

## The optokinetic response in zebrafish and its applications

Ying-Yu Huang<sup>1,2</sup>, Stephan C.F. Neuhauss<sup>2</sup>

<sup>1</sup> Swiss Federal Institute of Technology (ETH) Zurich, Department of Biology, Zurich, Switzerland, <sup>2</sup> Institute of Zoology, University of Zurich, Winterthurerstrasse 190, CH-8057 Zurich, Switzerland

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## 1. ABSTRACT

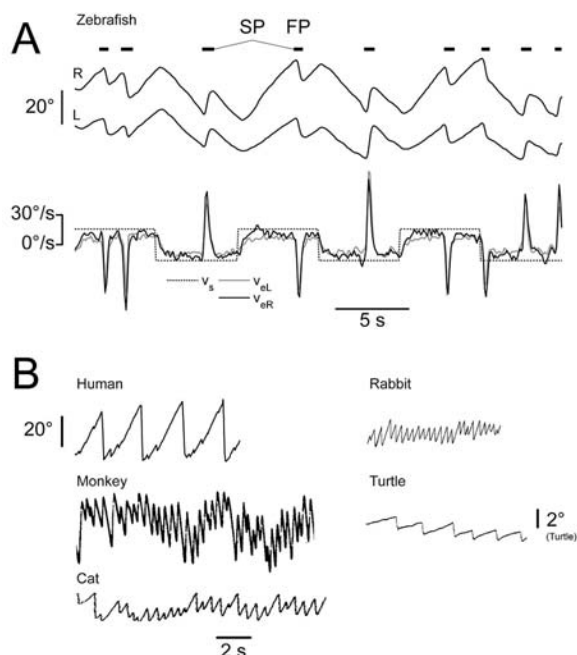
The optokinetic response (OKR) is a stereotyped eye movement in response to movement in the surround. The OKR serves to stabilize the visual image on the retina, and allows for high resolution vision. Due to its high selection value, all vertebrates display this basic behavior. Here, we review the properties of the OKR with a focus on the zebrafish, including methodological aspects of measuring eye movements in small larvae. The genetic amenabilities of the zebrafish model permit the use of this reflexive behavior in genetic screens. Such approaches have led to the isolation of mutant strains with specific defects in the visual pathway. In addition to the use of the OKR as a screening assay, mutations with characteristic abnormalities in the execution of this behavior will enable the analysis of sensory-motor control in great detail. A case in point is the *belladonna* mutation, where an axonal misrouting effect at the optic chiasm leads to a reversed OKR with a number of interesting properties.

## 2. INTRODUCTION

Visual acuity is indispensable for effective vision. Motion of the visual image on the retina, either caused by world- or self-motion, degrades visual acuity. It is, therefore, crucial for the visual system to be able to compensate for such image motion in order to restore visual acuity. Two sensory-motor systems have evolved to counteract such image drifts: the vestibulo-ocular reflex (VOR) and optokinetic response (also called optokinetic reflex, OKR) (1-3). Both work in concert to minimize the movement of an image on the retina, also referred to as retinal slip.

While both gaze stabilization systems activate the same extraocular muscles to evoke compensatory eye movements, they use different sensory input for calculating the velocity of the drifting image on the retina. The VOR uses head velocity information from the semicircular canals and otolith organs to generate eye movements opposite to

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**Figure 1.** Optokinetic response (OKR) in vertebrates. Upon stimulation with a horizontally moving stimulus, all vertebrates tested show a sawtooth-like eye position trace characteristic for the optokinetic nystagmus (OKN). Slow following responses of the eye (slow phase, SP) are interrupted by fast resetting saccades (fast phase, FP). A, OKR trace of 5 dpf larval zebrafish (top, eye position; bottom, eye velocity) ( $v_s = 16^\circ/\text{s}$ , monocular stimulation).  $v_s$ , stimulus velocity;  $v_{eL}$ , velocity of the left (unstimulated);  $v_{eR}$ , velocity of right (stimulated eye). B, the OKR of different vertebrates has highly similar properties although the efficiency can be quite different. Sample OKR eye position traces are given for human ( $v_s = 30^\circ/\text{s}$ , ref 49, Figure 1), monkey ( $v_s = 100^\circ/\text{s}$ , ref 59, Figure 12), cat ( $v_s = 25^\circ/\text{s}$ , ref 71, Figure 1B), rabbit ( $v_s = 32^\circ/\text{s}$ , ref 81, Figure 7), and turtle ( $v_s = 30^\circ/\text{s}$ , ref 96, Figure 8B).

head movement (4,5). However, it operates without an immediate feedback, and is, hence, a feedforward (open-loop) system (6,7). The OKR, a negative feedback (closed-loop) system driven by vision (8), supplements the VOR as it uses velocity information from the retinal ganglion cells to directly determine direction and magnitude of image motion on the retina (9,10). Whereas the VOR is most efficient at high frequencies (11), the OKR works best at low frequencies (12). Both systems complement each other to keep the line of sight stable despite of head and world motion (13-16).

The OKR consists of involuntary compensatory eye movements that are evoked through coherent whole-field motion on the retina (whether caused by ego- or world motion). In the laboratory, the OKR is usually elicited using a black-and-white striped drum that ideally revolves around the subject (17-20). The resulting slow eye movements following the drum rotation (slow phase) that are interrupted by fast resets in opposite direction (fast phase) are referred to as optokinetic nystagmus (OKN).

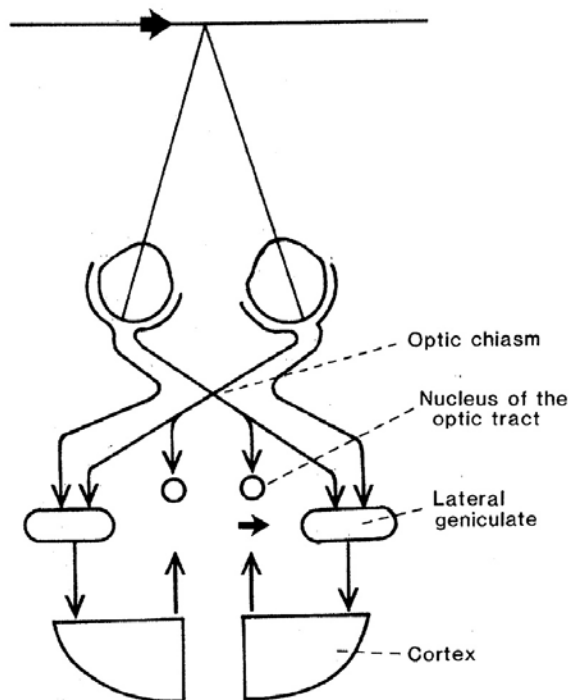
The terms fast phase and saccade are often used interchangeably since the fast phase of the OKN and horizontal saccades share the same anatomical substrate and display virtually identical velocity profiles (21).

