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Active mechanosensory feedback during locomotion in the zebrafish spinal cord

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The investigation of mechanosensory feedback to locomotion has been hindered by the challenge of recording neurons in motion. Genetic accessibility and optical transparency of zebrafish larvae provide means to revisit this question. Glutamatergic Rohon-Beard (RB) and GABAergic CSF-contacting neurons (CSF-cNs) are spinal mechanosensory neurons. Recent studies combining bioluminescence, silencing and optogenetic activation show that mechanosensory neurons enhance speed and stabilize posture during locomotion. RB neurons can modulate speed by projecting onto glutamatergic premotor V2a interneurons during fast swimming, while CSF-cNs inhibit V0-v interneurons sustaining slow swimming. Sensory gating, either through inhibition of sensory interneurons (CoPA) or though the direct inhibition of primary motor neurons by CSF-cNs, mediates postural control. Advanced optical methods have shed light on the dynamics of sensorimotor integration during active locomotion unraveling implications for translational research.

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Introduction

In humans, it is a well-known clinical fact that the loss of proprioception, that is, the sense of position of the joints, results in gait imbalance and an inability to walk properly, a condition termed 'proprioceptive ataxia'. Although oscillatory activity of motor neurons during locomotion is generated by spinal microcircuits and does not need sensory afferents, cutaneous and proprioceptive feedback can critically modulate ongoing locomotion [1]. In cats for instance, dynamic sensorimotor interactions adapt the locomotor pattern to the environment in a state and phase-dependent manner, depending on when these inputs occur within the step cycle [2]. Recent evidence from rodents indicate that a loss of proprioceptive feedback in animals lacking muscle spindles (group Ia/II afferents) results in degradation of joints coordination and flexor/extensor alternation [3].

The mechanisms and neuronal basis underlying the effects of mechanosensory feedback during active locomotion are not well understood. Recent advances in genetic targeting of populations of neurons within the spinal cord have allowed the dissection of spinal sensorimotor microcircuits at the cellular level. Genetic targeting of *Gad2*$^+$ inhibitory premotor interneurons in mice showed that these interneurons were involved in suppressing oscillations during smooth reaching movements [4]. Similarly, selective ablation and activation of a subgroup of *Chx10*$^+$ V2a interneurons in the cervical spinal cord of rodents demonstrated that they were part of a cerebellar-motor loop ensuring effective reaching [5]. In addition to proprioceptive sensorimotor circuits, the recent genetic targeting of cutaneous afferents responsible for light touch via the receptor ROR-alpha confirmed their role in corrective movements during ongoing locomotion [6].

In the last ten years, genetic targeting of sensory afferents allowed their electrophysiological characterization and selective manipulation during active locomotion. Nonetheless, probing the recruitment of mechanosensory feedback during ongoing locomotion *in vivo* remains a technical challenge. In mammalian species, the perturbation and recording of targeted neuronal populations within the spinal cord during ongoing locomotion is a daunting task. In this regard, the zebrafish larva offers several advantages such as: genetic amenability, optical transparency, and a relatively simple, stereotyped and quantifiable locomotor behavior. In this review, we will discuss recent *in vivo* investigations of mechanosensory feedback during ongoing locomotion in zebrafish larvae.

Quantitative analysis of behavior in zebrafish larvae

Animal behavior is remarkably versatile in all species. Yet, the locomotor repertoire of the zebrafish larva is relatively stereotyped [7•], with less than a dozen possible categories of maneuvers including 'slow swimming', 'fast swimming', 'prey capture' and 'escape response' [8]. This limited repertoire allows high throughput quantitative

analysis of tail kinematics during active locomotion of freely swimming animals [9]. On the other side, fictive locomotion patterns, obtained from electrophysiological ventral nerve root recordings, provide a quantitative measure of motor neuron recruitment when sensory feedback is absent [10]. In response to aversive stimuli (auditory, visual, chemo-sensory or mechano-sensory), the zebrafish larva's escape is a stereotyped motion away from danger. Similar escape responses have been described in many fish species and in *Xenopus* tadpoles [11]. The escape response of 5–9 days post-fertilization (dpf) zebrafish larva typically consists of an initial fast 'C-bend' followed by a counter bend and a subsequent swim of progressively decreasing tail beat frequency [8]. Therefore, the escape response can be separated between an initial fast swimming component (tail beat frequency above 30 Hz) followed by a slow swimming component (tail beat frequency below 30 Hz) [12].

