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The Development of Eye Movements in the Zebrafish (Danio rerio)

ABSTRACT: *We investigated the development of oculomotor activity in zebrafish embryos and larvae of ages 48-96 hrs postfertilization (hpf). The optokinetic response (OKR: smooth tracking movements evoked by a rotating striped drum) improved steadily after its onset at 73 hpf, and by 96 hpf had a achieved a gain (eye velocity/drum velocity) of 0.9, comparable to adult performance. Reset movements (the fast phase of optokinetic nystagmus) developed over 75–81 hpf. The vestibuloocular reflex (VOR: compensatory eye movements evoked by passive rotation of the head) developed over 74–81 hpf, and the associated reset movements, over 76–81 hpf. The VOR was qualitatively normal in dark-reared fish, which excludes an essential role for visual experience in its early development. Spontaneous saccadic movements (the fast shift of eye position) appeared between 81 and 96 hpf, and at 96 hpf had maximum velocities that were comparable to adults.*

These results are compared to, and found to be incompatible with, two earlier ideas of motor development: behavioral "differentiation" and "encephalization."   © *1997 John Wiley & Sons, Inc.* Dev Psychobiol **31:** 267–276, 1997

Keywords: *optokinetic nystagmus; vestibuloocular reflex; saccade; extraocular muscles; compensatory eye movements*

INTRODUCTION

Eye movements accompany locomotion in adult fish, diminishing the movement of the retinal images and making them more amenable to neural extraction of visual information (Walls, 1942). Body rotations about the longitudinal and transverse axes of the fish (pitch and roll, respectively) evoke compensatory rotations of the eyes in the opposite direction, to maintain the cornea vertical and the dorsal side of the eye up. Rotations about the vertical axis (yaw) are compensated similarly; e.g., as the fish turns clockwise in the horizontal plane, the eyes rotate counterclockwise relative to the head, roughly maintaining their initial orientations. In contrast to the static compensation for roll and pitch, the compensation for yaw cannot be maintained when the magnitude of the turn exceeds the range of movement of the eyes, so the eyes periodically jump quickly to new positions. Thus the ambulatory fish's horizontal eye movements alternate between smooth movements in a direction opposite to the head rotation and fast reset movements in the same direction as the head (goldfish: Easter, Johns, & Heckenlively, 1974; shark: Harris, 1965). Motionless goldfish move their eyes infrequently, and then only by making saccades, the very rapid flick of the eye from one stable position to another; slow drifts are very uncommon (Easter et al, 1974). In sum, fish eye move-

ments are relatively simple, predictable, and comprehensible in the context of vision.

Both visual and vestibular signals contribute to the compensatory movements (Easter & Johns, 1974). Visually evoked smooth eye movements are typically studied in a laboratory setting with a rotating striped drum, and these movements are known as the optokinetic response (OKR). Similar eye movements evoked through the semicircular canals of the vestibular apparatus are known as the vestibuloocular reflex (VOR). The two reflexes synergize under normal circumstances, when the fish moves through a stationary world. Moreover, they are strongly linked functionally. In adult fish the effectiveness of the VOR [measured by the gain: (angular velocity of the eye)/(angular velocity of the head)] is set largely by the visual experience of the fish (Pastor, De La Cruz, & Baker, 1992, 1994b; Schairer & Bennett, 1986a, 1986b), and both reflexes share common neural circuits (Pastor, De La Cruz, & Baker, 1994a). Interactions of these reflexes during development have not been studied.

The saccade is a qualitatively different eye movement from the smooth compensatory movements of the OKR and VOR. The saccade is a rapid ballistic movement, effected by a two-phase motor program that is completed too quickly for any sensory information to influence it. The first phase is a large pulse of tension to move the eye quickly toward its new position, and the second phase is a much lower, sustained value of tension to keep the eye at its new position (Robinson, 1964). This complex motor program thus depends critically on the appropriate match of the two phases, because if the first phase is either too strong or too prolonged relative to the second phase, the eye will be carried past its final point (overshoot), and if it is not strong or long enough, the eye will undershoot. Although saccades and the fast resets associated with OKR and VOR are both very rapid, they are usually classified as separate movements. Neither have been studied in a developmental context.

