Dispatches

Motor Control: Spinal Circuits Help Tadpoles See Clearly

A recent study suggests that animals can rely on internal expectations about their head movements, rather than vestibular sensations, to see what's in front of them.

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Anyone operating a hand-held camera is familiar with the distortion one's own movements can create in images. This is a common problem for visual creatures: how do you maintain visual acuity as you move around? For most, including humans, the solution is to actively stabilize the eyes in space. This ability has generally been attributed to vestibulo-ocular circuits, which detect physical displacements and provide compensatory signals to eye muscles [1]. In this issue, however, Lambert and colleagues [2] provide compelling new evidence that the neural signals driving gaze stabilization during locomotion arise centrally from within the spinal cord.

Before they metamorphose into frogs, tadpoles use their tail muscles to swim around much like fishes. When they are swimming quickly, the alternating bends of the body cause the head to wag back and forth (Figure 1A). Normally, this would make the visual field shift from side to side, but muscles controlling eye rotation serve to counteract the effects of swimming movements. As in all vertebrates, the lateral rectus muscles pull the eyes outward, while the medial rectus muscles pull them inward (Figure 1B). These antagonistic ocular muscles are appropriately driven during swimming to ensure that body bends to the left are associated with bilateral eye movements to the right, and vice versa. The end result is that the eyes remain facing forward despite lateral undulations of the body, which minimizes any self-generated motion blur (Figure 1A).

In an earlier brief report in *Current Biology* [3], this same group had demonstrated that compensatory oculomotor activity persists during 'fictive' swimming in an isolated brainstem/spinal cord preparation, and in the absence of vestibular signals. This provocative result implicated a copy of the out-going (or 'efferent') motor command in the production of compensatory eye movements and raised a number of important questions: Where does this efference copy arise? Is it relayed through vestibular circuits, or does it influence oculomotor circuitry directly? And, crucially, how do efference copy and vestibular signals interact in a moving animal?

Lambert *et al.* [2] have now answered these questions using a wide range of impressive techniques ideally suited to the *Xenopus* tadpole preparation. By performing simultaneous recordings of nerve activity in oculomotor and spinal nerves of immobilized tadpoles, they were able to show that compensatory oculomotor activity persists after midbrain removal, but disappears when the rostral spinal cord falls silent. A series of selective lesions and manipulations of neuronal excitability confirmed that the efference copy originates from the rostral spinal cord. Thus, spinal neurons carrying copies of the motor command drive firing in the appropriate ocular motor pools to pull the eyes in the opposite direction as the head (Figure 1B).

The authors had speculated in their earlier work that these efference copy signals might be relayed through the vestibular nucleus, a major driver of oculomotor circuits. Surprisingly, blocking excitatory neurotransmission in the vestibular nuclei was completely ineffective at preventing spinal-driven oculomotor activity during fictive

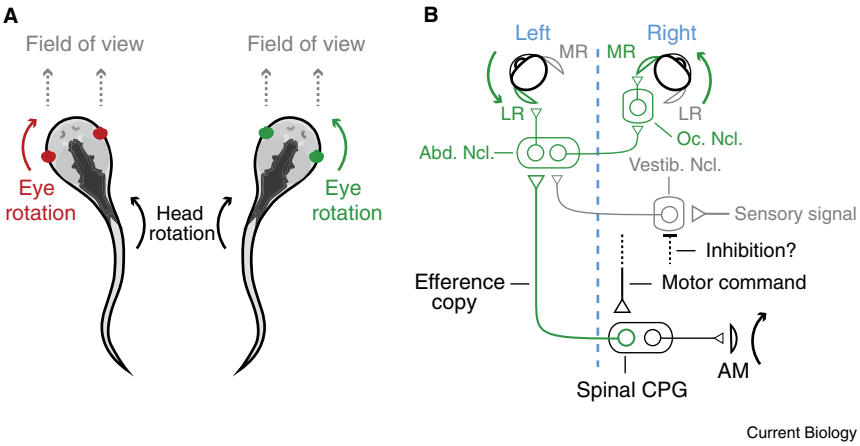

Figure 1. Counter-rotation of the eyes during swimming movements is now explained by a simple wiring diagram involving the spinal cord.

