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Current Opinion in Neurobiology

Mechanosensitive body–brain interactions in *Caenorhabditis elegans*

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Abstract

Proprioception and visceral mechanosensation provide important information about the location and deformation of the body parts in space and time. These deformations arise from muscle contraction during locomotion, but also from volume changes in organs that are subjected to stresses as a part of their physiological function. These internal morphodynamics give rise to periodic contraction–relaxation cycles with surprisingly constant amplitudes and the maintenance of these optimal driving patterns is remarkably robust against external and internal perturbations. One of the underlying reason for this robustness is an internal feedback mechanism in which specialized sensory cells and neurons signal the mechanical deformation of the inner workings of our organs, from the body to the brain, which subsequently adjust the driver to a predetermined physiological setpoint. Here, we review recent progress in the field of visceral mechanosensation and proprioception in *Caenorhabditis elegans* and discuss how future studies with this model can be used to gain insight into mechanosensory body–brain interactions in mammals.

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Current Opinion in Neurobiology 2022, **75**:102574

This review comes from a themed issue on **Neuroscience of Somatosensation**

Edited by **Miriam Goodman** and **Diana Bautista**

For a complete overview see the Issue and the Editorial

Available online xxx

https://doi.org/10.1016/j.conb.2022.102574

Keywords

Mechanosensation, Proprioception, *C. elegans*, Mechanoelectrical ion channel, Body-brain interaction, Corollary discharge, Interoception, mechanobiology.

Introduction

Interoception and the force from within

The five classical senses are the windows through which the brain constantly receives information about the surrounding. While hearing, vision, and olfaction provide a glimpse into the outside world from the far-field, the sense of touch requires physical contact between the sensory cell and the object to explore information about the mechanical properties of the environment [1]. In addition, the brain also constantly receives information from the inner workings of our body [2,3]. The most well-known is the vestibular sense during which mechanosensors in the inner ear adjust the position and orientation of the body and proprioception [4,5], the unconscious sense of our self.

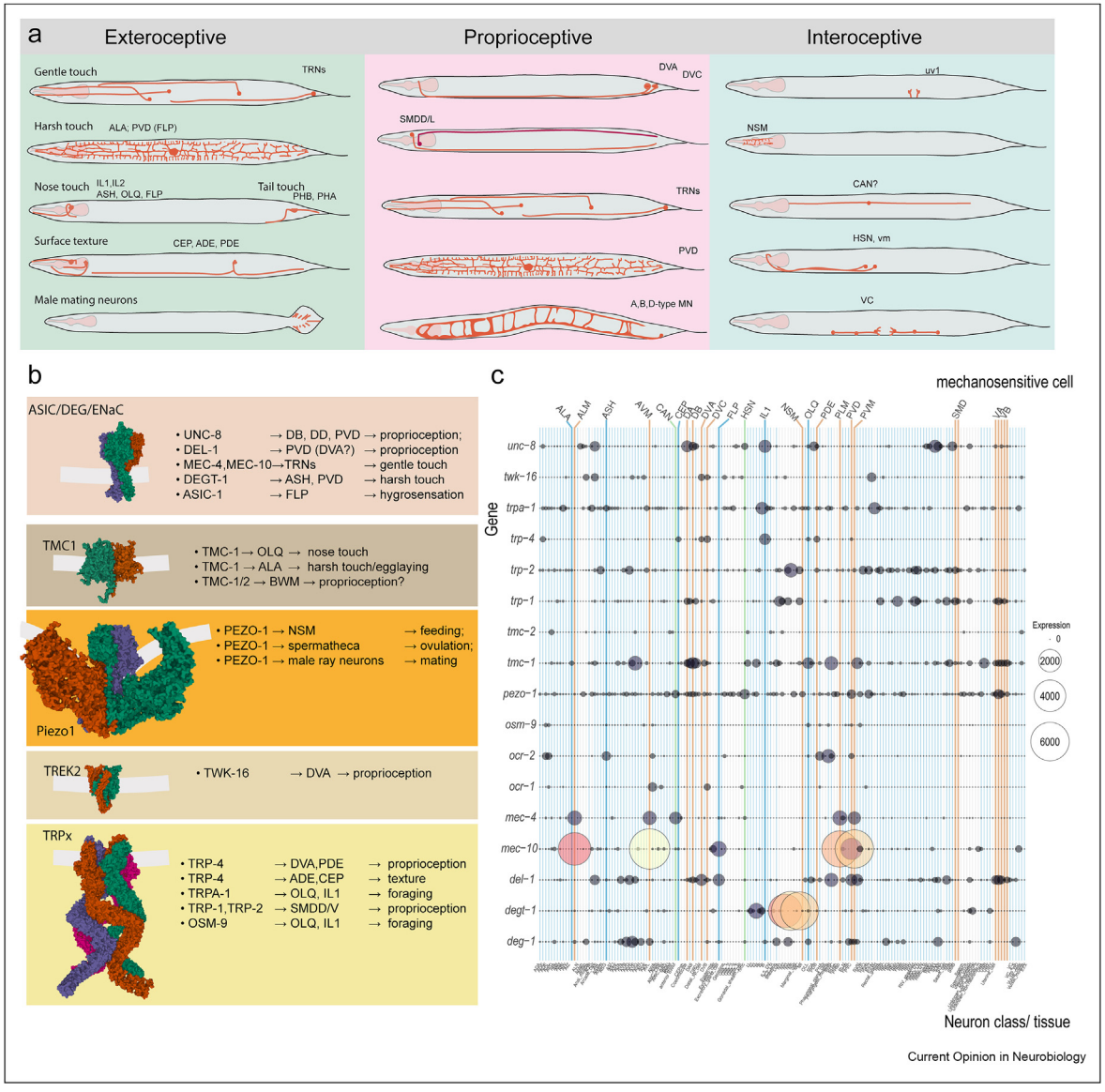
Visceral mechanosensation, on the other hand, has received wide attention only recently [6]. The mechanical body–brain interaction include, but are not limited to innervated organs that are subjected to morphodynamics and volume changes as a part of their physiology. In mammals, sensory neurons of vagus nerve innervate these target organs and generate a feedback signal upon mechanical deformation, that is, subsequently relayed to brain to adjust the "driver" setpoint [2]. At the molecular level, Piezo proteins constitute a major component of the mechanosenstive ion channel for proprioception [7], lung inflation [8], baroreception [9,10], bladder release [11] and possibly the gastrointestinal tract [12], but we have yet to learn how mechanical stresses distribute within the cellular and tissue environment to stabilize the active conformation of the ion channel. Because all of these processes require Piezo ion channels for their neuronal function in mammals, one is inclined to assume that a universal, common mechanism underlies mechanoreceptor activation [13].