In a recent article, we used OKR to investigate the ontogeny of vision (Easter & Nicola, 1996). Although we used tracking eye movements as behavioral indicants of vision, the first movements were sluggish and erratic, adequate for our purpose of determining that the fish could see but not of much help to the fish in stabilizing the retinal image or in resetting the eyes to a new position. In this article, we shift our attention from sensory reception to motor response, and describe the maturation of eye movements over roughly the 1st day posthatching.

Some of these results have previously been published as an abstract (Easter & Nicola, 1995).

METHODS

Fish

Embryos and larvae were obtained from our own outbred colony, and treated essentially as described earlier (Easter & Nicola, 1996; Wilson, Ross, Parrett, & Easter, 1990). Fertilized eggs were obtained daily with knowledge of the time of fertilization (to an accuracy of about 15 min). They were kept in petri dishes containing Embryo Rearing Solution (ERS: 0.004% $CaCl_2$, 0.0163% $MgSO_4$, 0.1% NaCl, 0.003% KCl, and a trace of methylene blue), inside an incubator at 28.5°C. When they were to be observed, individual fish were transferred one at a time into a petri dish filled with ERS, then viewed and videotaped in a dissecting microscope as visual or vestibular stimuli were presented (see below). All fish were used only once, at only one age.

Some fish were reared in the dark to assess the importance of visual experience in the development of the VOR. At 24 hpf or earlier, the eggs were placed inside petri dishes that had been spray-painted black on the outsides of both top and bottom halves and then checked visually to insure that there were no light leaks. They were placed inside an incubator with an opaque top and sides, and removed from the incubator minutes prior to observation. The first retinal axons arborize in the brain at about 48 hpf (Burrill & Easter, 1994; Stuermer, 1988), and the first outer segments appear on photoreceptors at about 60 hpf (Branchek & BreMiller, 1984) so dark-rearing that begins prior to 24 hpf deprives the fish of all visual experience.

Adult zebrafish were also examined. They were too active to allow them free movement, so their spinal cords were severed near the hindbrain (under deep anesthesia in 0.2% tricaine methanesulfonate) and after a recovery of several hours, they were videotaped similarly to the younger fish.

Stimuli

Visual. Embryos were removed from their chorion and positioned, dorsal surface up, in the petri dish. Hatchlings were similarly positioned. The arrangement has been described fully elsewhere (Easter & Nicola, 1996), but briefly, the fish were placed in a specially constructed, cylindrical glass chamber that rested on the center of the microscope stage and afforded the fish a panoramic view of the striped drum. The drum was visible to the fish over 360 degrees horizontally and 105 degrees vertically, including parts of both superior and inferior visual fields, and
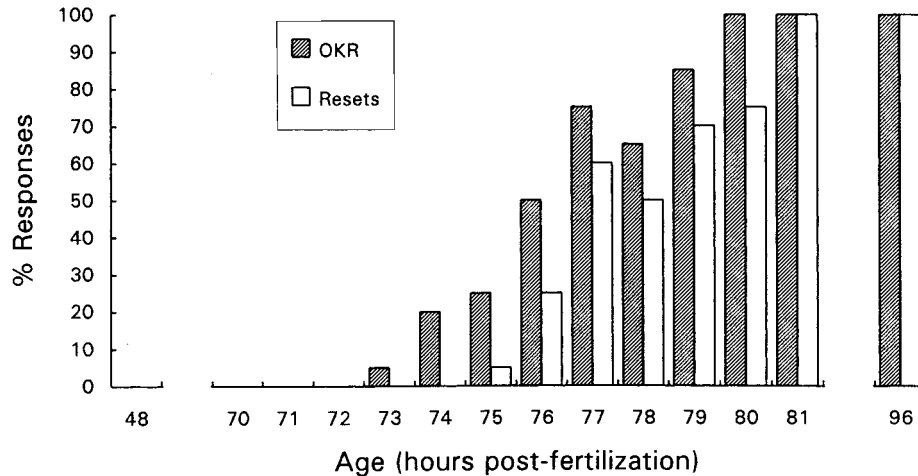
FIGURE 1 Onset of OKR and resets. The vertical axis shows the percentage of animals (of a total of 20 at each point) that responded to the rotating drum with either tracking (hatched bars) or resets (clear bars). A positive response for either implies that an animal made at least one tracking movement or reset during the time the drum was rotating. The data represented by the hatched bars were previously published (Easter & Nicola, 1996) and are included here for comparison with the clear bars and Figure 4.

was lined with alternating black-and-white vertical stripes, either 22.5 degrees or 45 degrees wide. The drum rotated around the vertical axis, either clockwise (CW) or counterclockwise (CCW), at velocities of 2.4 degrees/s and 6.5 degrees/s. Twenty fish were tested at each age: 48, 70–81 (1-hr intervals), and 96 hpf.

