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ORIGINAL COMMUNICATION

Moving or being moved: that makes a difference

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Abstract During head/body movements, gaze stability is ensured by transformation of motion-related sensory signals into respective motor commands. Passively induced motion in all vertebrates including amphibians evokes a robust vestibulo-ocular reflex, suggesting an equally important role of this motor reaction during actively induced motion. However, during self-induced movements including locomotion, motor efference copies offer a convenient additional substrate for counteracting retinal image displacements. During such locomotor activity in *Xenopus laevis* tadpoles, spinal central pattern generator-derived efference copies elicit spatio-temporally specific eye movements, which are functionally appropriate to offset swimming-related retinal image displacements. In addition, passively induced horizontal semicircular canal signals are suppressed, making intrinsic spino-extraocular motor coupling the dominating mechanism for gaze stabilization during locomotion. The presence of functionally appropriate efference copy-driven eye movements in adult frogs with limb-based locomotion suggests that this mechanism might play a role for gaze stability during rhythmic locomotion also in other vertebrates.

Keywords Locomotion · Efference copy · Vestibular system · Extraocular motoneurons · *Xenopus laevis*

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Introduction

Locomotion-related as well as passively induced head/body movements require concurrent gaze stabilization to prevent a degradation of optical information processing [1]. To avoid deterioration of the visual acuity, retinal image drift is minimized by dynamic counteractive eye and/or head adjustments [2]. These gaze-stabilizing reflexes have classically been attributed to sensory–motor transformations of motion-induced visuo-vestibular and neck/limb proprioceptive inputs [3]. While feedback sensory signals represent the only source of information about unexpected, passively induced perturbations of the head/body position, actively elicited, voluntary movements or locomotor activity generate intrinsic motor efference copies that contribute to gaze- and posture-stabilizing reflexes [4–6].

Following mechano-electrical transduction by vestibular hair cells, head motion signals are encoded by vestibular afferent fibers as modulated spike discharge, which is transmitted to central vestibular neurons [2]. While vestibular nerve afferent fibers encode both active and passive head movements as shown in monkeys for instance, the activity of a particular subset of central vestibular neurons is markedly attenuated during self-induced head movements [4, 5]. This suppressive influence on vestibular afferent inputs, related to self-generated head movements, is likely caused by neck proprioceptive and/or motor efference copies [3]. A comparable effect of the latter intrinsic signals on gaze control and vestibular sensation has also been demonstrated during rhythmic locomotion in larval and adult *Xenopus* [6–8].

Differentiation between contributions of head/body motion-evoked sensory inputs and self-motion-related intrinsic signals to gaze stabilization is a challenging task that requires an appropriate animal model and

methodological approach. Semi-intact, isolated whole head preparations of larval and adult amphibians offer such a possibility, as the motor commands underlying self-motion can be recorded in the absence of effective head/body movements [9]. Experiments in *Xenopus* thus allow deciphering the respective roles of locomotor efference copies and sensory–motor transformations for gaze stabilization during active versus passive head/body movements [6, 7, 10, 11].

Contributions of sensory–motor transformations to gaze stabilization

In amphibian larvae, oscillatory head movements during undulatory tail-based swimming are accompanied by concurrent oppositely directed eye movements (Fig. 1a). In the classical view, these compensatory eye movements derive from a transformation of motion-related sensory signals (vestibular, visual, proprioceptive) into extraocular motor commands (Fig. 1b). Since undulatory swimming of tadpoles such as those of *Xenopus laevis* occur essentially in the horizontal plane [12], horizontal semicircular canals are the main vestibular sense organs for self-motion detection in these animals. After post-embryonic anatomical completion of semicircular canals [13] and onset of functionality [14], a horizontal angular VOR can be reliably elicited. Non-invasive video recordings, performed in semi-intact whole head preparations of *Xenopus* tadpoles (Fig. 1c), show that sinusoidal turntable motion in fact triggers eye movements that are appropriate to compensate for a large part of the retinal image displacements during horizontal head/body rotation (Fig. 1d). Respective spatio-temporally adequate eye movements are also encountered during roll and tilt movements [14].