Ion channel gating: Where does the force come from?

Unlike light which travel across empty space, mechanical stresses, like sound, require a medium to propagate, with a rate and range that depends on the viscoelastic moduli. In principle, the elastic modulus is an emergent property of the sum of all molecular interaction that constitute the material. However, a general, anisotropic, linear elastic material is described by 21 material constants (generalized Hooke's law [14]). In such a scenario, a mechanical stress distributes differently along 21 distinct pathways (e.g. with different velocity and extent). In tissues, this is further confounded by the fact that mechanical properties are themselves a function of deformation (so called nonlinear materials [15]). Does the diversity in mechanoelectical (MeT) transduction channel reflect this mechanical diversity?

Perhaps. Recent data suggests that different ion channels select and transduce different force-transmission pathways and loading conditions [9,16–18], either during static or dynamic stresses [19], distension [7,20] and compression [21,22]. Even though the location and morphology of many mechanoreceptor cells is likely optimized for sensitivity to a mechanical stimulus [23,24,10,3] (Figure 1), a particular ion channel and its associated proteins must be tuned to maximize direction selectivity of the stimulation [25]. The ongoing debate is best illustrated with NOMPC, the founding member of the TRPN family [123], which originally embodied the gating spring hypothesis [26] but was recently shown to be involved in compressive mechanosensitivity in nematodes [18], and might itself be gated under compressive stresses [21,27]. *Caenorhabditis (C.) elegans* offers a huge repertoire of mechanosensitive receptor cells with ion channels that are

Figure 1



Mechanoreceptor function in *C. elegans*. **a:** Classification, location and morphology of mechanoreceptor cells involved in sensing mechanical stimulus from the outside, body wall muscle contraction and internal morphodynamics. **b:** Mechanoelectrical transduction (MeT) channels, their known site of action and functional significance. **c:** Expression profile of known and hypothesized MeT channels in each neuronal class and somatic tissue. Orange vertical lines indicate proprioceptors and proposed interoceptors, blue lines indicate exteroceptors involved in touch and surface composition. The size of the dots is proportional to expression level. Data extracted from the study by Taylor et al. [110]. High resolution interactive chart accessible under this link: Interactive Chart.

tuned to a particular exteroceptive, interoceptive or proprioceptive process (Figure 1). Thus, this review is dedicated to our (mis)understanding of the processes that drive our most fundamental feedback mechanism on visceral morphodynamics and what we can learn from *C. elegans* as a model animal.

