2. St Johnston, D., and Ahringer, J. (2010). Cell polarity in eggs and epithelia: parallels and diversity. Cell *141*, 757–774.

3. Nelson, W.J. (2003). Adaptation of core mechanisms to generate cell polarity. Nature *422*, 766–774.

4. Svitkina, T.M. (2020). Actin cell cortex: structure and molecular organization. Trends Cell Biol. *30*, 556–565.

5. Doerflinger, H., Zimyanin, V., and St Johnston, D. (2022). The Drosophila anterior-posterior axis is polarized by asymmetric myosin activation. Curr. Biol. *32*, 374–385.

6. Merkle, J.A., Wittes, J., and Schüpbach, T. (2020). Signaling between somatic follicle cells and the germline patterns the egg and embryo of Drosophila. Curr. Top. Dev. Biol. *140*, 55–86.

7. Heissler, S.M., and Sellers, J.R. (2014). Myosin light chains: Teaching old dogs new tricks. Bioarchitecture *4*, 169–188.

8. Lecuit, T., Lenne, P.F., and Munro, E. (2011). Force generation, transmission, and integration during cell and tissue morphogenesis. Annu. Rev. Cell Dev. Biol. *27*, 157–184.

9. Gan, W.J., and Motegi, F. (2020). Mechanochemical control of symmetry breaking in the Caenorhabditis elegans zygote. Front. Cell Dev. Biol. *8*, 619869.

10. Oon, C.H., and Prehoda, K.E. (2019). Asymmetric recruitment and actin-dependent cortical flows drive the neuroblast polarity cycle. eLife *8*, e45815.

11. Tsankova, A., Pham, T.T., Garcia, D.S., Otte, F., and Cabernard, C. (2017). Cell polarity regulates biased myosin activity and dynamics during asymmetric cell division via Drosophila Rho kinase and protein kinase N. Dev. Cell *42*, 143–155.

12. Hannaford, M.R., Ramat, A., Loyer, N., and Januschke, J. (2018). aPKC-mediated displacement and actomyosin-mediated retention polarize Miranda in Drosophila neuroblasts. eLife *7*, e29939.

13. Kelkar, M., Bohec, P., and Charras, G. (2020). Mechanics of the cellular actin cortex: From signalling to shape change. Curr. Opin. Cell Biol. *66*, 69–78.

14. Zhu, M., and Zernicka-Goetz, M. (2020). Principles of self-organization of the mammalian embryo. Cell *183*, 1467–1478.

15. Rigor, R.R., Shen, Q., Pivetti, C.D., Wu, M.H., and Yuan, S.Y. (2013). Myosin light chain kinase signaling in endothelial barrier dysfunction. Med. Res. Rev. *33*, 911–933.

16. Stull, J.T., Kamm, K.E., and Vandenboom, R. (2011). Myosin light chain kinase and the role of myosin light chain phosphorylation in skeletal muscle. Arch. Biochem. Biophys. *510*, 120–128.

17. Guo, S., and Kemphues, K.J. (1996). A non-muscle myosin required for embryonic polarity in Caenorhabditis elegans. Nature *382*, 455–458.

18. Majumder, P., Aranjuez, G., Amick, J., and McDonald, J.A. (2012). Par-1 controls myosin-II activity through myosin phosphatase to regulate border cell migration. Curr. Biol. *22*, 363–372.

19. Jiang, T., and Harris, T.J.C. (2019). Par-1 controls the composition and growth of cortical actin caps during Drosophila embryo cleavage. J. Cell Biol. *218*, 4195–4214.

20. Folkmann, A.W., and Seydoux, G. (2019). Spatial regulation of the polarity kinase PAR-1 by parallel inhibitory mechanisms. Development *146*, dev171116.

Efference copies: Side-eyeing across species

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Efference copies of movement-inducing neural signals have been proposed to serve a role in gaze stabilization. Prior work has demonstrated a spino-extraocular motor circuit in the tadpole that relays copies of spinal commands to extraocular motor neurons. A recent study demonstrates the presence of this circuitry in mice, suggesting a unique method of gaze stabilization in the locomoting mouse.

From eluding dangerous predators to reaching for a cup of coffee, movement is essential for survival. But with each movement comes a flurry of sensory feedback. How does the brain separate such 'reafference' that follows self-motion from other sensory information? Simply put, the brain talks to itself. For each voluntary movement, motor areas generate an efference copy — an internal duplicate of a movement-producing signal — and sensory-processing areas adjust their expectations[1,2]. If you've ever wondered why tickling yourself doesn't work, it's because an efference copy let your brain know that there was nothing funny going on.