The three spinalized adult zebrafish were too large for this setup. They were submerged in water in a petri dish at the center of a larger drum lined with 22.5-degree stripes and which rotated at 13 degrees/s. Following the observation, the fish were anesthetized and killed by cardiac cut.

Vestibular. The VOR depends on stimuli originating in the inner ear, and if the influence of this organ is to be evaluated in isolation, visual stimuli must be absent. Accordingly, the embryo or larva was positioned inside a drop of ERS in the center of a small petri dish, the bottom of which had a featureless white tape covering it, and a vertical cylinder of the same white tape surrounded the fish, leaving visual access to the microscope from above. Thus, most of the fish's visual field, save only the opening to the microscope above, was featureless. The experimenter manually rotated the platform supporting the petri dish and the shield at approximately 18 degrees/s, alternating CW and CCW, about 10 s in each direction, for a minute. Nine to 20 fish were tested at each age: 48, 70–81 (1-hr intervals), and 96 hpf, and the VOR was noted as ei-

ther present or absent, with no measurement of its gain. None of the fish were tested for OKR.

Data Acquisition and Analysis

The video records were replayed and the three kinds of eye movement were scored: smooth compensatory (OKR or VOR), resets, and saccades. If an individual made one or more movement of a particular kind during the entire recording session, that individual was scored as responsive and the development of eye movements was quantified as the percent of the individuals that responded versus their ages (Figures 1 and 4).

In addition, the videotaped images were analyzed graphically to extract quantitative information about eye velocity. The video recorder (Panasonic Time Lapse Video Recorder AG 6050) could be advanced a single frame at a time, and the onscreen clock that was always recorded provided an internal calibration of the frame advance. The horizontal orientations of the eyes were measured on the monitor screen by drawing a line parallel to the plane of the pupil, and the angles formed by these lines and the body axis were tabulated. Tracking eye velocities were measured in 5 animals at each of four ages (72, 76, 78, and 96 hpf) tracking 2.4 degrees/s drum velocities. The angles and times at both start and finish of tracking movements were noted. The gain (eye velocity/drum

velocity) was calculated. In a few fish, single 25-s periods were examined in more detail by measuring the angles of the eyes and body axis every six frames (10-Hz sampling rate). The fine structure of saccades and resets was obtained by measuring the angles in every frame (60-Hz sampling rate).

RESULTS

OKR

OKR was first seen at 73 hpf, and the percentage of responsive fish increased steadily to reach 100% by 80 hpf (Easter & Nicola, 1996), as shown by the shaded bars in Figure 1. Figure 2 illustrates the eye movements with selected records of 3 fish, ages 72, 78, and 96 hpf, all surrounded by a drum with 22.5-degree stripes rotating clockwise at 2.4 degrees/s. The records are qualitatively and quantitatively different for the three. The 72 hpf fish (Figure 2a) did not track the drum most of the time, and when it did, the gain was low. It made no reset movements; following the brief episodes of tracking, the eyes remained at their new positions and then drifted imperceptibly back toward a more central position (not shown). The 78 hpf fish (Figure 2b) tracked for more of the time, with a higher gain than in the 72 hpf example, and made frequent resets, including one in this record, at about 12 s. The 96 hpf fish (Figure 2c) made a full-blown optokinetic nystagmus, with clockwise tracking movements interrupted regularly by resets (at 11 and 21 s in this record). Figure 3 illustrates graphically the increase in gain over this period. The gain at 96 hpf was about 0.9, comparable to adult performance in the goldfish (Easter, 1972). In sum, the fish's OKR improved over the 4th day of life from nonexistent to adultlike.