Proprioception

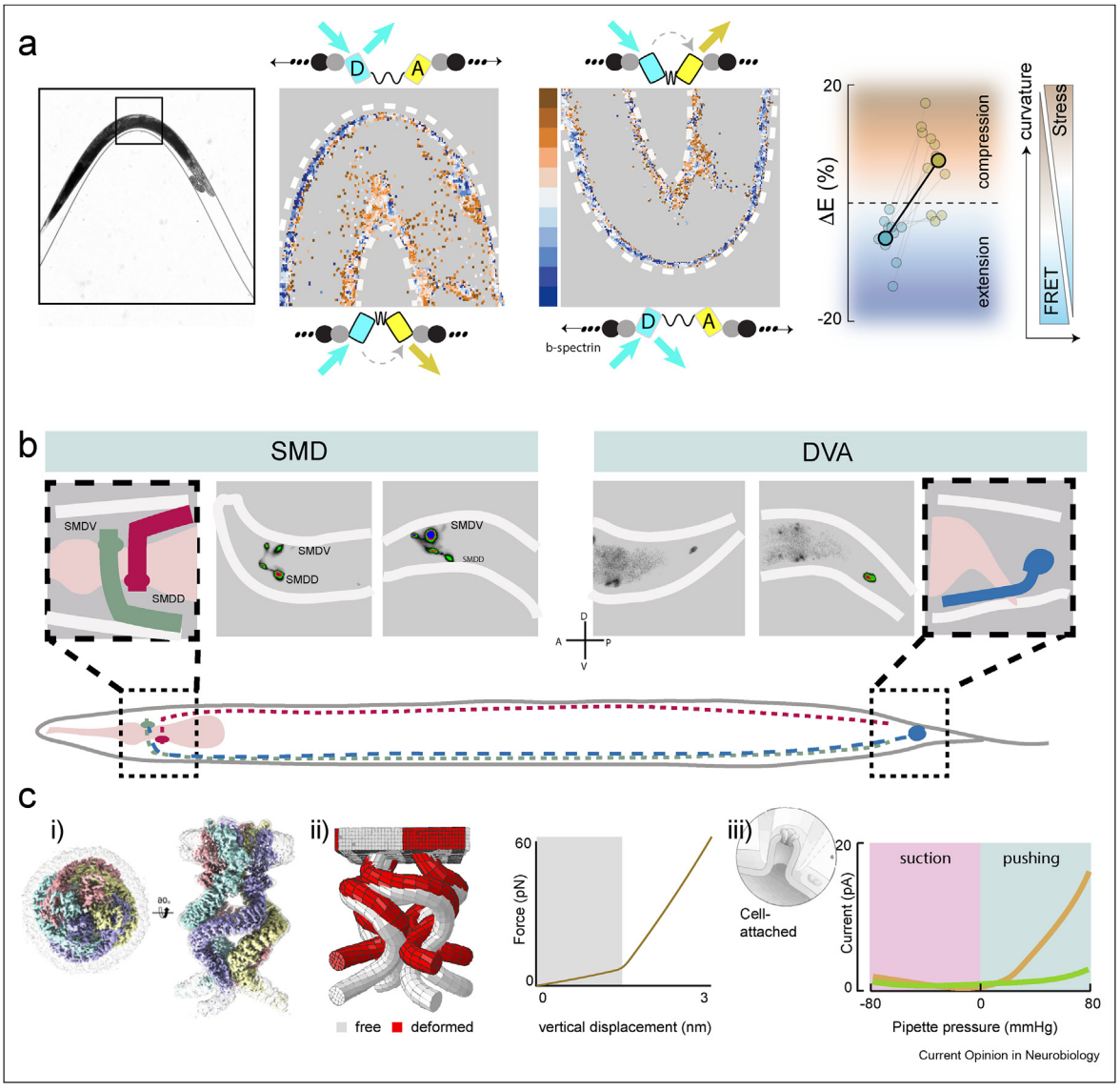
The mechanical coordination of locomotion