Recently, efference copies have been proposed to serve an additional vital role: to stabilize gaze. When you walk, your entire body moves up and down. Such a bobbing head ought to disrupt visual perception, especially when moving fast or on bumpy terrain. Well-conserved sensorimotor circuitry exists to transform perceived head movements into compensatory eye movements[3,4], and these computations rely on processing sensed instability. Sensation is not as quick as an efference copy. In 2008, Combes *et al.*[5] reported that copies of spinal commands for movement were relayed to motor neurons that move the eyes in tadpoles (Figure 1). These signals supplemented classical vestibulo-ocular circuitry, allowing for extraordinarily efficient gaze stabilization during locomotion. To date, it has remained mysterious whether such spino-ocular signals operate similarly in mammals. In a key step forward, new work reported in this issue of *Current Biology* by de Barros *et al.*[6] has demonstrated that these circuits, signals, and behavior are indeed conserved in mice.

In their study, de Barros *et al.*[6] first demonstrated a direct coupling between spinal motor activity and oculomotor activity during fictive locomotion. To accomplish this, the authors stimulated the sacral dorsal root in an *ex vivo* mouse

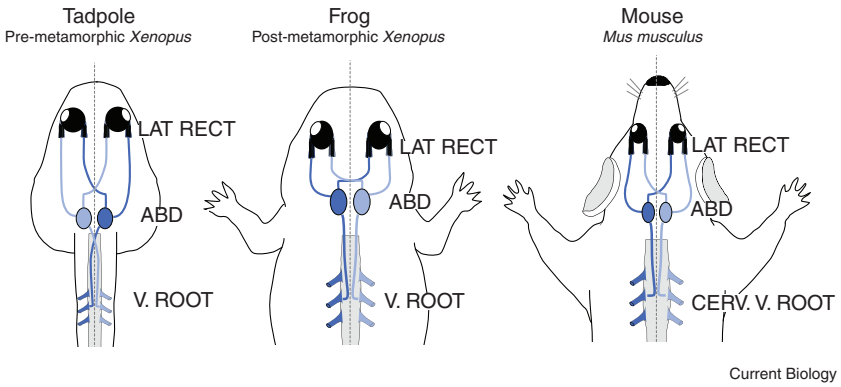

Figure 1. Ancient circuits for stable gaze persist in mice.
A spino-extraocular motor circuit has been proposed in the pre-metamorphic tadpole[5,10], juvenile frog[11], and mouse[6]. This circuitry is proposed to consist of spinal ventral roots monosynaptically coupled to the abducens nuclei. The abducens nuclei are a bilateral extraocular motor neuron pool in the brainstem innervating the lateral rectus, an extraocular muscle that moves the eye laterally. Motor neurons of the right abducens nucleus innervate the right lateral rectus muscles of both eyes; motor neurons of the left abducens nucleus innervate the left lateral rectus muscles of both eyes. In the mouse and frog, left limb activity is associated with leftward eye deflection. In the tadpole, ventral root activity is coupled to the contralateral abducens nuclei; interestingly, post-metamorphosis, this connectivity becomes unilateral. In the mouse, monosynaptic coupling between the spine and the abducens nuclei has been localized to the cervical spine. Across these species, lateral eye movement has been demonstrated to occur in sync with locomotion. V. ROOT, ventral root; CERV. V ROOT, cervical ventral root; ABD, abducens nuclei; LAT RECT, lateral rectus. Dark blue, left limb tract; light blue, right limb tract.

prep while simultaneously recording activity in the cervical and lumbar dorsal roots of the spine, as well as the abducens nuclei in the brainstem (the extraocular motor neurons mediating lateral eye movements). As expected, the cervical and lumbar dorsal root activity followed the evoked sacral root activity, that is, hindlimb movement in step with ipsilateral forelimb movement as would be seen in a walking mouse. Further, left cervical root activity was out of phase with right cervical root activity: When the left cervical root activity increased, right cervical root activity decreased and vice versa. These patterns reflect the one-foot-in-front-of-the-other gait during normal walking. Excitingly, the abducens motor neuron activity also matched the activity of these spinal motor neurons. The eye motor neurons were active synchronously with ipsilateral spinal motor neurons: left and right abducens neurons fired out of phase with each other and in phase with spinal motor neurons of the same side. This experiment was the first indication of functional coupling between motor neurons responsible for gait and motor neurons responsible for eye movement.