A large body of work in the last decade has identified that even so-called reflexes involve distributed networks in the brain and spinal cord [13,14]. In the hindbrain, supraspinal control of the escape response in zebrafish and other teleost fishes consists of an array of 300 reticulospinal neurons including the 'Mauthner cells' and their homologs [15]. Mauthner cells receive sensory inputs from visual, vestibular and auditory afferents and project to contralateral spinal motor neurons via a large myelinated descending axon. In zebrafish, escape responses can be triggered by mechanical stimuli to the head or to the tail, auditory stimuli [16], looming visual stimuli [17,18] as well as chemosensory stimuli [19]. Ablation and calcium imaging studies showed that these different sensory modalities differentially recruited Mauthner cells or their homologs, leading to escapes with different delays and possible subsequent kinematics [7•,16,20]. In the spinal cord, primary and secondary motor neurons are recruited by reticulospinal neurons to initiate the escape. Once the escape response is triggered, premotor interneurons can modulate the kinematics of locomotion by forming modular microcircuits that are recruited as a function of speed [21]. Further downstream, motor neurons are organized following the size principle (Heinemann 1960s). Primary motor neurons are located dorsally and innervate fast muscles. Receiving direct inputs from Mauthner cells, these neurons are responsible for the initial large amplitude C-bend and subsequent fast swim (30–100 Hz). In contrast, secondary motor neurons are located more ventrally and drive swimming at slower frequencies (10–30 Hz) [22]. Premotor interneurons recruited at distinct (low or high) locomotor frequencies are characterized by distinct morphological, physiological and genetic properties. For example, *Chx10*$^{+}$ glutamatergic V2a interneurons recruited at high locomotor frequencies are located dorsally. On the other hand, glutamatergic interneurons recruited at low frequencies include ventral V2a interneurons and glutamatergic V0-v interneurons expressing the *dbx1b* transcription factor [23].

Multiple elements can modulate escape kinematics. First, the efficiency of the initial recruitment of primary motor neurons on one side during the C-bend is enhanced through inhibitory commissural interneurons (termed CoLo for 'commissural local' in the zebrafish larva), which provide monosynaptic inhibition onto contralateral primary motor neurons at each segment [24,25]. In addition, there is evidence for a spinal circuit involving endocannabinoids that silence the slow module during the initial fast swimming [26]. The well-studied and relatively simple neuronal circuit underlying the escape response provides a great model to tackle questions such as: what are the mechanosensory inputs to the escape circuit, and how do timed mechanosensory inputs modulate motor output?