C. elegans moves itself forward using dorso-ventral contraction of their body wall muscles, which leads to a sinusoidal locomotion pattern with a constant amplitude that is remarkably robust against external perturbations. Of the 302 neurons in *C. elegans*, more than a third have been described to be mechanosensitive and a large fraction of them are sensitive to internal muscular contractions and stresses generated during body movement, owing to the importance of coordinated locomotion for animals survival. Among the best characterized proprioceptors are the motor neurons themselves [28,29], including A, B, and D-type neurons, and possibly muscles (based on the expression of mechanosensitive TMC-1) [30]. In particular, ventral and dorsal B-type motor neurons propagate curvature information from anterior to posterior body segments [28], are phase-locked to the body angle during forward locomotion, and opposite in phase to one another. Interestingly, these oscillations persist also in neurons physically and functionally decoupled from the rest of the network [31] or behaviorally silent animals [32], suggesting that these patterns can be entrained into the network. However, the identity of the mechanosensitive ion channel is not known in B-type motor neuron, and neither was it shown that the motor neurons can sense mechanical stresses cell autonomously [33]. Even though A-type motor neurons show a similar functional specialization for backward locomotion [34], it is not yet entirely clear to what extent A-type motor neurons use proprioception to tune the backward locomotion wave. In addition to A-type neurons, DVC presents a likely candidate for backward proprioception, based on its synaptic polarity and mechanosensor expression [35]. Further supporting the role of mechanosensitivity of the motor circuit comes from a recent study, in which direct mechanical stimulation of the dendrites of D-type motor neurons *in vivo* resulted in large mechanosensitive currents [36] that depended on the DEG/ENaC ion channel *unc-8* [36]. Thus, one may speculate that D-type neurons are proprioceptive, and indeed, *unc-8* mutants also show a decreased body curvature during forward locomotion [37], even though it is not clear if UNC-8 regulates body posture through D-type neurons. The study further showed that this stretch signal suppresses reversal behavior through direct, synaptic inhibition of AVA [36], but no prediction can be made if D-type activity is phase locked to body bending angle. In summary, D-type motor neurons have two roles, as they relax body wall muscles, and have a proposed proprioceptive activity. How the proprioceptive signals and the motor control within the D-type neurons are decoupled, and how the proprioceptive activities of B-type and D-type neurons are coordinated, is an area for future research.

The aforementioned dual function of a single neuron in behavioral control is a common principle by which a compressed nervous system makes "space" for all necessary computations [38]. DVA, for example, is another proprioceptor with a dual regulation [39], which adjusts body posture positively through neuropeptides NLP-12 [40] or two-pore K channels TWK-16/TREK2 [18] and negatively through TRP-4/NOMPC and UNC-70/β-spectrin [39,18]. How does the dual regulation of DVA coordinate proprioception? A recent study suggested that TRP-4-dependent Ca^{2+} activity in DVA is locally confined to ventral body bends, and limited by stretch-dependent activity of the hyperpolarizing potassium channel TWK-16 [18]. This compartmentalized, local signalling thus complements the local mechanosensing of the motor system. Such parallelization of neuronal processing might be a key feature of a nervous system with neurons at a small scale limit that are subjected to intrinsic channel noise [41,42].

The polymodal sensory neuron PVD is well known for its capability to sense harsh touch [43] and proprioceptive inputs [44]. This dual function relies on two different sets of DEG/ENaC/ASIC ion channels, DEGT-1 for nociception and DEL-1, UNC-8, and MEC-10 for proprioception, respectively [45]. The ion channel trio form heteromers to activate calcium transients during sinusoidal locomotion—signals that are restricted to the proximal dendrites (2°,3°) of PVD and cause a local activation of NLP-12 release. The most distal dendrites (4°), however, were only required for harsh body touch, consistent with the localization of DEGT-1. Importantly, the movement-induced Ca^{2+} signals activated locally, but did not spread throughout the axon—on the contrary, harsh touch induced a global Ca^{2+} response [45]. This indicates that local processing of sensory information represents a key component of the computational repertoire and can only happen through an electrical compartmentalization of the elaborate dendritic structures. Such compartmentalization was also shown for RIA [46] and DVA [18]. In contrast to PVD and RIA, the compartmentalization in DVA is not structurally confined, but dynamically regulated by emergent mechanical stresses due to body bending (Figure 2a). An interplay between a stretch-sensitive TWK-16/TREK2, preventing misfiring and suppression of neuronal activity under stretch, and the compression sensitive TRP-4 is thought to generate a locally confined "active sensory zone" and read out movement-induced stresses originating in the spectrin cytoskeleton [18] (Figure 2a,b). Together, PVD and DVA constitute two neurons in which different ion channels select different force transmission pathways.