VOR

The VOR developed over nearly the same time course as OKR, but about an hour later (Figure 4: 74–81 hpf, compared with Figure 1: 73–80 hpf).

The similar time courses of the development of these two reflexes raises the possibility that the apparent VOR might actually be a cryptic OKR. In other words, the VOR tends to keep the angles of the eyes fixed in space as the head rotates, and this compensation could be achieved in the absence of a vestibular input, and driven by a visual signal, if the rotating fish could see some high-contrast part of the stationary world that lay beyond its featureless white shield. In the arena that we used, the only part of the stationary

world that was visible to the fish was the bottom of the microscope objective, and this was a relatively small window and had low contrast. We evaluated its potential role by rotating a high-contrast target (broad black-and-white stripes) in that area in the presence of stationary fish. It evoked no response, so we conclude that visual cues had been adequately blocked by the shield and the VOR had been adequately tested.

We examined the influence of visual experience on the VOR during embryogenesis by rearing some fish in total darkness. At 5 days postfertilization, an age when the VOR is normally well developed, the darkened containers were removed from the incubator and put onto the stage of the dissecting microscope and uncovered. Within the first few seconds of observation, it was evident that the fish that tilted laterally (as many do at this age) maintained their corneas vertical, so the vertical static response did not require any visual experience. The petri dishes were rotated manually about the vertical axis, and the body axis of those fish near the edge of the dish rotated in the same sense. They also made appropriate compensatory movements; i.e., their eyes counterrotated against the direction of head movement. We did not measure the gain of these movements, but qualitatively, they appeared normal. We conclude that VOR develops independently of visual experience, at least qualitatively.

Reset Movements and Saccades

Prior to 96 hpf, all rapid eye movements were resets made in connection with OKR or VOR, and their onset lagged about 2 hr after the onset of the compensatory show movements (Figures 1, 4). Spontaneous saccades were first noted at 96 hpf, so they must have appeared between 81 and 96 hpf. At 96 hpf, they were well coordinated; that is, the abrupt shift from one position to the next was generally achieved without big overshoots or undershoots (Figure 5a), suggesting that the two phases of the saccadic motor program were well matched from the beginning. Moreover, their velocities were roughly the same as in adults (Figure 5b). Like the compensatory slow movements, the fast movements also developed rapidly over the course of the 4th day of life, progressing from nonexistent to adultlike.
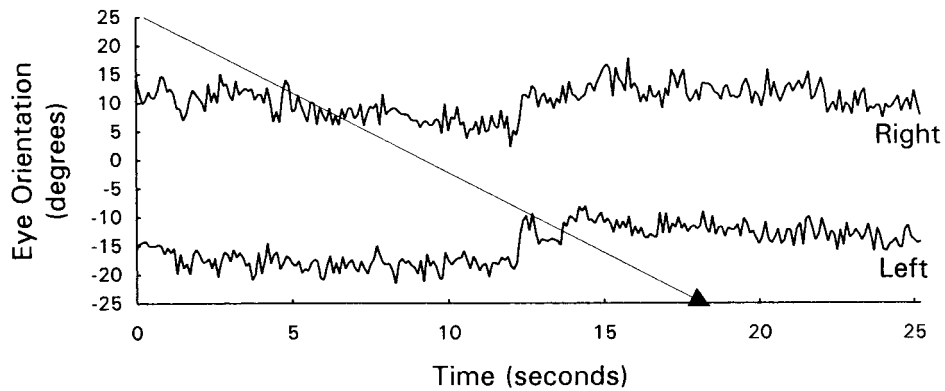
DISCUSSION