Electrophysiological recordings of the extraocular motor discharge from the lateral rectus (LR) nerve in semi-intact preparations revealed the dynamic profile of motion-evoked responses (Fig. 1e). During horizontal sinusoidal rotation with a turntable, the peak discharge modulation of the LR nerve increases with stimulus magnitude, while the responses are slightly delayed with respect to turntable velocity (upper right plot in Fig. 1e). Roll or tilt oscillatory movements evoke extraocular motor discharges that, however, are phase-timed to the turntable position, likely due to additional contributions of head position signals from the utricle [14]. Horizontal sinusoidal motion stimulation with increasing frequencies results in a gradually decreasing peak discharge and a concurrent delay of the maximal response with respect to stimulus frequency (lower right plot in Fig. 1e). The overall extraocular motor response dynamics of larval *Xenopus* during passive head motion is thus qualitatively similar to that reported for other vertebrates [2]. However, quantitative differences in gain and phase magnitudes exist and are likely related to semicircular canal dimensions and to the sensitivity of the peripheral motion-receptive structure [14]. Nonetheless, tadpoles possess the necessary computational capabilities for sensory–motor transformations that are well suited for gaze stabilization during passive head/body motion.

Contributions of motor efference copies to gaze stabilization

Propulsive locomotion in anurans is stereotyped and produced by rhythmic tail undulations in tadpoles and by bilateral synchronous hind-limb kicks in adult frogs [9]. The rhythmicity of the underlying tail/limb muscle contractions derives from the oscillatory activity of spinal CPG networks. During locomotion, *Xenopus* larvae display oscillatory head movements that are phase-coupled to the propulsive tail undulation (Fig. 2a). This indicates that head movement dynamics and concurrent retinal image displacements during swimming can be predicted from the locomotor kinematics [12]. Compensatory eye movements to offset the disruptive effects of locomotor activity can, thus, at least theoretically, be calculated based on signals directly related to the temporal structure of the locomotor activity.

Spinal CPG activity produces rhythmic locomotor commands [16] but also efference copies that reflect intrinsic mirror images of the motor activity [17, 18]. These locomotor efference copies represent a spatio-temporally suitable neural signal for eliciting compensatory eye movements to stabilize retinal images (Fig. 2b). During actual locomotion, a potential impact of the latter signals, however, is indistinguishable from contributions of head-/body motion-related proprioceptive or vestibular inputs. This ambiguity can be circumvented in amphibians, in which the central nervous system (CNS) after its isolation is still capable of spontaneously generating rhythmic locomotor activity [9]. In fact, swimming-related locomotor commands can be recorded in such isolated tadpole preparations as burst discharge of spinal ventral roots (termed fictive swimming). This allows identifying contributions of motor efference copies to gaze stabilization during episodes of self-motion in the absence of sensory feedback signals.

