial resolution. This architecture would separate different types of flow information at the periphery and likely ease the task of processing inputs at higher order brain centers such as the toris semicircularis (New et al. 1996; Plachta et al. 2003).

13.5.1 Single Neuromast Stimulation can Elicit Motor Behavior

In order to examine how lateral line inputs are correlated to motor output, it is possible to apply a controlled stimulus to a single neuromast while recording ventral root responses in a paralyzed preparation (Liao 2010; Liao and Haehnel 2012). To confirm that a neuromast is stimulated, the intracellular responses of afferent fibers are recorded while images of the deflected neuromast are captured by a high-speed video camera. Stimulation of a single terminal neuromast with a water jet shows that tail neuromasts play an important role in generating avoidances responses such as fast swimming and escapes (Fig. 13.5a). In contrast, there are fewer motor responses when a D2 neuromast (generally contacted by younger afferent neurons) is stimulated (Fig. 13.5b–d). The soma size of afferents contacting D2 and terminal neuromasts did not seem to be correlated to the elicited spike frequency (Fig. 13.5e).

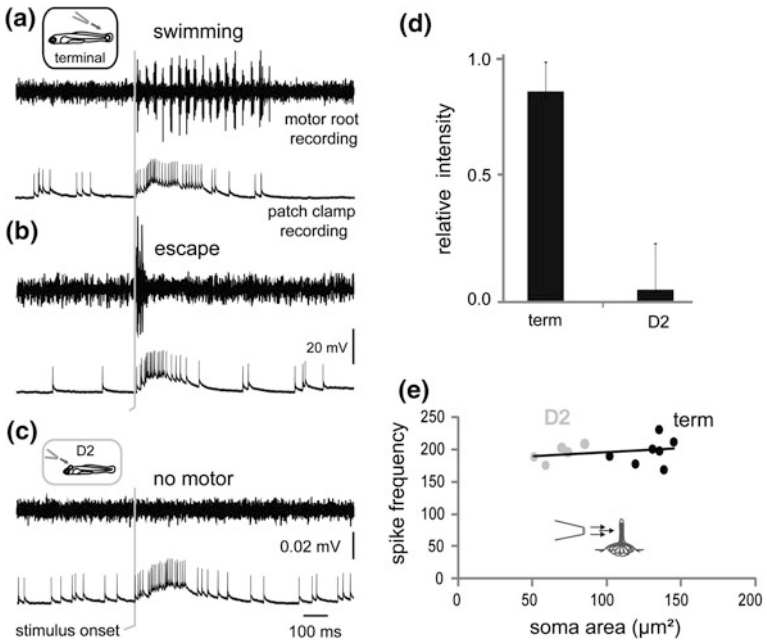

Fig. 13.5 Body location of a stimulated neuromast can determine the probability of a fictive motor response. A water jet directed at a terminal neuromast causes the connected afferent neuron to fire and elicits either a swimming (**a**), or escape response (**b**). **c** The same water jet stimulates the D2 neuromast but does not elicit a reliable motor response. **d** Across individuals there is more motor activity when a terminal neuromast is stimulated compared to a D2 neuromast. **e** A water jet to D2 and terminal neuromasts elicits no difference in afferent neuron spike frequency, suggesting that different projections into the hindbrain rather than spiking activity causes the distinct motor responses observed

13.5.2 Older Afferents are Involved in Fast Avoidance Behaviors

The age-related function we see in the afferent neurons of the lateral line system is part of a broader unifying principle of neuronal organization. This idea has a precedence in motor systems; in the spinal cord, large motor neurons and interneurons responsible for powerful movements develop first, while smaller motor neurons and interneurons develop later to facilitate finer motor control (Cope and Sokoloff 1999; Bhatt et al. 2007; McLean et al. 2007). In the hindbrain, neurons form distinct stripes with overlapping neurotransmitter and transcription factor phenotypes and are assembled according to the strength of an associated motor behavior (Kinkhabwala et al. 2010; Koyama et al. 2010). For example, in the medial-most glutamatergic stripe the dorsal neuropil is contacted by older, ventral neurons that are responsible for generating powerful movements such as fast swimming and the escape response. Similarly, in the lateral line system it seems

that there is a pattern whereby older afferents that contact multiple neuromasts are also integrated into neuronal stripe organization in the hindbrain. As in the medial glutamatergic stripe for motor systems, the dorsal neuropil in the lateral-most glutamatergic stripe in the lateral line system is also contacted by older cells, which are connected to tail neuromasts (Fig. 13.3b). In this way, the dorsal hindbrain projections of afferent neurons contacting tail neuromasts would be favorably positioned to quickly inform fast motor behaviors, leaving the projections of rostral neuromasts to direct slower motor behaviors.

The central projections of the lateral line have been documented to make extensive contacts to various regions of the brain. The MON is the first processing stage in an ascending lemniscal pathway that includes additional processing stages in the midbrain (torus semicircularis and optic tectum) and forebrain (McCormick 1989). There is also a direct connection between the lateral line and the Mauthner cell that confers an ability to quickly translate flow magnitude and direction into appropriate escape behaviors (Hatta and Korn 1999). The critically important speed of the Mauthner escape response has been shown to benefit from fewer processing stages involving both the anterior (Mirjany and Faber 2011) and posterior (Faber and Korn 1975) lateral line system (Eaton et al. 1977; Faber et al. 1989). Considering the physiology of afferent neurons and their pattern of contact onto hindbrain stripes, this idea suggests that the L5 neuromast–MON circuit could circumvent higher order processing centers in order to (1) make fine adjustments to swimming speed, and (2) provide another mechanism to initiate swimming in addition to the L5 neuromast–Mauthner cell circuit. Stimulation of terminal neuromasts can uniquely influence motor behaviors due to the intrinsic properties and hindbrain projections of their associated afferent neurons, given that there does not seem to be larger numbers of afferent representation for terminal neuromasts (Haehnel et al. 2011). In this way, selective stimulation of the larval lateral line may modulate a range of motor behaviors, from the initiation of escape responses to the modulation of swimming speed.

As zebrafish mature it is likely that the simple organization present at the larval stage becomes obscured through patterns of growth and plasticity (Gaze et al. 1974; Fraser 1983; Chiba et al. 1988). For instance, afferent neurons could selectively change their synaptic strengths with their hair cell partners. This process has been shown to play a part in focusing an originally distributed set of connections, such as in the visual cortex and neuromuscular junction (Bennett and Pettigrew 1974, 1975; Brown et al. 1976; Hubel et al. 1977; Thompson 1985). In addition to the physiological heterogeneity between afferent neurons that may arise from intrinsic channel density and activity (Eatock et al. 2008; Sarrazin et al. 2010; Trapani and Nicolson 2011), this raises the possibility that with age synaptic rearrangement can change the contact strength of older afferent neurons onto multiple neuromasts. This would increase the functional complexity of the system beyond what is documented here in larvae. These findings may turn out to be limited to early stages of development, but it is unlikely that this initial organization would be substantially re-arranged at later stages of growth. Instead, this

initial scaffold may be built upon and elaborated, rather than dismantled and reconstructed, according to current challenges that the hydrodynamic environment poses on the organism as it matures into adulthood.

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