In the 19th century, Jan Evangelista Purkinje (22, cited in, ref 23) was the first to describe the slow eye movements following a moving whole-field stimulus (in that case, it was a parade) and the co-occurring fast phases in reverse direction. Although other authors had also been aware of this eye movement phenomenon (e.g., Ernst Mach (24) and Hermann von Helmholtz (25) as cited in, ref 26), it was not until Róbert Bárány (27) that the importance of this type of nystagmus was fully appreciated (26). He coined the term train nystagmus (Eisenbahn-Nystagmus). Even today, one of the everyday situations in which the OKN is most salient is on a moving train when observing the eye movements of another person who is looking out the window. Due the similarity to the vestibular nystagmus, Ohm (28) named it optical turning nystagmus (optischer Drehnystagmus). At the International Ophthalmological Congress at Amsterdam in 1929, a general agreement was reached to use the term optokinetic nystagmus (OKN) suggested by Borries (29), which is still in use today (for a review see, ref 26). Soon after, the study of the OKN in humans was complemented with animal studies. The pioneering work of Ter Braak (30) in rabbits, dogs, and monkeys has immensely extended our knowledge about the nature of the OKN (Figure 1A).

The OKR is a crucial neural system for animals because it maintains optimal visual acuity, which is imperative for orientation in space, hunting for prey, or escaping from predators. Given the high selective value of this behavior, Walls (1) stated that the “optokinetic nystagmus has been found in every mobile-eyed vertebrate in which it has been looked for” (p. 73). To date, the OKR has been studied most thoroughly in primates, including humans (21,31-50) and monkeys (12,13,16,17,51-66). It has also been identified in other mammals such as cat (65,67-76), rabbit (9,10,18,19,77-83), mouse (84-88), rat (89-91), ferret (92,93), and guinea pig (94), and in some lower vertebrates such as frog (95,96), fish (zebrafish, refs 97-104; goldfish, refs 20,101,105-108; medaka, refs 101,109; other teleost, ref 110; dogfish, ref 111; rainbow trout, ref 112), turtle (96,113,114), reptiles (115,116), and bird (pigeon, refs 113,117-119; chicken, refs 120,121). Moreover, many invertebrates that are not equipped with specialized camera-type eyes have movable eyes (simple or compound eyes) and may also display optokinetic behavior (2), which has been confirmed for water fleas (122), mysid shrimps (123), and crabs (124,125).

In this review, we will focus on the optokinetic system in zebrafish (a teleost), a new and promising genetic model for vision research. One advantage of using zebrafish to study the OKR is that, like rabbits (8), they do not have foveate vision, and thus, the OKR is not complicated by selective visual attention (i.e., smooth pursuit). Also, the OKR develops extraordinarily rapid in zebrafish (98). On the top of that, the OKR in itself is an expedient means for studying vision: Reflexive behavior

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**Figure 2.** Cortical and subcortical OKR pathway. Illustration of the direct subcortical pathway to the nucleus of the optic tract (NOT) and the indirect cortical pathway via the lateral geniculate nucleus (LGN) and the visual cortex (70).

such as the OKR is robust (because it is mediated by subcortical pathways) and does not require any training (23,54,98), making it an excellent behavioral paradigm for basic retinal research.

### 3. THE OPTOKINETIC RESPONSE IN VERTEBRATES

Different species show a highly congruent optokinetic response (OKR), although the efficiency of the response varies considerably (Figure 1). The gain, computed as slow phase eye velocity divided by stimulus velocity, is a widely used measure for OKR efficiency. The OKR gain is affected similarly by stimulus velocity, age, contrast, and light intensity in all investigated species. Except for some neonatal animals that show an overcompensating OKR (gain > 1) (120,126), the OKR generally fails to perfectly compensate the retinal slip (gain < 1), an effect that becomes increasingly pronounced at higher stimulus velocities (12,69,101,120). The gain generally increases during early development (more slowly for high stimulus velocities), reaches a plateau (38,64,101,120,127), and decreases with age (128). Sometimes, a gain reduction can be observed in early development (79,120), presumably due to the lower gain requirement after onset of the angular vestibulo-ocular reflex (101). The optokinetic contrast-sensitivity curve shows an inverted-U shape in all species that have been examined. Above threshold contrast, the gain increases

linearly with log contrast (20,69,121,129). When light intensity is abruptly reduced, the OKR gain diminishes, but recovers to the same level shortly after (20).

When the eye reaches a peripheral position, the slow phase of the OKR is interrupted by a resetting fast phase, also referred to as a saccade. With few exceptions (110,115), the slow and fast phase of the OKR occur simultaneously and in the same direction in both eyes. In other words, optokinetic eye movements are conjugate (64,79,107,118,130). Aside from the actual peak velocity, the properties of the fast phase are also highly similar in the investigated species. The velocity profile and the linear relationship between peak saccadic velocity and amplitude are universal and have been described in goldfish (131-133), rats (134), cats (135), monkeys (136), and humans (21,48,137,138).

The curious observation that lateral-eyed vertebrates, such as rabbit (19,30,79,139,140), chicken (95,120), pigeon (118), guinea pig (95), rat (89,130), frog (95,141,142), turtle (96), goldfish (20,106), and rainbow trout (112), show a characteristic asymmetry of the OKR in temporal-to-nasal (T-N) direction under monocular stimulation has been a topic of much speculation and active research. It has been hypothesized that the relative insensitivity to N-T motion in lateral-eyed animals is adaptive because it prevents undesirable eye tracking of the scene as it passes by when the animal moves forward (79). The T-N asymmetry may be linked to complete crossing of the optic pathways (143, cited in, ref 116), lack of a fovea (116), or lateral position of the eyes (118). In contrast, adult frontal-eyed vertebrates with a fovea or an area centralis (cat, ref 127; monkey, ref 56; human, ref 41) exhibit a similarly vigorous response in both directions, although with a slightly higher efficiency in the T-N direction, particularly at higher stimulus velocities (cat, refs 70,139; human, refs 41,144). The adaptive value of the relatively symmetrical OKR in frontal-eyed animals may be related to binocularity (118) and smooth pursuit as it helps stabilize a selectively attended object (39).