Figure 2



Multiscale force transmission during proprioception. **a:** Compressive and tensile stresses emerge in the spectrin cytoskeleton due to positive and negative curvatures reminiscent of forward crawling. The same animal expressing a tension sensitive FRET reporter is immobilized inside a curved microfluidic channel while recording confocal images in two different body postures. On the convex and concave side, FRET values are lower or higher, respectively, than in straight configuration indicating that spectrin can bear extension and compression. After the study by Das et al. [18] **b:** Neuronal response to mechanical deformation. Snapshots of calcium dynamics in SMDV and DVA proprioceptors. Activity of both neurons arise during ventral bends, when their axon is under compression. Ventral side towards the bottom. **c:** Proposed molecular deformations to imposed compressive mechanical stress. i) Average projection density of NOMPC derived from CryoEM in top and side view [111]. Reproduced with permission from [1,122] ii) A finite element model of NOMPC subjected compressive stresses compared to force free state. The graph shows the result of a simulation of the force required to deform the ankyrin repeat domain. Upon intersubunit contact, force rises abruptly, indicating stiffening of the domains. Compression is linked to rotation of the transmembrane domain and pore opening. Reproduced with permission from [21] iii) Experimental cell-attached electrophysiology of a single channel under negative (suction) and positive (pushing) pressure [27]. Green line represent cells with without NOMPC.

Computational models for *C. elegans* body–brain interactions

A large diversity of computational models have been deployed to understand proprioception in vertebrates and invertebrates [47]. The known structural connectome of *C. elegans* offers unprecedented possibilities to visualize the impact of peripheral and visceral mechanosensation and predict animal behavior [48–50].

Inspired by the wealth of functional and genetic information [51,52], mathematicians and engineers aspired to construct a biologically-informed network model and predict behavior under the influence of the internal mechanosensors. Niebur et al. were the first to implement the importance of proprioceptive feedback in a purely mechanical model [53]; however, without neuronal feedback. More recent models combined the

neuroanatomy with physical constraints and active/passive actuators [54] that predict complex behavioral repertoire [55] and differences in gait in changing environments [56,57]. This was accomplished with a weighted, time-dependent suppression of the proprioceptive signal [55] (with neuropeptides as the relevant biological correlate) or incorporating the head motor neuron circuit and the ventral nerve cord circuit [58].

However, despite the promise of network models to provide a systems view of cell function, the importance of some proprioceptors like DVA have not entered the mathematical frameworks [56,58] explicitly. Most models that incorporate mechanics make assumptions that internal proprioceptors become stretch activated, recent work in DVA; however challenges this paradigm and was shown to activate under compressive stresses [18]. When DVA was sensitized to elongational stresses, it lead to a failure to propagate sinusoidal body wave, whereas, modeling experimental finding in which DVA activates under compressive stress and deactivated under stretch is sufficient to propagate undulatory wave during locomotion [18]. In summary, the connectivity diagram is required but not sufficient to explain cell functions, and information like synaptic polarity [51], mechanical properties [59] and stress sensitivity need to be considered.