Development of Ocular Motor Function

The rapid improvement in eye movements during the 4th day—the progress from nonexistent saccades and
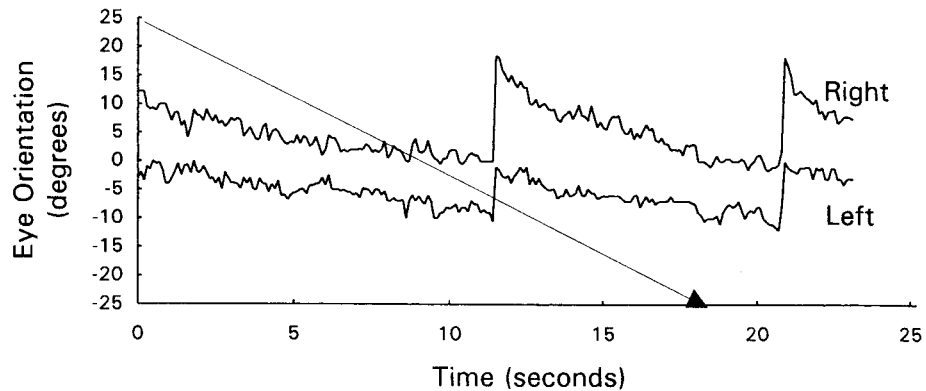
72 hpf
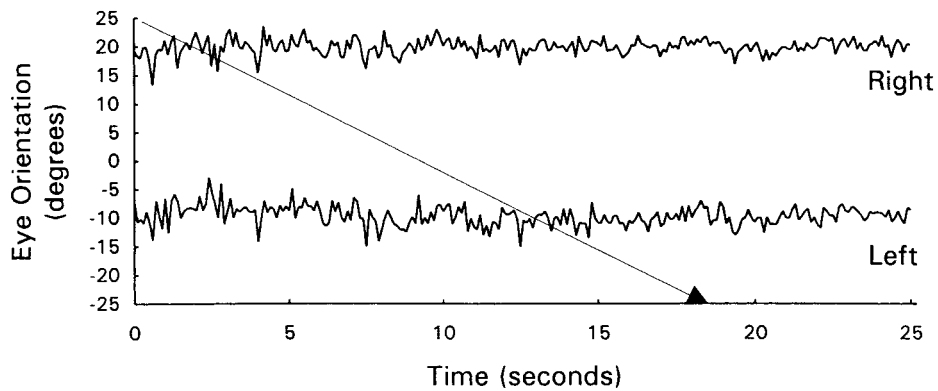
a

78 hpf

b

96 hpf

c

FIGURE 2 Records of OKR. The vertical axis shows the orientations of the eyes, sampled at 10 Hz, versus time. The high-frequency noise was mostly a result of the measurement process because it could be reduced significantly with replicate measurements of each position, but we judged that the reward was not worth the considerable extra effort. Throughout the 25-s episode in all three cases, the drum rotated clockwise at 2.5-degrees/s (see diagonal line) so if the eyes were tracking the drum accurately, they should have the same slope as the diagonal. Three different ages are shown: (a) 72 hpf, which tracked very sluggishly and without resets, (b) 78 hpf, which tracked more accurately and had infrequent resets, and (c) 96 hpf, which showed essentially adult behavior with accurate tracking and frequent resets.
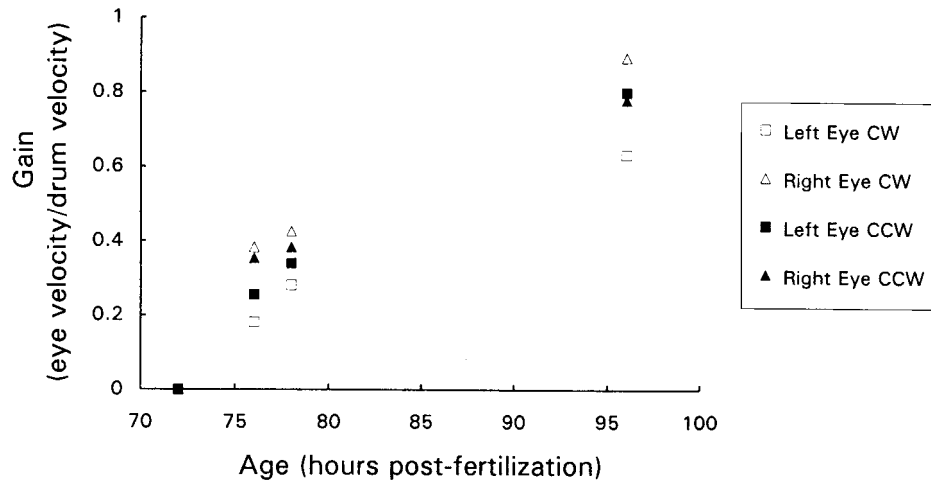
FIGURE 3   Gain of OKR (eye velocity/drum velocity, computed as described in the text) is plotted against the age of the fish. Abbreviations in legend: CW—clockwise rotation, CCW—counterwise rotation.