This intriguing difference between lateral-eyed vertebrates displaying an asymmetrical OKR while frontal-eyed vertebrates apparently do not, spurred a number of investigations. Mainly lesion studies were used to explore this dichotomy. They led to the hypothesis that the OKR in lateral-eyed vertebrates may be predominantly driven by a direct retinopretectal (subcortical) pathway with a T-N preference, whereas, in frontal-eyed vertebrates, the phylogenetically older subcortical pathway may have been overshadowed by a counterbalancing indirect corticopretectal (cortical) pathway with a N-T preference (36,65) (Figure 2). Indeed, knocking out the cortical pathway by ablation of the visual cortex in cats and monkeys substantially biases the OKR toward the T-N direction (73,145-147). Conversely, inactivation of the subcortical pathway by sectioning the chiasm (and the corpus callosum in monkeys) results in an N-T predominance (54,70). Further support for the "overshadowing" hypothesis is provided by developmental studies: After showing a T-N predominance postnatally, the

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OKR in cats (127), monkeys (64,65), and human infants (38) gradually becomes symmetrical, suggesting that, in frontal-eyed vertebrates, the subcortical pathway matures first, and then is overshadowed by the cortical pathway. While the cortical pathway requires visual exposure in order to mature (70,148), the subcortical pathway seems to be hardwired (126,149,150).

Even though the OKR in both lateral-eyed afoveate and frontal-eyed foveate vertebrates has the ultimate goal to guarantee visual stability, additional oculomotor systems such as smooth pursuit have evolved in foveate vertebrates, requiring modifications in the original OKR pathway. The indirect cortical input to the nucleus of the optic tract (NOT) may be one such modification. Within the subcortical pathway, the NOT receives primarily input from the nasal hemiretina of the contralateral eye (65,70) and contains direction selective units with a strong preference for ipsiversive movement (cat, ref 151; rabbit, ref 152). Even in adult humans, stimulation of the nasal hemiretina produces an OKR with T-N preference (153). In contrast, the cortical pathway of the OKR receives both ipsilateral and contralateral input (65,70), is closely related to stereoscopic vision (38), and largely depends on the foveal visual field (39,144), suggesting a strong correlation between the OKR and smooth pursuit in frontal-eyed foveate vertebrates (154).

When stimulated with a unidirectionally rotating stimulus for a prolonged period of time, the build-up of the OKR slow phase consists of a fast velocity buildup, called the “direct” component, and an “indirect” component that is characterized by a slower gradual increase to the steady-state velocity (12). The direct component has been related to the smooth pursuit system and neuronal activity changes in the flocculus, whereas the indirect component has been associated with the optokinetic after-nystagmus (OKAN) and a velocity storage mechanism that correlates with neuronal activity changes in the vestibular nuclei (155). The OKR of birds (120) and lateral-eyed animals such as adult goldfish (20,107), rat (89), and rabbit (156) almost entirely consists of the indirect component. The indirect component is also predominant in cats, which may be related to the relatively poor smooth pursuit (68). Whereas, in monkeys, both the direct and indirect component are well developed (12,16,59), the human OKR largely relies on the direct component (37). The apparent evolutionary course from the indirect to the direct component may be related to the development of the fovea (157) or the cortical input to the NOT (147,158).

The neuronal substrate of the OKR is very similar across species. The anatomical centerpiece is the pretectal NOT and the dorsal terminal nucleus of the accessory optic system (NOT-DTN), which has been identified in all mammals investigated (rat, ref 159; rabbit, refs 152,160; guinea pig, ref 161; cat, ref 75,151,162,163; ferret, ref 164; wallaby, ref 165; monkey, refs 61,63,166-168, human, ref 169). Direction selective neurons in the NOT-DTN respond to retinal slip velocities (i.e., the error signal of the negative feedback loop of the OKR) in ipsiversive direction (10,151,152,170). The subcortical pathway is characterized

by direct input of the retinal ganglion cells to the NOT-DTN. In lateral-eyed mammals, the direct input is predominant (171) and almost exclusively from the contralateral eye (172). Some mammals additionally have an indirect cortical input to the NOT-DTN (158,161,173-175). Neurons in the NOT-DTN project to the caudal half of the ipsilateral dorsal cap of the inferior olive, the nucleus prepositus hypoglossi, the nucleus reticularis tegmenti pontis, the dorsolateral pontine nucleus, and the contralateral NOT-DTN. The information is conveyed indirectly via the climbing and mossy fiber pathways to the flocculus of the cerebellum, and directly, to the medial vestibular nucleus. These structures project to the nucleus oculomotorius, nucleus abducens, and nucleus trochlearis, which on their part, innervate the extraocular muscles (176,177; reviewed in, refs 23,178-180).

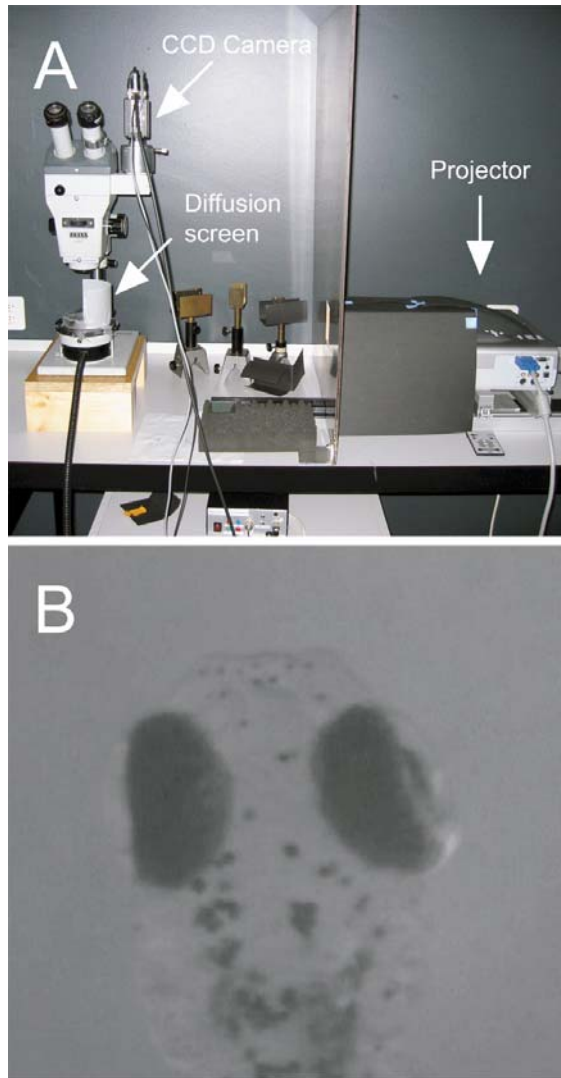
A functional equivalent of the NOT has also been found in bird (the pretectal nucleus superficialis synencephali) (119,181,182) and frog (183). In contrast, the neuronal substrate of the OKR is largely unknown in fish. A regeneration study in goldfish revealed that the pretectal area may be involved in the OKR (184). Furthermore, direction selective neurons in the pretectum of rainbow trout respond to optokinetic stimuli and show the characteristic T-N asymmetry present in the mammal NOT (112). The optic tectum, on the other hand, appears not to be necessary for a functional OKR (185). Thus, the OKR in fish, analogous to that in mammals and birds, may be mediated by pretectal nuclei.