During episodes of fictive swimming in semi-intact preparations of larval *Xenopus* (Fig. 2c), indicated by rhythmic burst discharges of spinal ventral roots, both eyes perform left–right oscillations (orange trace in Fig. 2d). The extraocular motor bursts in the LR nerve underlying these horizontal eye movements are strictly phase-coupled to the contralateral spinal ventral root activity (dashed line in Fig. 2d). This phase coupling is restricted to horizontal
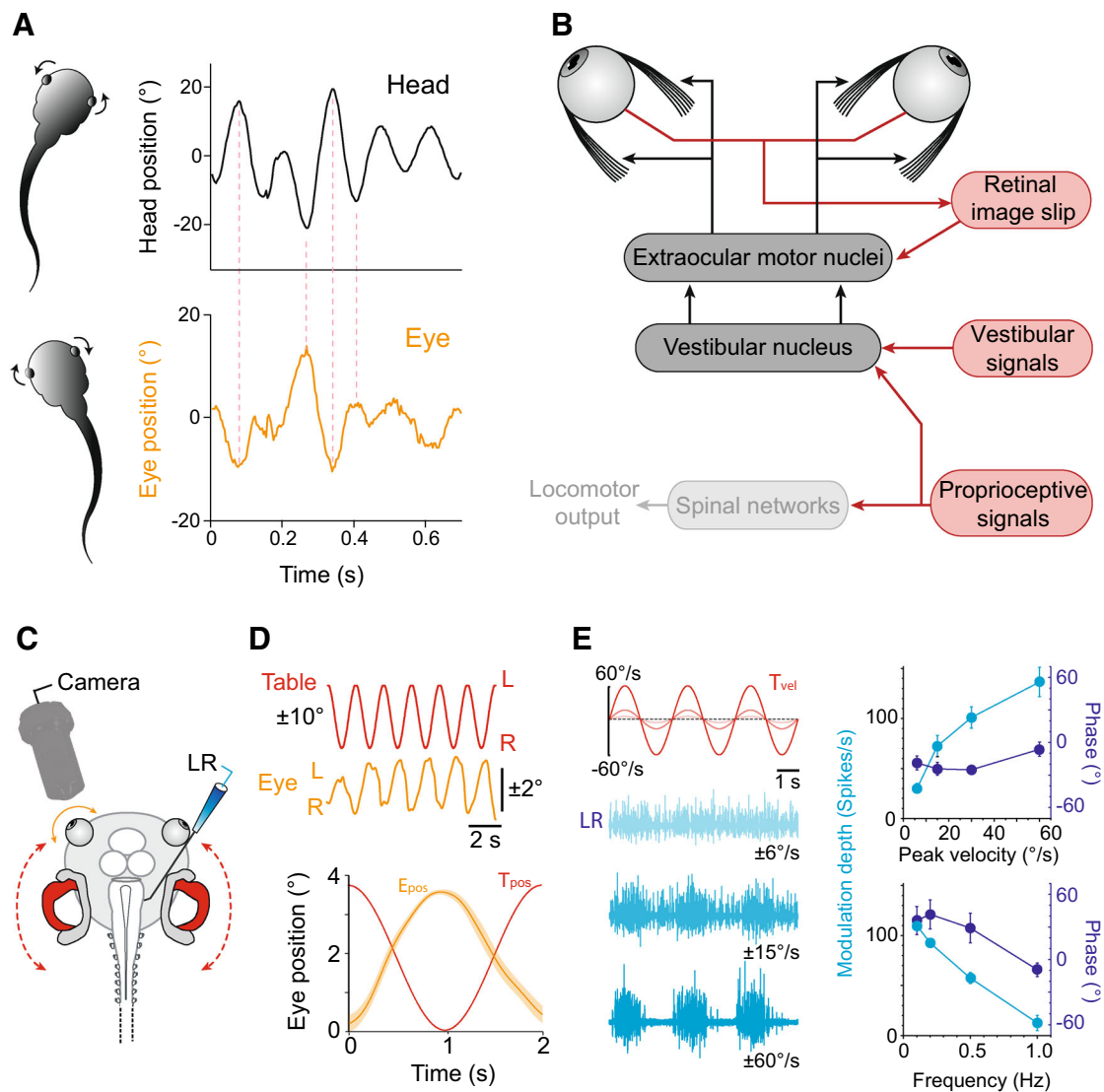
Fig. 1 Contributions of sensory signals to gaze-stabilizing eye movements. **a** Schematic view of undulatory swimming of larval *Xenopus* (*left*); alternating head oscillations (*upper right plot*) are accompanied by oppositely oriented eye movements (*lower right plot*); from Beraneck, Lambert and Straka, unpublished data. **b** Schematic organization of the neuronal circuitry for sensory–motor transformations underlying gaze-stabilizing eye movements. **c**–**e** Isolated whole head preparations of larval *Xenopus* (**c**) employed for optical recording of eye movements (**d**) and electrophysiological

recordings of multi-unit spike discharge from the LR nerve (**e**) during horizontal turntable rotation (*red dashed lines* in **c** show movement direction); eye movements are oppositely directed to the table motion as indicated by the average over a single cycle (compare *orange* and *red curve* in the *lower plot* in **d**); three cycles of LR nerve spike discharge modulation (*blue traces*) during horizontal table rotation (0.5 Hz; *upper traces*) at different peak velocities (left in **e**); bode plots of the response dynamics at 0.5 Hz (*upper right* in **e**) and 30°/s (*lower right* in **e**). **d** and **e** are based on data from [10, 11]

extraocular motor nerves, i.e., LR and medial rectus (MR; Fig. 2e) and absent from motor nerves innervating vertical and oblique eye muscles [15]. The coupling pattern is functionally specific and compatible with conjugate movements of both eyes in phase opposition to swimming-related head movements in intact animals. Since sensory signals are removed in these stationary semi-intact preparations, the extraocular motor commands must originate from locomotor centers within the CNS. In fact, surgical lesions and pharmacological manipulations indicated that

locomotor efference copies derive from the first ten spinal segments and are mediated by an ascending pathway that excites LR motoneurons and internuclear neurons in the abducens nucleus monosynaptically [15]. This connectivity complies with the activation of bilaterally synergistic extraocular motoneurons for horizontal conjugate eye movements [2].