Because locomotion involves the coordinated activity between forelimbs and hindlimbs controlled by different spinal regions, de Barros *et al.*[6] next investigated which parts of locomotion were coupled to lateral eye movement. To get at this question, the experimenters induced fictive locomotion while interfering with communication between different regions of the spinal cord. When synaptic transmission was blocked in the cervical spinal cord, direct stimulation of the sacral dorsal root generated activity in the lumbar ventral root but did not elicit any activity in the abducens nuclei. Further, when the spinal cord was transected below the cervical spine, stimulation of the cervical spine alone was sufficient to drive activity in the abducens nuclei. Together, these experiments demonstrate that locomotor activity from the cervical ventral root is indispensable to drive coordinated activity in the abducens nuclei.

de Barros *et al.*[6] next set out to trace the relevant circuit that linked the cervical ventral root and the abducens motor neurons. To test if these motor neurons directly communicated with cervical ventral root neurons, the experimenters used an injectable rabies virus tracer. Rabies virus is powerfully specific, propagating retrogradely between directly connected neurons and leaving a trail of replicated virus in its wake[7]. The experimenters injected rabies virus into the lateral rectus muscle, then waited. Over the span of several days, the rabies virus replicated within the muscle cells, and then worked backwards through the brain, infecting the motor neurons that directly project to the muscle, and then the neurons that directly project to the motor neurons. The experimenters looked to see where the rabies virus ended up. Unsurprisingly, rabies virus was found in the abducens motor neurons that innervate the lateral rectus muscle. As time passed, more rabies virus was found in the vestibular nuclei that project to the abducens nuclei. As these neurons are part of the classical vestibulo-ocular reflex circuit that relays sensed instability to ocular motor neurons[8,9], this finding was an important control. Intriguingly, rabies virus was also found in cervical spinal neurons, illustrating a direct (monosynaptic) link between spinal neurons and abducens motor neurons in mice.

With evidence of direct functional coupling through defined anatomical circuitry, de Barros *et al.*[6] next set out to observe this spinal-ocular coordination in action. To assay locomotor-derived eye movements of a mouse on a treadmill while minimizing visual/vestibular signals, the experimenters placed mice on a treadmill in the dark (vision) while their heads were held stationary (vestibular). Additionally, the mice were decerebrated, removing descending cortical motor commands. As the treadmill ran, video recordings of limb and eye movements were collected. When the animals moved slowly, no relationship was recorded between eye and limb movements. When the animals picked up the pace, though, the eyes began to move horizontally in conjugate to each other and to the forelimbs. As mice adopted faster gaits, the frequency of eye movements matched the speed of locomotion. These movements were mostly synchronized between the ipsilateral forelimbs and eyes, in line with the *ex vivo* direct stimulation experiments. Together, these observations support a functional role for an efference copy signal between the cervical spine and oculomotor neurons in controlling mouse gaze.

Earlier work from the Straka lab[5,10] described an efference copy sent from locomotor pattern generating circuitry in the spine to extraocular motor neurons in pre-metamorphic *Xenopus* tadpoles. These authors reported that undulatory

swimming resulted in lateral head displacement, which was accompanied by synchronized lateral counter-movements of the eyes. The results presented by de Barros *et al.*[6] mark the first report of this circuitry in a mammal. The conservation of this phenomenon between species is remarkable, and of course suggests more questions, such as why lateral eye movements? While tadpoles swim with undulatory movements (a lateral wave), mouse gait, like humans, ought to displace the head primarily in the vertical plane. Interestingly, while decerebrated mice displayed lateral eye movements during trot-like locomotion, vertical eye movement was largely absent.

An explanation for this discrepancy could be due to the idea that this circuitry is vestigial, a gaze-stabilization tactic in earlier organisms that move primarily in the lateral plane. A few years after this circuitry was identified in the tadpole, von Uckermann *et al.*[11] reported that this circuitry persists in post-metamorphic *Xenopus* during swim, first demonstrating the presence of this circuitry in a four-legged animal (Figure 1). Additionally, it is possible that some lateral head displacement occurs in tetrapods that requires gaze stabilization. Forelimbs and hindlimbs move in sync ipsilaterally and out of sync contralaterally, requiring a continual shift in weight during locomotion. This could likely result in a left-right displacement of the head, given its proximity to the cervical spine. Prior work in the cat demonstrated such lateral head movement during left and right limb movement[12]. Another possibility could be that this efference copy works in tandem with classic vestibulo-ocular reflex signaling to stabilize gaze during horizontal displacements evoked during fast locomotion. For instance, running quickly or across an uneven terrain could result in irregular or dramatic lateral head displacement, which could be corrected more quickly by an efference copy prediction.