## 4. PROPERTIES OF THE LARVAL OPTOKINETIC RESPONSE IN THE ZEBRAFISH

The first step on the road to the study of vision in zebrafish was taken by the pioneering work of Clark (97) in his unpublished doctoral thesis. In zebrafish, the optokinetic response (OKR) emerges shortly after hatching as early as 73 hours post fertilization (hpf) and gradually improves until reaching a gain of 0.9 comparable to that of adult goldfish at 4 days post fertilization (dpf) (99). The OKR is fully mature by the time when zebrafish larvae begin foraging for food (97). The rapid development makes it possible to study the OKR already at the larval stage, usually starting at 5 dpf to be sure that the OKR is fully developed (186). Although this comes with several obvious advantages, the small size of zebrafish larvae poses a particular challenge to the OKR testing apparatus.

The OKR can be evoked horizontally (17,19,20), vertically (48,72,78), torsionally (47,60,78,187,188), or even by stationary stimuli with flashing light or intermittent presentation (189). The horizontal OKR is of considerable clinical relevance (31,190), by far the most studied, and the only type of OKR (in response to moving stimuli) studied in zebrafish. Hence, the following discussion will be confined to horizontal OKR stimulation. Testing the OKR involves several non-trivial methodological steps: animal immobilization, optokinetic stimulation, and recording and analysis of eye movements (Figure 3). Below, we follow these steps and contrast different methodological approaches under each step.

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**Figure 3.** Experimental setup for the measurement of the optokinetic response (OKR). **A**, Experimental apparatus. The stimulus generated by the projector is mapped onto a diffusion screen through two lenses and an iris diaphragm. The larva is embedded in a dish filled with methylcellulose in order to immobilize the larva. **B**, Frame taken by a high-resolution CCD camera, which records the eye movements of the larva and sends the data to a computer where it is analyzed and displayed.

### 4.1. Animal immobilization

In order to record a clean OKR without the interference of the vestibulo-ocular reflex (VOR), it is essential to prevent body movements during the optokinetic stimulation. A frequently used way to accomplish this is to place the larva in agarose (2%) or methylcellulose (2-6%). Both embedding media are nontoxic and viscous thereby suppressing whole-body movement without substantially constricting eye movements (191). However, in methylcellulose, successful restraint (97,186) and effective aspiration (oxygen diffusion through the skin) (192) is only possible up to an age of 7 dpf. Furthermore, the OKR gain

is considerably reduced (191). To overcome these problems, an alternative method has been proposed in which the body of the fish is embedded in a block of low-melting temperature agarose with the head and the gills exposed to water (191).

### 4.2. Optokinetic stimulation

It is well established that the OKR can be readily evoked by a revolving optokinetic drum fitted with vertical black and white stripes (17-20), a random dot pattern (35,105), or by two tangent screens with moving belts lined with black and white stripes (20,110). In the zebrafish, a rotating black-and-white striped drum is capable of inducing a robust OKR (97). While sine-wave (sinusoidal) gratings have been favored for computer-generated stimuli (100,102,104,193-196) as they move more smoothly when digitally projected (197), square-wave bars have consistently been used in rotating drums (98,101,186,197,198). Different velocity profiles have been employed to examine the OKR: unidirectional rotation of the optokinetic drum for testing velocity storage (101); bidirectional velocity steps (101,102,104) and sinusoidal drum rotation (101,191) for assessing the linearity of the OKR. As gradual changes of stimulus properties are not tractable by classical optokinetic drums, electronically generated stimuli have been used (69,199). In zebrafish, computer-controlled sine-wave gratings have been generated by a digital light projector (199) and directed onto a 360° white paper drum through a sophisticated projection process (100,193-195), or mapped on a cylindrical diffusion screen (102). Computer-generated stimuli allow for continuous variation of velocity, spatial/temporal frequency, contrast, color, and any other stimulus property. As such, the optokinetic “movie theater” is a crucial extension and refinement of the traditional rotating drum.

Most optokinetic paradigms rely on binocular stimulation. However, monocular stimulation has been applied recently as an alternative (100-102). Even though generally leading to lower gains (101), monocular stimulation makes it possible to scrutinize the unstimulated eye and to draw inference about the cross-feed of retinal motion information. For instance, Rick *et al.* (200) found that the unstimulated eye of the achiasmatic zebrafish mutant *belladonna* (see also section 5) moves faster than the stimulated eye, which is opposite to the situation in wild type.

### 4.3. Recording of eye movements

Visual inspection (microscope or camera mounted on microscope) has been sufficient for the measurement of eye movements in behavioral screens and developmental studies, where the presence, absence, or notable impairment of the OKR had to be determined (98,99,186,195,197,201,202). Quantification required manual measurement of the eye position on each video frame (99,200,203,204), a method that is obviously not suitable for quantitative analysis of the OKR on a large scale. A diversity of methods has become available to automatically acquire eye position, such as electrooculography (64,135,205,206), scleral search-coil

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technique (87,207,208), infrared reflection devices (209), and Hall-effect sensors (210). Even though widely used in goldfish (105,107,133), the scleral search-coil technique is not applicable in larval zebrafish due to its small size. Instead, video imaging, a non-invasive method, has been the technique of choice. Image series are acquired via a CCD camera mounted onto a microscope, stored in a computer (100,200,211), and processed on-line or off-line by eye tracking algorithms (101,102,104,191,193-195,212). Compared to 1000 Hz reached by the scleral search-coil method (208), the sampling rate of video imaging is relatively low (between 2 and 60 Hz). Eye position data acquired through video imaging tends to be noisy, and therefore, has to be filtered (101). For that purpose, eye position time series have been processed with a sliding average (102,191) or a Gaussian smoothing kernel (104, goldfish and humans, refs 213,214). It is noteworthy that the optokinetic setup described by Rinner *et al.* (102) is currently the only one that features both computer-generated stimuli and fully automatic eye movement analysis.

### 4.4. Analysis of eye movements

In the quantitative analysis of the OKR, eye velocity is the most important variable. It is obtained by numerical differentiation of eye position (99,101-104,215). Removal of artifacts like whole-body movement or irregular eye movements is best achieved manually (101). Next, the slow and the fast phase have to be identified. Although this is a trivial task for the human observer (98,103,186,200), it is a challenge for automated eye movement analysis. Computer algorithms take advantage of the ready identifiability of fast phases (high peak velocity and the large acceleration at onset, refs 101,132) by applying a velocity (102,216) or an acceleration threshold (101,104,217; goldfish, refs 132,133,213). A velocity cut-off value is not as effective as an acceleration criterion because the velocity range of smaller and slower fast phases overlap with that of the quickest slow phases (217). The remaining segments after detection of the fast phases are the slow phases. In some studies, the slow phases needed to have a minimum duration (104,132,133,213) and/or yield a satisfactory regression fit (101,132,133).