The fast burst–pause alterations of efference copy-driven LR nerve (Fig. 2d, e) discharge (∼5 Hz [15]) suggest that the monosynaptic excitation from ascending spinal
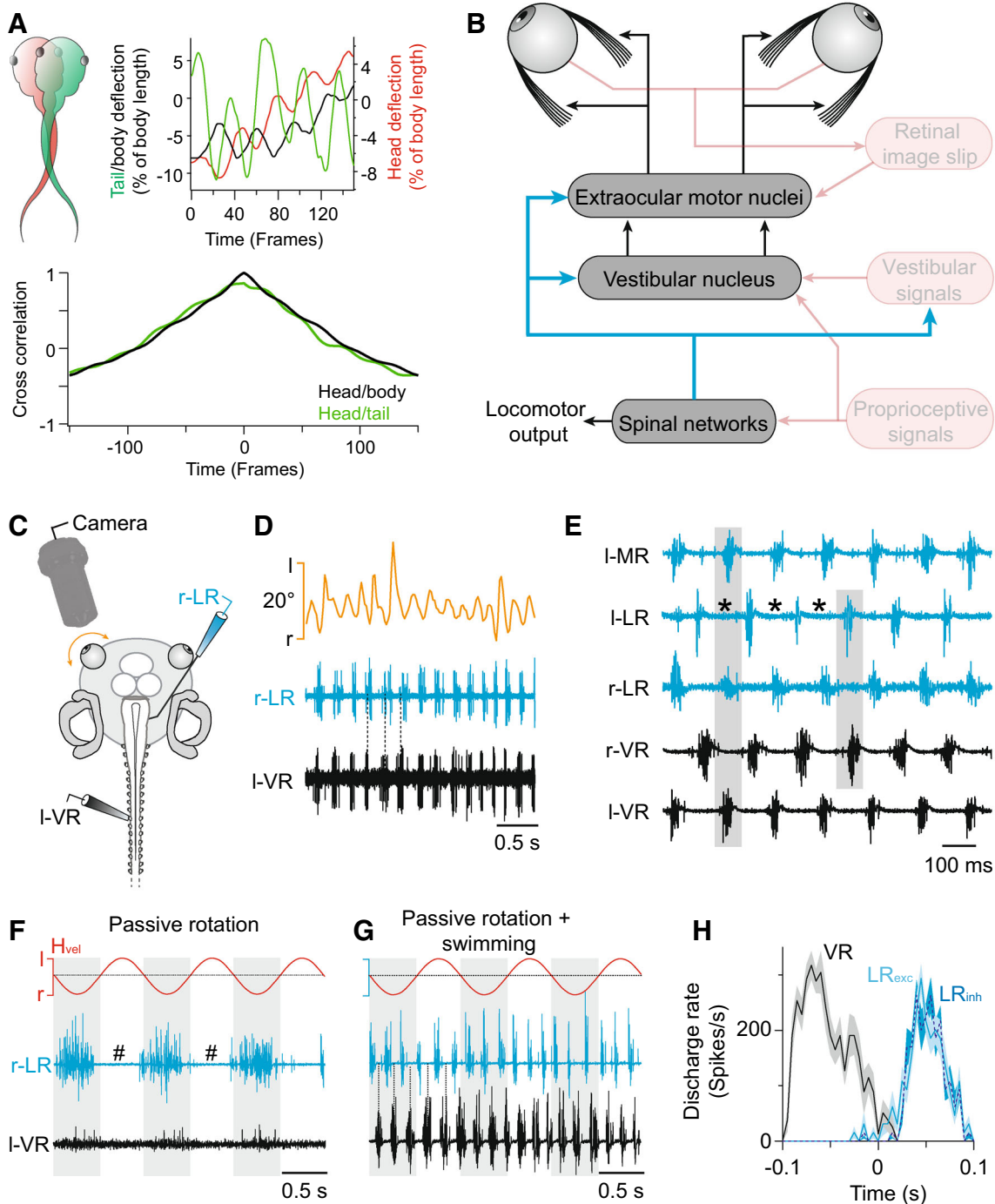
neurons onto abducens motoneurons is mediated by glutamate *via* postsynaptic AMPA receptors. This complies with the pharmacological profile of vestibular excitatory inputs from contralateral central vestibular neurons onto a particular group of abducens motoneurons with dynamic firing patterns during passive head/body motion [19]. Assuming a similar organization of spinal and vestibular excitatory inputs to the latter motoneurons, locomotor efference copy-driven bursting would be mediated

preferentially by AMPA receptors and to a minor extent by NMDA receptors [19]. If the inter-burst period during the efference copy-driven rhythmic discharge (* in Fig. 2e) derives from a transient pause in the ascending excitation or from an inhibitory synaptic input that alternates with the spinal excitation is unknown. An active inhibition could derive from a separate ascending spinal connection that directly mediates an inhibition in alternation with the spinal excitation. Alternatively, it could arise from putative