This work reported by de Barros *et al.*[6] demonstrates a unique circuit for lateral eye movement in the locomoting mouse (Figure 1). The ability of the brain to use efference copies to predict how vision will be distorted, and to correct these distortions more efficiently, suggests a powerful complement to classic vestibular reflexes. The question of the utility of this circuit in a tetrapod opens new avenues of research to tackle the topics of ethological relevance, as well as the question of how this circuit develops alongside traditional gaze stabilization circuitry[9,13]. Together, this work will advance our understanding of the mechanisms used to control gaze during locomotion.

REFERENCES

1. Bell, C.C. (1981). An efference copy which is modified by reafferent input. Science *214*, 450–453.
2. Poulet, J.F.A., and Hedwig, B. (2006). The cellular basis of a corollary discharge. Science *311*, 518–522.
3. Szentágothai, J. (1950). The elementary vestibulo-ocular reflex arc. J. Neurophysiol. *13*, 395–407.
4. Angelaki, D.E. (2009). Vestibulo-ocular reflex. In Encyclopedia of Neuroscience, L.R. Squire, ed. (Amsterdam: Elsevier Ltd), pp. 139–146.
5. Combes, D., Le Ray, D., Lambert, F.M., Simmers, J., and Straka, H. (2008). An intrinsic feed-forward mechanism for vertebrate gaze stabilization. Curr. Biol. *18*, R241–R243.
6. de Barros, F.F., Bacqué-Cazenave, J., Taillebuis, C., Courtand, G., Manuel, M., Bras, H., Tagliabue, M., Combes, D., Lambert, F.M., and Beraneck, M. (2022). Conservation of locomotion-induced oculomotor activity through evolution in mammals. Curr. Biol. *32*, 453–461.
7. Ugolini, G. (2011). Rabies virus as a transneuronal tracer of neuronal connections. Adv. Virus Res. *79*, 165–202.
8. Horn, A.K.E., and Straka, H. (2021). Functional organization of extraocular motoneurons and eye muscles. Annu. Rev. Vis. Sci. *7*, 793–825.
9. Schoppik, D., Bianco, I.H., Prober, D.A., Douglass, A.D., Robson, D.N., Li, J.M.B., Greenwood, J.S.F., Soucy, E., Engert, F., and Schier, A.F. (2017). Gaze-stabilizing central vestibular neurons project asymmetrically to extraocular motorneuron pools. J. Neurosci. *37*, 11353–11365.
10. Lambert, F.M., Combes, D., Simmers, J., and Straka, H. (2012). Gaze stabilization by efference copy signaling without sensory feedback during vertebrate locomotion. Curr. Biol. *22*, 1649–1658.
11. von Uckermann, G., Le Ray, D., Combes, D., Straka, H., and Simmers, J. (2013). Spinal efference copy signaling and gaze stabilization during locomotion in juvenile *Xenopus* frogs. J. Neurosci. *33*, 4253–4264.
12. Zubair, H.N., Beloozerova, I.N., Sun, H., and Marlinski, V. (2016). Head movement during walking in the cat. Neuroscience *332*, 101–120.
13. Bagnall, M.W., and Schoppik, D. (2018). Development of vestibular behaviors in zebrafish. Curr. Opin. Neurobiol. *53*, 83–89.

Olfaction: One receptor drives opposite behaviors

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Many odorants are attractive at low concentrations but repulsive at higher concentrations. A new study demonstrates that, in *Caenorhabditis elegans*, a single odorant receptor acts in two different neuron pairs to mediate both attractive and repulsive responses to an odorant.

Animals from worms to humans detect and respond to a remarkable number of odorants. Although many odorants are either appetitive or aversive across concentrations, a subset are appetitive at low concentrations but aversive at higher concentrations[1,2]. One well-known example is the chemical indole, which is perceived by humans as having a floral scent at low concentrations but a fecal smell at higher concentrations[3]. How different concentrations of an