(A) When *Xenopus* tadpoles swim, the body undulates back and forth, causing the head to rotate to the left and right. These movements are associated with eye rotations in the opposite direction, which maintains a relatively fixed field of view in front of the animal. (B) The out-going ('efferent') motor command reaches the spinal cord and activates the spinal central pattern generator (CPG), initiating a body bend via axial muscles (AM) in the tail that rotates the head to the right. Spinal interneurons relay this signal (efference copy) across the body back to the ocular motor pools, which generate bilateral eye rotation to the left. Within the abducens nucleus (Abn. Ncl.) are motoneurons that drive lateral rectus (LR) muscle activation and interneurons that activate motoneurons in the ocular nucleus (Oc. Ncl.), which in turn drive medial rectus (MR) muscle activation. Sensory signals arriving via the vestibular nucleus (Vestib. Ncl.) target the same nuclei, but are presumably inhibited by an as yet unknown pathway. For simplicity, only the circuit driving leftward eye movements is illustrated (green in A). A blue dashed line separates the left and right sides of the body.

swimming. Along with stimulation experiments showing short-latency spinal-oculomotor connections, these findings demonstrate that spinal neurons bypass the vestibular nucleus to make direct connections to the circuits driving eye movements (Figure 1B).

These experiments were conducted primarily in head-fixed preparations, leaving open the major question of how normal vestibular signals might combine with efference copy information to drive ocular reflexes. This question is at the heart of the puzzle of how the brain combines sensory signals about the *results* of self-motion with internally generated efference copy signals about *predicted* self-motion.

To address this issue, the authors performed a technically demanding set of experiments in the intact, immobilized tadpole. First they measured the oculomotor activity driven by sinusoidal rotation around a vertical axis (that is, as though the tadpole were on a turntable). The resulting vestibular signals indeed drive appropriate compensatory oculomotor activity. Next they checked that fictive swimming also drives oculomotor circuits, consistent with the other findings in this paper. Finally, they combined the two signals: sinusoidal rotation at one frequency simultaneous with fictive swimming at a higher frequency. The result? The oculomotor response is entirely driven by swimming efference copy, with no contribution from vestibular signals in the horizontal plane.

The fact that vestibular signals are dispensable for corrective eye movements during locomotion is surprising. What are the vestibular inputs doing? One potential answer provided by this work is that the vestibular signal cancellation appears to be selective for the horizontal plane. When the preparations were manipulated with a roll stimulus (one ear up and one ear down), vestibular signals were additive, albeit somewhat sublinearly, with efference copy signals. The implication is that vestibular inputs are unmasked when sensory feedback from movements does not match that predicted by a *task-specific* efference copy signal.

These findings share some similarities with an important series of experiments in monkeys by Cullen and Roy [4], who demonstrated that firing in the vestibular nuclei is tightly correlated with head velocity during passive, experimenter-driven head movements — but this activity is absent during active, animal-driven movements. Thus, it appears that in both systems the animals use an internally generated model of movement to suppress central vestibular signaling (Figure 1B).

A major open question going forward is the identity of this suppressive circuit. In fact, there are likely to be several such circuits. Studies in monkeys suggest that vestibular cancellation is selective for expected movement: suppression occurs only when 'proprioceptive' sensory input from neck muscles matches expected neck motion [5]. In contrast, the current study [2] shows that tadpoles cannot process even unexpected horizontal vestibular signals during swimming, suggesting a less selective circuit mechanism. Tadpoles and fishes lack trunk muscle spindles [6], leaving open the possibility that mammals evolved a more selective proprioception-based suppression circuit. The circuit basis of either a general or a selective suppressive mechanism will be important for understanding how the brain fuses self-generated and external information about movement.

What is the relevance of these findings in tadpole to mammalian oculomotor control circuits? If visual acuity relies progressively more on efference copy signals as locomotion speeds up, vestibular signaling could become less relevant at faster speeds. Indeed, humans with vestibular deficits are paradoxically more stable during running than during walking [7,8]. Thus, spinal circuits may influence not only local musculature, but the entire way we see the world.

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http://dx.doi.org/10.1016/j.cub.2012.07.007

Evolution: Mitochondrial Burden on Male Health

In many animal species, males suffer more from age-related disease than females. Is there a common cause for this burden on male health? Recent work supports the theory that the female transmission of mitochondria disproportionately increases the mutation load in males.

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Mitochondria usually pass from mother to offspring, while males rarely transmit mitochondria. Selection is, therefore, blind to male-specific mitochondrial phenotypes. A mutation with a strongly deleterious effect in males but only a weak effect in females is nearly neutral, because only the female-specific consequences can be selected. This sex-biased 'selective sieve' inevitably causes deleterious mitochondrial mutational effects to accumulate more strongly in males than in females [1].