A simple, but not very reliable (101,146), indicator of the slow phase velocity (SPV) is the saccade (fast phase) rate (100,193-195,200,218; rabbit, ref 18). Alternatively, the SPV has been calculated as mean eye velocity (101,102) or maximum eye velocity (104) during a slow phase. The early build-up and the sustained part of the slow phase can be analyzed separately (19,59,101). Although not done so far in zebrafish, SPV can also be computed as the slope of a regression line fitted to eye position of a slow phase (monkey, ref 219; goldfish, ref 213). However, curve fitting techniques (sine waves) have been applied for calculating the maximum eye velocity during sinusoidal stimulation (101) and for eye position data during bidirectional velocity steps (212). Beside SPV, the gain (SPV / stimulus velocity) is frequently reported as a measure of the input-output efficiency. The fast phase (saccade) of the zebrafish OKR has been first analyzed by

Easter and Nicola (99) who plotted peak saccade velocity vs. amplitude. The relatively linear relationship (consistent with reports in other species, refs 132,134,135,137) justifies the use of the peak saccade velocity-amplitude ratio as a measure of saccade performance (101). The average peak saccade velocity (irrespective of amplitude) is another measure of saccade performance (104), albeit not as reliable as the velocity-amplitude ratio.

### 4.5. Development of eye movements in zebrafish

The OKR in zebrafish develops rapidly between 48 and 96 hpf. An observable slow phase of the OKR emerges in 5% of the larvae as early as 73 hpf and is present in all larvae at 81 hpf (98). In parallel, the slow phase gain gradually increases, eventually reaching an adult-like magnitude of 0.9 at a drum velocity of 2.4°/s (99). However, at higher stimulus velocities such as 50°/s, the gain equals 0.5 at 6 dpf and reaches a stable maximum at 0.7 between 24 and 34 dpf. By sinusoidal drum rotation, it can be determined how much the OKR lags behind the stimulus. Between 6 and 34 dpf, the phase lag gradually declines. Interestingly, the monocular gain shows a significant reduction with increasing age. Moreover, the slow phase is jerky in younger animals (10 dpf), which has been attributed to the yet limited number of motor neurons (101).

The appearance of the fast phase slightly lags behind the slow phase, but is displayed by all larvae at 81 hpf (98). In all species tested, including zebrafish (101), the peak saccadic velocity follows a linear relationship with the saccade amplitude (21,132,134-136). That is, the greater the amplitude (eye displacement) the more rapidly is the saccade performed. Therefore, saccadic performance can be expressed by a single number: the peak saccadic velocity-amplitude ratio. At 96 hpf, this ratio comes close to adult performance (99), but continues to slightly increase, reaching 15 1/s by 34 dpf, with the saccade frequency quadrupling in the same time frame (101).

Between 72 and 96 hpf, the area of the functional retina increases by 24° to 163° with the cone mosaic becoming slightly denser increasing the maximal theoretical visual acuity from 3.17° to 2.97° (98). Thus, the size of the functional retina and visual acuity are both sufficient to resolve the stripes of the optokinetic drum and detect their movement. After being hyperopic at 39 hpf, the lens begins to gradually shift its focal point such that a sharp image is projected onto the retinal plane at 68 hpf. The extraocular muscles begin to develop at 60 hpf, but are incomplete until 66 hpf. All six muscles are present at 72 and 96 hpf; however, they are thicker and the myofibrils more numerous at the later stage (98).

Since the OKR begins to appear when the eye becomes emmetropic and the extraocular muscles mature, one can conclude that these are the limiting factors of the OKR development. Although the ability to resolve the stripes is necessary for a working OKR, improving vision does not play a determining role in its development because the retina and the lens are ready before OKR onset. Moreover, the retinal ganglion cell axons reach their targets

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in the brain proper within a similar time frame, and may therefore be another crucial element in the OKR development. It is important to note that the OKR is always executed in the correct direction (following the drum), and no spontaneous eye movements (except saccades) can be observed in the absence of drum rotation. This together with the fact that visually deprived fish immediately display a full-blown OKR at 5 dpf suggests that the polarization of the OKR is hard-wired and does not require visual experience (98, see also dark reared rabbits, 150).

At 5 dpf, the OKR attains adult-like performance in low-challenge conditions and is robust and fully present in all normally developed larvae. Hence, 5 dpf is particularly important for mutants and morphants (larvae with targeted gene knock-down by morpholino oligos) as, by then, OKR dysfunctions can be reliably detected. However, OKR efficiency continues to enhance beyond 5 dpf and may not reach completely mature performance until the juvenile-larval transition (~35 dpf).

### 4.6. Function properties of the larval optokinetic response

In zebrafish larvae, the OKR has been widely used as a tool, particularly in the context of behavioral screens (186,195,197,201,202), but has not received much attention in its own right. The OKR in zebrafish larvae is not a special case: The properties are highly similar to those observed in mammals, birds, and other fish (see Section 2).

The optokinetic eye movements in larval zebrafish are conjugate (101). There is no overall selectivity in either clockwise or counter-clockwise direction, and the average slow phase gain (SPG) of both eyes is essentially identical (101,103). At low spatial frequency, SPG and eye amplitude are greater in response to temporal-to-nasal (T-N) stimulation (103), which is consistent with other lateral-eyed animals that have no or little cortical input to the pretectal area (36,65,70). This asymmetry can be observed under binocular viewing conditions and in the stimulated, but not unstimulated, eye under monocular viewing conditions (103). Besides, the unstimulated eye exhibits a smaller gain compared to the stimulated eye (101,103,200). In contrast, the directional asymmetry is reversed (i.e., the gain of the N-T direction is higher) at higher spatial frequency. It has been hypothesized that the nasal (high density of ganglion cells) and temporal (general selectivity for the T-N direction of direction-sensitive ganglion cells) retina respond differently to whole-field motion and that this response depends on spatial frequency (103). A similar reversal occurs in human infants when the stimulus is isoluminant (e.g., green and red bars of identical brightness), but the underlying process is still unclear (42). It would be interesting to expose zebrafish larvae to isoluminant stripes and test if the directional preference is also reversed.

In agreement with the findings in goldfish (20), chicken (121), cat (69), and human (129), the optokinetic contrast-sensitivity function of zebrafish larvae has an inverted-U shape and the SPG increases linearly with log contrast. For a given stimulus velocity, the SPG also forms

an inverted-U shaped curve when plotted against either the spatial frequency or temporal frequency. Except for very low light intensities, the SPG remains relatively constant across a wide range of light intensities (102). When challenged with increasing stimulus velocity, the SPG steadily decreases (101,102,104), whereas the amplitude shows little change (100,103). Prolonged exposure to a unidirectionally moving stimulus leads to an initial quick increase in slow phase velocity without a subsequent gradual buildup (101). Finally, the fast phase of the OKR has a linear relationship between peak saccadic velocity and amplitude (191).