OKR to adult levels of both—was probably attributable to improved muscle function. Although all six extraocular muscles are present at 72 hpf, they enlarge considerably over the period 72–96 hpf, becoming thicker and increasing their contractile protein (Easter & Nicola, 1996).

The improvement of the gain of the OKR is presumably useful to the fish's ability to extract visual information as it moves through the water; a relatively stable visual image is more easily analyzed than one in motion, so the more accurately the eye movements

null out the image movement, the better the fish can analyze its surroundings.

In contrast to the universal utility of OKR, the role of saccades is quite variable, depending on the particulars of the visual system. In foveated animals, saccades are involved in the act of fixation ("looking at" an object, or imaging the object on the fovea) (reviewed by Robinson, 1968). But zebrafish, like all other fresh-water fish that have been examined, lack a fovea and do not fixate, so the saccades probably serve only to redirect the eyes, putting them in a position to
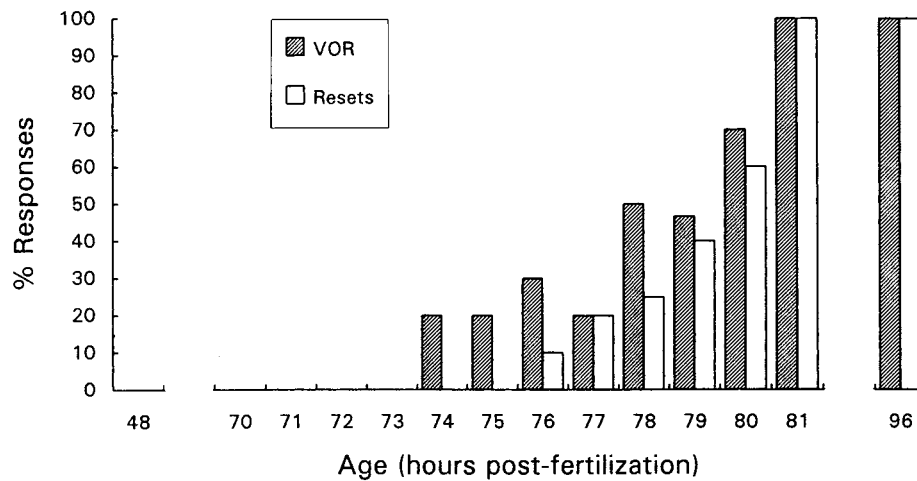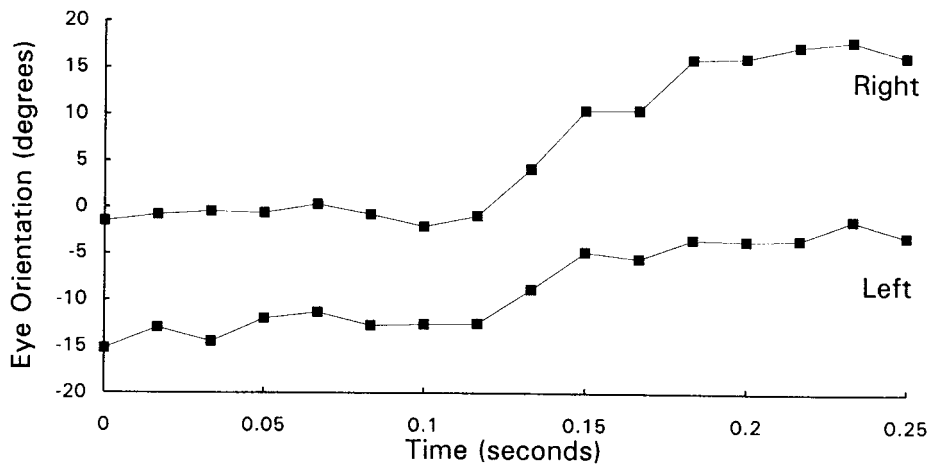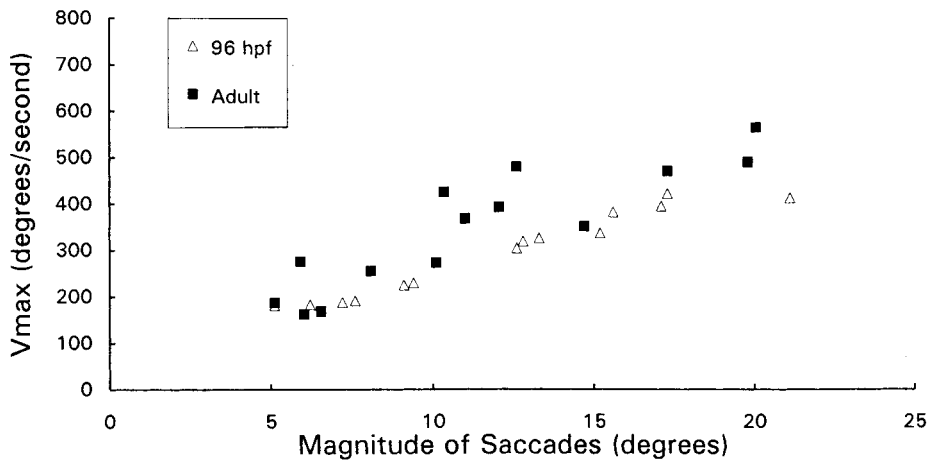