Mechanosensory feedback enhances speed

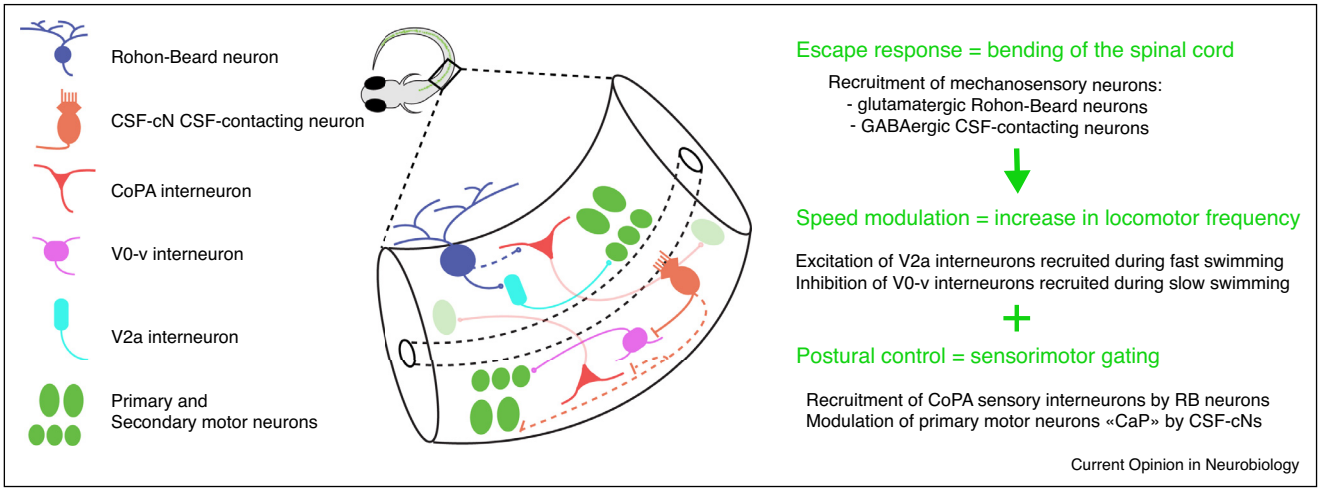
We found multiple lines of evidence that mechanosensory feedback originating from diverse sensory cell types contribute to speed enhancement.

Glutamatergic Rohon-Beard neurons

Rohon-Beard (RB) neurons are large glutamatergic sensory neurons located in the dorsal spinal cord, appearing as early as 1 day post fertilization (dpf) [27]. These cells were long thought to be promptly replaced by dorsal root ganglions (Figure 1), even though many remain past the first week of development (Dr Wyart, unpublished observation). Many studies have demonstrated, in zebrafish and *Xenopus*, that RB neurons are mechanosensitive neurons responding to light touch with either a single or few action potentials [28,29••]. In zebrafish larvae, RB neurons synapse onto glutamatergic CoPA (for 'commissural primary ascending') interneurons, which in turn project to V2a interneurons [30]. Starting during embryogenesis (21 hours post-fertilization), a simple motor behavior consisting in a contralateral coiling of the trunk, referred to as a 'touch response', can be triggered by a mechanical stimulus to the tail. Using transection experiments, Pietri *et al.* showed that touch responses in zebrafish embryos relied on an intraspinal loop involving RB and CoPAs, similar to the cutaneous reflex described in *Xenopus* [31]. Interestingly, in 24 hour post fertilization (hpf) zebrafish larvae, optogenetic stimulation of a single RB neuron which elicits a single spike, is sufficient to trigger a full escape [32]. This observation suggests that at early stages of development, spinal mechanosensory neurons can recruit larger networks within the spinal cord, possibly involving CoPAs and V2a interneurons and driving the escape behavior. Apart from triggering escape or touch responses, is there a role for mechanosensory neurons in modulating ongoing locomotion?

Taking advantage of a bioluminescent reporter GFP-Aequorin, Knafo *et al.* monitored the activity of spinal

Figure 1



Circuits underlying mechanosensory feedback in the zebrafish spinal cord.

motor neurons in moving zebrafish larvae. The authors compared bioluminescence signals from motor neurons in actively moving larvae compared to immotile mutant siblings or pharmacologically induced paralysed larvae. They observed reliably that recruitment of spinal motor neurons was enhanced during active locomotion [29••]. In order to investigate the role of sensory feedback, the authors silenced glutamatergic mechanosensory neurons (trigeminal, dorsal root ganglia, RB neurons) using the Botulinum toxin B light chain *BoTxBLC* [33] driven by the *isl2b* promoter. Remarkably, *BoTxBLC* larvae exhibited earlier transitions between the fast and slow components of the escape response, resulting in overall lower speeds and longer swim durations. Optical activation and fluorescence-targeted electrophysiological recordings revealed the intraspinal responsible for the observed effect. They showed that RB neurons synapse onto the dorsal-most V2a interneurons selectively recruited during fast swimming. This observation suggests that mechanosensory feedback from spinal RB during the initial phase of the escape response could contribute to the enhancement of speed via mechanosensory feedback [29••].