The functional neuroanatomy of the OKR in zebrafish is not well understood (220). Studies in rainbow trout (112) and goldfish (184) implicate that, also in larval zebrafish, the pretectum may be the visuomotor interface of the OKR. A tracing study has identified 10 distinct retinofugal arborization fields (AF) (221). It has been suggested that, in zebrafish, AF-6 may be the functional equivalent of the mammal nucleus of the optic tract (100) and correspond to the OKN-mediating nucleus proposed by Rick *et al.* (200). Monocular stimulation leads to motion in the unstimulated eye, albeit with a lower slow phase velocity, indicating that the motor neurons receive ipsilateral and contralateral input (101,200). Like in goldfish (185), the slow phase of the OKR does not depend on the optic tectum (AF-10) in zebrafish larvae. However, the saccade frequency is reduced, suggesting that the optic tectum plays a role in the fast phase of the OKR (100).

## 5. THE OPTOKINETIC RESPONSE IN ZEBRAFISH AND ITS APPLICATIONS

Since the optokinetic response (OKR) in zebrafish larvae is readily inducible by large field movements in the surround at early larval stages where the larvae is still supported by its yolk supply, this behavior is ideally suited as a screening tool to isolate mutant larvae with defects in vision. The zebrafish is one of the most widely used vertebrate model organisms, mainly in the context of developmental genetics. The superb genetics of the zebrafish and the early emergence of this simple and robust behavioral response open the attractive opportunity to combine genetics with behavior in a simple vertebrate. Using the execution of a visually mediated behavior as a screening assay extends previous screens relying on visual inspection, giving the opportunity to isolate mutant strains with functional defects in the absence of overall morphological changes. Such screens may lead to the isolation of physiological mutants.

The pioneering study of Clark (97) already proposed to use stereotypic responses to light to screen for visual mutant strains created by chemical or X-ray mutagenesis. By placing the dish inside a rotating drum fitted with high contrast black and white stripes, a robust OKR can be elicited and easily scored through a dissecting scope. Larvae failing to follow the moving stripes can easily be identified and picked for further analysis. Depending on the genetic design of the screen, a Mendelian ratio of larvae needs to show the defective OKR to argue

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for a heritable trait. Such visually impaired larvae can then be analyzed in more detail to locate the defect in the visual pathway. A number of experimental options are available, ranging from in-depth optokinetic analysis through histology and electrophysiological approaches.

The untimely death of George Streisinger, in whose laboratory most zebrafish research, including optokinetic analysis was pioneered, and the absence of efficient chemical mutagenesis by ethyl-nitroso-urea (ENU), prevented the realization of the full potential of such behavioral screens at the time. The potential of such a screen was realized over a decade later by John Dowling and colleagues (186). By screening 266 mutagenized genomes of third generation larvae of ENU-mutagenized fish, they isolated 18 strains with abnormal OKR. This not only validated the concept of behavioral screens in zebrafish, but also showed that mutants with abnormal optokinetic properties are quite common. Subsequent screens, including a shelf screen of 450 mutant strains from the Tübingen stock center (197), and a novel large scale screen (195) isolated a wealth of mutant strains. Further analyses of these strains, mainly by detailed retina morphology, electroretinography, cellular physiology, and neuronal tracing, revealed the underlying cause of the visual defect, including its molecular nature, for a growing number of these mutants. Mutants affected in nearly all conceivable aspects of retinal morphology and physiology have been identified and have been reviewed in more detail elsewhere (202,222,223).

By far the most common phenotype is the degeneration of photoreceptors in the outer retina. In many of these mutant strains, photoreceptor degeneration is part of a syndrome with characteristic extraretinal defects. For instance, a group of mutants with outer retina degeneration, hearing defects, and kidney cysts have been isolated (224,225). Molecular cloning of one of the *oval* mutant revealed mutations in the IFT88 gene. This gene codes for an intraflagellar transport protein, highlighting the importance of intraflagellar transport for the maintenance of ciliated sensory structures, including photoreceptors (226). Other mutants display characteristic defects in the photoreceptor synapse. In the *nrc* (*no optokinetic response c*) mutant, the phenotype is caused by a mutation in the synaptojanin 1 gene. This gene codes for a polyphosphoinositide phosphatase involved in clathrin-mediated endocytosis and actin cytoskeletal rearrangement at conventional synapses. Cone photoreceptor synapses devoid of this protein display unanchored synaptic ribbons and a reduced number of abnormally distributed synaptic vesicles (227). Homozygous larvae for the *macho* gene lack neuronal activity in retinal ganglion cells due to a deficit in sodium conductance, preventing the generation of action potentials (228). A mutant displaying not a visual impairment, but rather eye movement abnormalities, will be discussed in more detail in the following section.

All of the above mutant strains were identified as visually impaired by the simple rotating drum paradigm using white light for illumination. This experimental paradigm can be refined by modification of the stimulation

paradigm. By illuminating the drum with red light, Brockerhoff and colleagues isolated a color blind mutant strain (*partial optokinetic response b; pob*) showing defects under red but not white illumination (201). Positional cloning revealed that the *pob* locus encodes a novel conserved 30-kDa protein, likely to be involved in protein sorting and/or trafficking (229). Although the drum paradigm is well suited for large-scale screening, it is at best a semi-quantitative measure of visual performance. In order to measure optokinetic performance in a precise quantitative way, we developed a semi-automatic behavioral paradigm building on the previously described drum paradigm. Instead of having a real drum providing the visual stimulus, in the “movie theater”, the immobilized larvae view a screen onto which computer generated patterns are projected via a video beamer, which gives greater control over stimulus properties. Eye movements are digitally recorded by a video camera using infrared illumination of the larva and analyzed in real time by custom-made software (102). This allows for a quantitative assessment of visual performance, enabling the precise behavioral measurement of various properties of the larval visual system (e.g., visual acuity). This method is more time-consuming than the simple qualitative assessment used for screening and therefore more useful for the in-depth analysis of previously identified mutant strains.