FIGURE 4   Onset of VOR and associated resets. The format is similar to that of Figure 1, but the stimulus is different. In this case, the fish was rotated about the vertical axis in a visually featureless field, and both compensatory movements (hatched columns) and reset movements (clear columns) were scored.

FIGURE 5 Saccades, (a) The time course of a pair of simultaneous saccades. This is the same format as in Figure 2a-c, except that the horizontal axis is expanded and the eye positions were sampled at 60 Hz. (b) The maximum velocity of saccades as a function of the magnitude of the entire saccade. Several saccades of various sizes were measured from plots such as a for both 96 hpf larvae and adults. The biggest step in each saccade was measured and was multiplied by 60 (the sampling rate) to give the maximum velocity reached during the saccade (v_{max}).

examine a different part of the world. Assuming once again that a moving retinal image is more difficult to analyze than a motionless one, then the obligatory shift of position will be most useful if it is accomplished quickly, and as we have seen, the larval saccades quickly achieve adultlike speed.

Determinants of VOR

Like all reflexes, VOR can occur only if the sensory, integrative, and motor components are functional. Haddon and Lewis (1996) have shown that sensory neurons destined to produce the eighth cranial nerve

are numerous at 42 hpf and hair cells on the cristae of the semicircular canals are evident at 60 hpf, so the sensory structures are in place some hours in advance of the behavioral VOR, which first appeared at 74 hpf. The extraocular muscles become functional around 72 hpf (Easter & Nicola, 1996) and OKR follows an hour later, confirming the functional motor link. But VOR is delayed another hour, which suggests that the onset of VOR is limited by the completion of the sensorimotor neural circuit originating in the eighth cranial nerve. The results of Kimmel, Patterson, and Kimmel (1974) were also consistent with the idea that sensorimotor circuits beginning in the inner ear

were relatively late. They monitored the whole-body startle response, which involves the axial musculature rather than the eye muscles, and found that the first startle response evoked through the ear also occurred early on the 4th day postfertilization, more than a day after the axial musculature had become functional and touch-evoked startle could be evoked (Grunwald, Kimmel, Westerfield, Walker, & Streisinger, 1988).