Mapping the force transmission pathway during proprioception

DVA with its single ventral axon was shown to activate under compressive stresses, as a result of animal bending towards the ventral side [18]. This counterintuitive "stretch" receptor modality seems only unconventional on first sight, but many other mechanoreceptor cells in *C. elegans*, *Drosophila* [25,60] and mammalian osmoreceptors [61] have been shown to activate under compressive stresses. SMD neurons, another class of proprioceptive motor neurons, coordinate head bend during forward locomotion [62], and their activity is phase-locked with anterior body bends, a strong indicator for proprioceptive activity [18,62,28]. Similar to DVA, SMDV activated preferentially on ventral body postures [62,63] (Figure 2b), indicating a preference for their response to compressive stresses. Interestingly, SMD also express TRP ion channel homologs, TRP-1 and TRP-2 of the TRPC family, which harbor short intracellular ankyrin repeats. The much longer ankyrin repeat domain of NOMPC, TRP-4 or TRPA homologs were subject to a long debate about the gating spring involved in ion channel gating under mechanical tension [64]. Recent theoretical and experimental findings however suggests that the solenoid ankyrin repeat domain is critical to transfer compressive load from the cytoskeleton to the transmembrane domains to elicit gating of the pore and a stabilization of the open state probability under pressure [21,27,18] (Figure 2c). TRPA-1 is yet another mechanosensitive ion channel with a long ankyrin domain harboring 17 repeats with orthologs in mouse and humans that are important for various mechanical functions [65]. Mutations in *trpa-1* gene modulate multiple behaviors, including the response to nose touch, foraging but also proprioception in the head [66]. The neuron through which TRPA-1 function in head bending proprioception, is not known, neither whether or not it shares compressive gating properties with NOMPC. In *C.* elegans, ankyrin-containing proteins also influence mechanosensation indirectly. UNC-44, a giant protein with a large ankyrin repeat domain with 23 repeats was shown to associate with TMC-1 ion channels through CALM-1/CIB as an adaptor protein [30]. This ternary TMC/CIB/Ank complex is critical for cell autonomous mechanosensation in OLQ and body wall muscles [30]. Through coupling with UNC-33/UNC-119, UNC-44 was shown to connect to microtubules [67], and it is interesting to speculate whether or not stresses from the microtubule cytoskeleton enable gating of TMC ion channels.

Corollary discharge

Along with proprioceptive feedback, the motor neurons may themselves directly inform the central nervous system and send an efferent copy to the brain [68]. Such corollary discharge (CD) normally functions in the nervous system to segregate self-caused sensations from externally-caused sensations. It does this, partially, by attenuating the nervous system's response to self-caused sensations. What sounds seemingly abstract has important consequences and is targeted to suppress sensory responses that might originate from internal body movements. We experience this every day when we move our eyeballs, such that the obtain picture is "motion" corrected. Passively moving the eyeballs with the finger tips leads to a shifting and tilting frame. CD thus prepares the nervous system for a self-generated stimulus. In *C.* elegans, evidence for CD has been presented in the interneuron AIY [69] and RIA [46], which both originate from the motor system. In contrast to many system in which CD suppresses behavioral responses, the motor copy imprinted into AIY reinforces and stabilizes a thermosensory response. With this function, CD provides robustness and eliminates spurious responses due to transient temperature fluctuations [69]. In addition, the touch response was hypothesized to initiate a CD signal [70], in which the motor circuit silences antagonistic circuit through an yet to be identified system of interneurons. More likely, the motor circuit might generate a inhibitory signal to cancel spurious activation of mechanosensors such as TRNs that result from body deformations during fast movement [71]. Taken together, peripheral input into the brain involves mechanosensory, but also motor feedback.

Visceral mechanosensation

Despite our comprehensive knowledge of proprioception, our understanding how neurons sense organ morphodynamics in *C. elegans* is limited. The sensation of force in visceral processes presents a formidable conceptual challenge, as the morphodynamic movements need to be detected in the background of omnipresent sinusoidal body waves that inevitably deforms the entirety of the body during locomotion. Not surprisingly, many visceral processes, such as oviposition [71,72] and evacuation [73] are coupled to a specific motor state.

Osmosensation

ASH and other ciliated nose mechanoreceptor serve as polymodal sensory neurons and are known to activate to broad range of chemical, osmotic and mechanical stimuli [74]. Dedicated internal osmosensors have not been described in *C. elegans*, though the processes of the excretory canal were proposed to act as an internal osmoregulator [75]. The canal is tightly associated with three fasciculated neurons, ALA, BDU and CAN [75]. Intriguingly, BDU [76] and ALA [77] have been proposed as high threshold mechanosensors, and CAN likewise expresses an unusually high amount of mechanosensitive PEZO-1, the *C. elegans* homolog of the mammalian Piezo proteins and MEC-4, the MeT channel for gentle touch (Figure 1c). Thus, it is intriguing to hypothesize that these neurons might be involved in mechanical osmoreception through sensing volume changes in the canal processes.