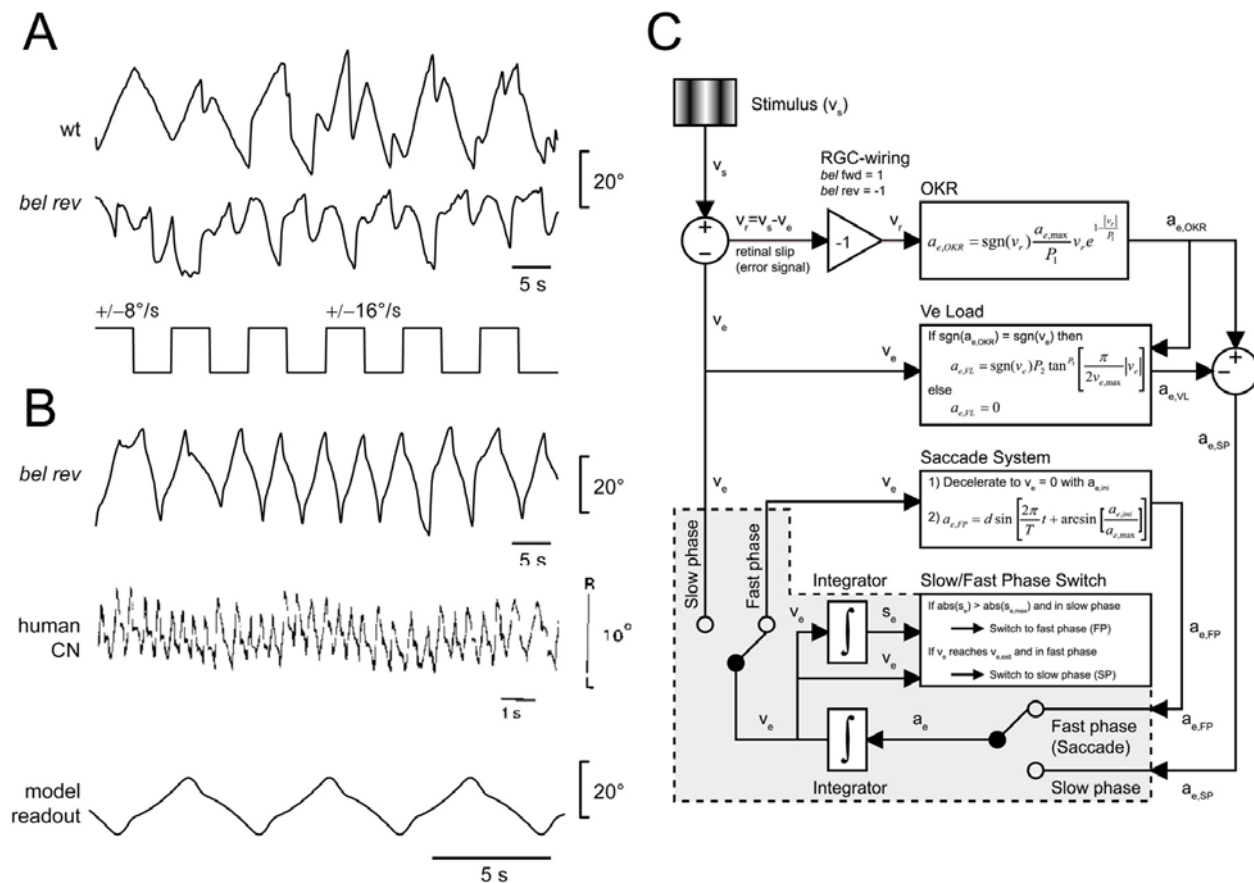
Recently morpholino antisense technology has been developed for the zebrafish (230). This technique permits the efficient blockage of splicing or translation of any gene of choice. Such larvae are deficient of these proteins of choice for up to 5 days post fertilization, allowing for a visual behavioral assessment. In one such experiment the role of a cone photoreceptor specific opsin kinase (G-coupled receptor kinase 7, Grk7) in light adaptation has been demonstrated (212). Since the larval zebrafish retina is cone-dominant, future studies using this method will yield new insights into cone photoreceptor function.

## 6. OCULOMOTOR DISEASE MODELS

The zebrafish mutant *belladonna* (*bel*) provides an exciting showcase of how abnormal oculomotor behavior can be linked to a neuroanatomical pathology, and how valuable such insights are to understand oculomotor diseases in humans, such as congenital nystagmus (CN). The *bel* mutant was originally identified in a screen due to the ipsilateral retinotectal projection, and it was named for an abnormal gap between the lens and the pigmented epithelium, which makes the pupils appear as if they were dilated (atropine, also called belladonna, is a drug that leads to a dilation of the pupils) (231,232). A recessive mutation in the zebrafish *Lhx2* homolog (a gene that encodes a Lim domain homeobox transcription factor required for forebrain patterning and midline axon guidance) is responsible for the *bel* phenotype (233). The retinal ganglion cells (RGCs) project ipsilaterally in about 45% of the homozygous *bel* mutants (i.e., these mutants are achiasmatic), while the projection is normal in the other mutants (i.e., contralaterally) (200). The hallmark of the *bel* mutants is the reversed horizontal optokinetic response



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**Figure 4.** Abnormal oculomotor behavior of zebrafish mutant *belladonna*. **A**, Eye position traces of wild type (wt) displaying a normal optokinetic response (OKR) (top) and *bel rev* showing a characteristic reversed OKR (middle) in response to bidirectional reversed OKR (bottom, 6 steps at 8°/s and 6 steps at 16°/s). **B**, Spontaneous eye oscillations (SOs) observed in *bel rev* when presented a still grating (top) resemble those in human congenital nystagmus (CN) (middle, ref 267, Figure 4). These traces show a typical bidirectional jerk waveform that can be replicated by our parsimonious mathematical model upon sign-inversion of the retinal slip velocity input (bottom, ref 104, Figure 7F). **C**, Diagram of the mathematical model that we used to simulate normal OKR, reversed OKR, and SOs (ref 104, Figure 6A).

(OKR) (197) that exclusively occurs in achiasmatic *bel* mutants (*bel rev*), indicating that the ipsilateral projection of the RGCs may be responsible for the reversed OKR (200). In contrast, *bel* mutants with normal contralateral projection display a normal forward OKR (*bel fwd*) with a saccade rate similar to wt siblings (200), but with a considerably reduced gain (104).

In order to understand the mechanism leading to the reversed OKR, we thoroughly examined the oculomotor behavior of *bel rev* (104). Contrast sensitivity and peak saccadic velocity in *bel rev* is similar to *bel fwd* and wt. The normal saccadic performance implies that *bel rev* are unlikely to have a significant motor deficiency. In agreement with an earlier study (200), we found that the slow phase gain of the reversed OKR in *bel rev* is above unity at low stimulus velocities. Based on these data, we hypothesized that the ipsilateral RGC projection feeds a reversed retinal slip velocity input to the optokinetic system, eliciting eye movements that “compensate” for the retinal slip in the wrong direction. In other words, the

optokinetic system of *bel rev* acts like a self-reinforcing positive feedback loop. In order to verify this hypothesis, we built a parsimonious mathematical model (Figure 4C) that produces a normal OKR as observed in *bel fwd* (and wt) and tested how the model output is altered if the sign of the retinal slip velocity input is reversed. Indeed, the resulting OKR of the model is reversed and perfectly replicates the waveform characteristics observed in *bel rev* (104) (Figure 4A).