Our observations put a limit on the interdependence of OKR and VOR by showing that VOR was qualitatively normal even in the absence of visual experience. The significance of this finding will be clearer after a brief summary of previous work that linked the two reflexes. The link between OKR and VOR has been studied since M. Ito (1970) first noted that the VOR is an "open-loop" response. This term describes the fact that the movements of the eyes have no direct effect on the signal that stimulated them, the flow of fluids in the semicircular canals. This is in contrast to the case of OKR, in which the signal that stimulates the eye movements is the movement of the image on the retina; the eye movements operate to reduce this stimulus by moving in the same direction as the stimulus, thus "closing the loop." It is difficult to set the gain of the open-loop system without reference to some outside standard, and the closed-loop system of the OKR apparently provides the standard. Ordinarily, an organism moves through a stationary world, and self-motion generates shifts in the retinal image that evoke OKR. The visual signals are consistent with the signals from the inner ear, and the gain of the VOR is set at approximately -1; the eyes' rotation is equal and opposite to the head rotation. A host of studies on adult animals, mostly primates but some fish (e.g., Schairer & Bennett, 1986a, 1986b), have shown that the gain of the VOR can be increased or decreased by several hours of exposure to an experimentally altered visual world. For example, if a restrained fish is rotated in one direction and a surrounding striped drum in the opposite direction so that the eyes must rotate twice as fast as the body to stabilize the retinal image, the gain of the VOR (tested in the dark) exceeds unity. Conversely, rotating the fish and the drum in the same direction, but the drum faster, causes the eyes to rotate in the direction of head rotation rather than against it, and in these fish the VOR decreased well below unity. Thus, the adult is susceptible to the effects of training, but certain limits to the plasticity seem to exist. The basis of these limits was uncertain; they could have been built in from the beginning, as the direction of OKR seems to be (Easter & Nicola, 1996), or they could depend on experience. Our demonstration that dark-reared fish had a qualitatively correct VOR

showed that the sign of this reflex is set independently of experience.

Ontogeny of Behavior

Classical views of the ontogeny of behavior include two conclusions that our results did not support.

The first is the idea of integration (Carmichael, 1934), that fragmentary motor acts are initially made spontaneously before being incorporated in sensorimotor reflexes. As Tracy (1926) stated: "The afferent system, in its gradual development through the growth processes of the organism, 'captures' the primitive motor system. . . " (p. 354). This idea was derived from observations of the contraction of the axial musculature, and has been used successfully to describe the synthesis of complex action patterns (reviewed by Berridge, 1994). But it does not accord with our observations of eye movements. The slow horizontal movements were never made spontaneously; they were always associated with an appropriate stimulus, either rotation of the head or of the striped drum. Likewise, resets only occurred in association with tracking movements. These observations suggest that the neural substrates for these movements developed without significant tuning by the environment on the basis of internal instructions.

The second is that the neural control of behaviors developed with a caudorostral progression, what Armstrong and Higgins (1971) called *behavioral encephalization.* According to this concept, the animal was first under control of spinal centers, then those of the hindbrain, and finally those of the midbrain. Like the first conclusion, this one was based on observations of the undulatory activity caused by the axial musculature, in this case, in the bullhead embryo. Kimmel et al. (1974) agreed that the zebrafish fit the same pattern, and identified the spinal, hindbrain, and midbrain phases as 24–28, 48–96, and beyond 96 hpf, respectively. Our observations limit the generality of this idea because eye movements evoked by visual stimuli (the second cranial nerve) and carried out in part by commands to the medial rectus muscle from the midbrain (the third cranial nerve) occurred at about the same time or slightly before those evoked by vestibular stimuli (the eighth cranial nerve). Moreover, whole-body startle responses evoked by visual stimuli first appeared at 68 hpf (Easter & Nicola, 1996), about the same time as ear-evoked startle responses (Kimmel et al., 1974). We conclude that behavioral development does not progress caudorostrally, but has a more nearly simultaneous onset at all levels, depending on

the particular chronology of the relevant sensory, integrative, and motor elements.

This conclusion is in broad agreement with recent work on zebrafish embryos. The first neurons appear between 16–18 hpf in isolated clusters spaced out along the entire central neuraxis and in the peripheral nervous system (Metcalfe, Myers, Trevarrow, Bass, & Kimmel, 1990; Myers, Eisen, & Westerfield, 1986; Ross, Parrett, & Easter, 1992). The longitudinal tracts, linking the various levels of the neuraxis, form soon thereafter—within a few hours—further weakening the case for a caudorostral gradient.

SUMMARY

We have shown that zebrafish eye movements and their underlying reflexes mature quite rapidly over the course of the 4th day postfertilization, the first full day outside the egg. Both compensatory slow movements and fast resets/saccades first appear whole, and in behaviorally appropriate contexts, not as spontaneous undirected fragmentary motor acts as some earlier models of motor development have proposed. Both OKR and VOR begin with the right polarities, independent of experience. By the 5th day, when the fish enter the water column to begin life without the nutritive support of a yolk sac, visuomotor function is at adult levels of performance.

NOTES

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