GABAergic cerebrospinal fluid contacting neurons

RB neurons are not the only sensory neurons candidates for integrating mechanical inputs within the spinal cord (Figure 1). Recent studies on cerebrospinal fluid-contacting neurons (CSF-cNs), also known as Kolmer-Agduhr (KA) cells, have revealed that these cells provide sensory feedback associated with spinal bending during locomotion. CSF-cNs are GABAergic ciliated neurons located in the ventral spinal cord along the central canal found in virtually all vertebrate species [34,35]. In the zebrafish larva, optical stimulation of CSF-cNs using the light-gated channel LiGluR has been shown to induce slow swimming, revealing a projection onto central pattern generators in the spinal cord [36]. Recent investigations took advantage of the expression of the transient receptor potential channel Pkd2l1 to selectively target CSF-cNs in the spinal cord [37,38]. Performing functional imaging via a genetically encoded calcium indicator [39,40], Böhm *et al.* showed that CSF-cNs are selectively recruited by active muscle contraction as well as passive tail bending, but not during fictive locomotion where muscle contraction is blocked [41••]. The mechanosensitivity of CSF-cNs shows an interesting asymmetry. While dorsal lateral CSF-cNs are only recruited during lateral bending on one side [41••], ventral CSF-cNs are recruited solely during longitudinal bending. The mechanosensitivity of CSF-cNs was confirmed *in vitro* in lamprey spinal cord [42•] as well as in zebrafish primary cultures where the critical role of Pkd2l1 in mechanoreception has been established for the first time using a genetic knock out approach (Sternberg *et al.*, in revision). Future research should focus on what role ASIC channels [42•] and Pkd2l1 (Sternberg *et al.*, in revision) play in mechanoception. It would be interesting to know whether the mechanosensory properties of CSF-cNs may be conserved in mammals. To the best of our knowledge, no investigation of CSF-cN response to mechanical stimuli has yet been reported in mammals.

In *pkd2l1* zebrafish mutants, in which CSF-cNs do not respond to mechanical stimuli, locomotor frequency during acoustic escape responses of freely moving zebrafish larvae was decreased, indicating a role for CSF-cNs in enhancing speed of locomotion [41••]. The same result was obtained when silencing CSF-cNs with the botulinum toxin light chain [41••]. ChannelRhodopsin-mediated mapping revealed that CSF-cNs synapse on ventral

premotor V0-v (MCoDs) interneurons involved in sustaining slow locomotion [43] as well as onto CaP primary motor neurons and CoPA sensory interneurons. The mechanisms underlying CSF-cN dependent increase of locomotor frequency during escapes could be due to silencing of V0-v interneurons as well as ipsilateral phase-locked inhibition of CaP motor neurons, resulting in faster repolarization and increase in firing frequency. In order to decipher between these hypotheses, it will be necessary either to perform electrophysiological recordings of mechanosensory neurons during minor muscle contraction or to mimic the recruitment of mechanosensory neurons with light-patterned optogenetics targeting only one side of the spinal cord.

Mechanosensory feedback contributes to postural control

Another role for sensory feedback to the spinal cord is to maintain postural balance during movement. During locomotion in zebrafish larvae, dorsal and ventral axial muscles are simultaneously activated in rostrocaudal waves by spinal motor neurons. Primary motor neurons are therefore recruited in a synchronous fashion by premotor networks. Optogenetic stimulation of V2a excitatory interneurons demonstrated a segregation between dorsal and ventral premotor circuits [44]. This differential control of axial muscles is involved in generating torque for postural correction and depends on descending vestibular supraspinal afferents [44]. Sensorimotor gating within the spinal cord may also be used to prevent locomotion errors.

During embryogenesis, zebrafish embryos exhibit spontaneous movements, referred to as coiling. Knogler *et al.* showed that during coiling, spinal CoPA interneurons located contralaterally to the bend received prolonged glycinergic inhibition, which is shunting excitatory inputs from RB neurons [45••]. Shunting of CoPA interneurons was observed either in phase with the recruitment of ipsilateral motor neurons during spontaneous fast locomotion or after a brief activation in response to touch stimuli [45••]. Such sensorimotor gating could prevent undesirable activation of spinal motor circuits by mechanosensory feedback during self-generated movements.