Beside the reversed OKR, *bel rev* also show spontaneous eye movements (i.e., spontaneous oscillations, SOs) when presented with still black-and-white bars (104). However, the SOs discontinue in the dark and in the absence of a pattern in the illuminated visual field, indicating that the SOs depend on visual input. The slow phase velocity of the SOs responds to different contrast much in the same way as the reversed and forward OKR. Thus, we suspected that the SOs are caused by the same defect (i.e., ipsilateral projection of the optic nerves) in the optokinetic feedback loop as the reversed OKR. If this

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hypothesis holds true, it should be possible to reproduce SOs with the same model that was able to generate a reversed OKR. It turns out that the waveform characteristics of the major types of SOs can be replicated by the model when the stimulus velocity is set to zero (Figure 4B) (104). In addition to the oculomotor instability, *bel rev* display a curious swimming behavior, best described as circling, that is induced by self-motion perception (Huang *et al.*, submitted).

We now have reviewed the three aberrant behaviors of *bel rev*, reversed OKR, SOs, and circling that are closely related to one another. Although the neuronal substrate of the OKR is not known in zebrafish, our model makes a strong case that the ipsilateral projection of the RGCs, presumably to the pretectum, is responsible for the optokinetic phenotype of *bel rev*. More support for this idea comes from studies in other animals. For instance, induced ipsilateral retinotectal projections lead to reversed OKR, SOs, and circling in goldfish (234) and amphibians (235). The same abnormal behaviors were elicited when rotating the eye balls by 180° (236), or transplanting them to the contralateral side (235,237). Additionally, in black Belgian sheepdogs, a heritable achiasmatic condition (238,239) was associated with oculomotor instabilities. However, reversed OKR and postural abnormalities have not been reported (240,241). All of these cases have in common that the retinal slip velocity input (afference signal) to the optokinetic system is reversed in some way. It is, therefore, likely that both the oculomotor and postural instabilities are directly attributable to the reversed retinal slip velocity input.

CN (also called infantile nystagmus) is a disorder characterized by involuntary oscillations of both eyes, present at birth or shortly after (242). CN is predominantly caused by genetic disorders that affect the visual pathways. Albinism (243), foveal hypoplasia, cataract (244), and aniridia (245) generally impair the functioning of the eye. As a result, proper calibration of the visual feedback systems fails, which may lead to CN (246,247). Further downstream, axonal misprojections of the optic fibers such as complete crossing in albinism (248), hypochiasma (249), and achiasmia (250) (in humans, about 45-50% of the optic nerve fibers remain uncrossed) may also contribute to CN. Etiological models propose saccadic termination abnormality (251), loss of damping of the normal pursuit-system velocity oscillation (252), and abnormal development of oculomotor areas (253) as additional causes of CN.

In the zebrafish mutant *bel rev*, we showed that axonal misrouting of the RGCs is causative of the SOs via inversion of the retinal slip velocity input (104). The waveform characteristics of the SOs are highly similar to those observed in human CN (254,255). Moreover, positive feedback models created to explain human CN are essentially equivalent to our model for the optokinetic behavior in *bel rev* (251,256). Thus, it is conceivable that the SOs may actually be a CN, and consequently, *bel rev* may be a model of human CN caused by axonal misrouting. Axonal misprojections of the optic fibers in

humans highly correlate with CN, sometimes with reversed OKR, and possibly with impaired postural balance. For instance, complete contralateral projection of the optic fibers (248), CN, and reversed OKR (257,258) are all typical features of albinism. Hypochiasma is also associated with CN and reversed OKR (249,259). Along the same lines, humans with achiasmia (260) display CN (Dell'Osso, L.F.: Original ocular motor analysis of the first human with achiasmia: documentation of work done in 1994. OMLAB report #090506, 1-21, 2006. [http://www.omlab.org/OMLAB\\_page/Teaching/teaching.html](http://www.omlab.org/OMLAB_page/Teaching/teaching.html); see also, refs 241,259,261). Similar to circling in *bel rev*, head tremor/nodding (262,263) and slight impairment in visually controlled postural balance (203,264,265) have been reported in CN patients. Although they do not experience exaggerated self-motion perception (203), self-motion perception may still be involved in head tremor/nodding and reduced postural balance as these behaviors may have developed in the first place to reduce such vection phenomena.

The evidence presented above leaves little doubt that the results obtained in zebrafish mutant *bel rev* can be extended to human CN, especially when visual pathway abnormalities are involved. The mathematical model for *bel rev* demonstrates that the inverted retinal slip input, caused by the visual pathway abnormality, evokes a reversed OKR and a CN with exponentially increasing slow phase velocity (104). Thus, whenever a CN with increasing exponential velocity form and/or reversed OKR is observed in humans (e.g., ref 266), visual pathway abnormalities may be the possible underlying cause. The reversed OKR may be a particularly good differential diagnostic feature of CN linked to visual pathway abnormality because, although other forms of CN may also display exponentially-shaped slow phases, such CN patients are not expected to show a reversed OKR. The etiology of CN is still not well understood, primarily owing to the considerable variety in the underlying pathology. *bel rev* may prove to be a useful oculomotor disease model to explore the etiology of CN.

## 7. PERSPECTIVES

The optokinetic response (OKR) in the zebrafish larva has been mostly used to screen offspring of mutagenized families to isolate mutants with visual defects. Such screens have been very successful and mutants from these and new screens will continue to provide insight into the genetics of visual system development and function. Most of the analyzed mutants to date are affected at the level of the retina, and such mutants will continue to deepen our understanding of visual processing in the retina.

Apart from utilizing this behavior as a tool to uncover blind larvae in genetic studies, the behavior itself merits exploration. The anatomical substrates of the OKR circuit are still largely unknown in lower vertebrates. The universality of this behavior in vertebrates raises interesting questions about its evolutionary development. The neural circuit underlying optokinetic eye movements is one of the few circuits where we might be able to gain deep insights into the evolution of and is one of the areas of the brain

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where we might gain a deep understanding of the coevolution of an adaptive behavior and its underlying anatomical substrate. Therefore a better understanding of the anatomical organization of this neural circuit in lower vertebrates is of pivotal interest.

Future screens will likely reveal mutations that do not disturb sensory input, but rather affect the brain circuits directly. Such mutants will make it possible to study the formation and function of the underlying neural circuit by genetics means. Here the small larval zebrafish brain with a limited number of stereotypic neuronal projections combined with its full experimental and optical accessibility will yield an important experimental advantage. The ever increasing tool box of transgenic animals and optic recording techniques will soon enable physiological studies in the intact larval brain, possibly while performing a behavior. The OKR is one of the behaviors where such a functional whole-circuit analysis might be possible in the near future.

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**Send correspondence to:** Stephan C.F. Neuhauss, Institute of Zoology, University of Zurich, Winterthurerstrasse 190, CH-8057 Zurich, Switzerland, Tel: 41-0-44-635-6040, Fax: 41-0-44-635-6897, E-mail: stephan.neuhauss@zool.uzh.ch

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