◄Fig. 2 Contributions of locomotor efference copies to gaze-stabilizing eye movements. **a** Coupling of head/body/tail movements (*red/black/green*) during swimming in larval *Xenopus*, visible as respective oscillations over several swim cycles and plotted as cross-correlogram of body/tail and head deflections; modified from [12]. **b** Schematic organization of the neuronal circuitry for conveying spinal locomotor efference copies onto brainstem gaze control centers. **c**, **d** Isolated whole head preparations of larval *Xenopus* (**c**) employed for optical recording of eye movements (*orange trace* in **d**) and electrophysiological recordings of multi-unit spike discharge from the right LR nerve and a left spinal ventral root (VR; *blue and black traces* in **d**) during an episode of fictive swimming; from Schuller and Straka, unpublished data. **e** Multi-unit recordings of the bilateral LR and left MR nerves (*blue traces*) and bilateral VR (*black traces*) during fictive swimming, illustrating spino-extraocular motor coupling patterns; modified from [6]. **f–h,** right LR nerve and left VR discharge activity (*blue* and *black* traces in **f**, **g**) during passive *horizontal rotation* (*red trace* in **f**, **g**) in the absence (**f**) and during fictive swimming, indicated by VR bursts (**g**); comparison of fictive swimming-associated LR nerve bursts during *rightward*, excitatory (LR$_{exc}$; *light blue*) and *leftward*, inhibitory phases (LR$_{inh}$; *dark blue*) of the *horizontal angular* VOR (**h**); asterisk in **e** and hash in **f** indicate pauses during efference copy-mediated LR bursts (**e**) and the inhibitory component of rotation-induced LR discharge (**f**), respectively; modified from [15]

homo-segmental, midline-crossing inhibitory interneurons that are activated by ascending excitatory spinal neurons on the contralateral side. Independent of the two possibilities, an alternating spinal excitation–inhibition of abducens motoneurons might have a similar spatially specific pharmacological organization as the push–pull connectivity of the horizontal VOR, which includes a crossed glutamatergic vestibular excitation and an uncrossed glycinergic vestibular inhibition (# in Fig. 2f) [19].

Spino-extraocular motor coupling during self-motion in *Xenopus* tadpoles is spatio-temporally appropriate for eliciting compensatory eye movements and potentially sufficient to offset retinal image displacements during real swimming. A role of sensory signals for eye movements during locomotion was tested in larval preparations with intact inner ears and vestibulo-ocular connections but otherwise isolated CNS [15]. Passive horizontal rotation in such preparations in the absence of fictive swimming evokes a modulated spike discharge in the LR nerve (Fig. 2f), compatible with a functional VOR (Fig. 1d). However, passive head rotation during an episode of fictive swimming fails to evoke a summation of efference copy and horizontal semicircular canal-derived activity in the LR nerve (Fig. 2g). In fact, efference copy-triggered LR bursts have similar magnitudes independent of their occurrence during the excitatory (LR$_{exc}$) or inhibitory (LR$_{inh}$) phase of the horizontal rotation (see light and dark blue curve in Fig. 2h). This cancelation of angular horizontal VOR signals during locomotor activity is plane-specific since vertical motion-induced LR discharge during

episodes of fictive swimming are integrated with spinal locomotor efference copies [15].

Conclusions

Larval *Xenopus* express a robust VOR behavior with spatio-temporally adequate eye movements during externally induced head/body motion [14]. This indicates that the sensory–motor transformation in these animals is well suited to offset the disruptive effects on retinal image stability during passive head/body motion. In contrast, during self-motion, spinal locomotor efference copies evoke compensatory eye movements, while simultaneously suppressing the horizontal angular VOR. While the cancelation of the latter occurs at least in part at the sensory periphery [8], central vestibular circuits must, in addition, be involved in this process. The underlying mechanism likely includes inhibitory influences of intrinsic signals on sensory inputs comparable to the cancelation of vestibular inputs during active head movements in monkeys [4, 5, 20, 21]. The mechanistic basis for gaze-stabilizing eye movements, thus, differs between actively and passively induced head/body movements. Because efference copies evoke functionally appropriate eye movements also during limb-based swimming in adult frogs [7], these intrinsic signals might also contribute to gaze and posture stability during rhythmic locomotion in other vertebrates including mammals [22].

Compliance with ethical standards

Conflicts of interest The authors declare no conflict of interest.

Ethical standards The content of this review complied with all ethical standards.

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