Interestingly, spinal mechanosensory pathways originating from RB and CSF-cNs were recently investigated, showing a similar convergence on CoPA interneurons. Optogenetic-mediated mapping showed that CSF-cNs selectively inhibited a subclass of primary motor neurons (CaP) but also CoPA sensorimotor interneurons [46•]. Repetitive stimulation of CSF-cNs induced silencing of both CaP motor neurons and CoPA interneurons during fast locomotion events. Since, ventral CSF-cNs are recruited by longitudinal muscle contraction during locomotion, it was hypothesized that these neurons could be involved in postural control during active locomotion. Interestingly, zebrafish larvae in which CSF-cNs were silenced by botulinum toxin displayed twice more frequent rollover events in response to acoustic stimuli inducing escape responses, compared to control animals. This observation suggests that CSF-cNs may not only modulate speed of locomotion during escapes but could also participate in maintaining postural balance [46•]. In these experiments, the silencing of CSF-cNs with Botulinum toxin occurred all throughout development. Further investigations relying on mapping the projections of CSF-cNs in the hindbrain and acute silencing of CSF-cNs at the larval stage will be necessary to confirm this hypothesis.

Conclusions

Over the last decade, the zebrafish larva has emerged as an exciting animal model in systems neuroscience, allowing the combination of advanced optical methods for monitoring and manipulating genetically identified populations of neurons with physiological recordings and behavior. This merger of genetic accessibility, optical transparency and simple quantifiable behavior make this model particularly well-suited to dissect sensorimotor circuits during active locomotion *in vivo*. Recent studies focusing on the spinal cord revealed novel roles for spinal sensory neurons already known to be touch-sensitive (RB) or whose function was previously unknown (CSF-cNs). In addition to eliciting locomotion, these neurons also modulate ongoing movements *in vivo*, enhancing speed or maintaining postural balance during escape responses.

Similarly in invertebrate species, *Drosophila* provides an exciting animal model to study sensorimotor integration during locomotion [47]. Flies face similar challenges of rapidly processing different sensory inputs during flights, and integrating with other sensory modalities in a contextual manner [47]. There is a large body of work on the role of mechanosensory feedback during locomotion in insects. In the stick insect for example, Hellekes *et al.* showed that 'reversal' of postural reflexes during voluntary movements was modulated according to the type of motor behavior being executed [48].

It remains to be elucidated to what extent the recent findings discussed here in Anamniotes, are applicable to Amniotes, and in particular mammals with muscle spindles and Golgi tendons as proprioceptive organs. Nonetheless, homology in progenitor domains conferring genetic identity of spinal interneurons provides new avenues to investigate well-conserved neuronal populations, and test their contribution in mechanosensory feedback during locomotion.

Looking beyond modulation of locomotion, mechanosensory feedback might also have important roles on morphogenesis during the development of the spine. It is well

known for clinicians that alteration of sensory function, and in particular proprioceptive deficits, can lead to spinal deformity. Similarly, knockout mice lacking proprioceptive receptors, both muscle spindles and Golgi tendon organs, develop torsion of the spine, known as the hallmark of adolescent idiopathic scoliosis [49]. In this regard, a recent study relying on mutants with defective cilia exhibiting scoliosis, revealed a link between cerebrospinal fluid dynamics influenced by cilia function and spine curvature in juvenile zebrafish [50]. Correction of the mutation and restoration of cilia motility rescued the phenotype by preventing torsion of the spine. Interestingly, syringomyelia, a debilitating neurological disorder in which a cavity is formed within the spinal cord due to CSF flow disturbance, is often associated with scoliosis as well [51,52]. Could failure to integrate mechanical or chemical signals from the CSF lead to abnormal development of the spine? The field of sensorimotor signaling in the spinal cord might lead to unexpected discoveries in the years to come.

Conflict of interest statement

Nothing declared.

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