Pharyngeal and intestinal activity

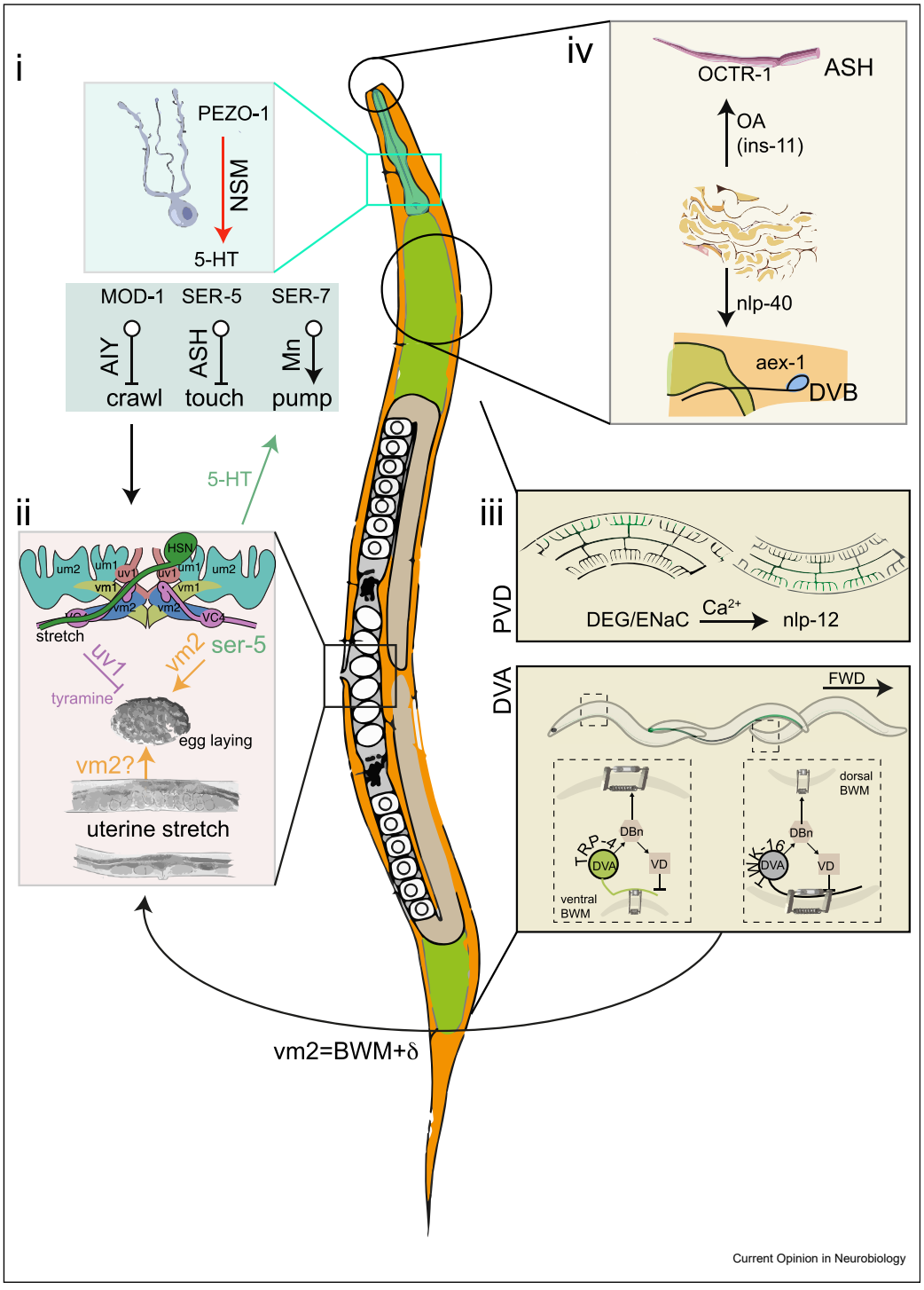
C. elegans has the ability to sense substrate texture, which was associated to discriminating food sources [78,79]. The neuronal substrates for this modality are the ciliated CEP neurons and the enteric NSM neuron. Whereas CEP senses the roughness of the substrate the animals crawl on using TRP-4 ion channels [78], NSM has sensory ending directed towards the internal pharyngeal volume and expresses PEZO-1 [80]. It was shown that PEZO-1 regulates the pharyngeal pumping frequency in response to the osmolarity and stiffness of the ingested food source [80]. Nevertheless, ingested microspheres alone were not able to activate NSM Calcium dynamics [81]. Because NSM activation secretes serotonin and thus modulates different neurons (Figure 3), PEZO-1, as well as DEL-3 and DEL-7 constitute important players in the *C. elegans* gut–brain axis [81,80,82].

The *C. elegans* intestine is postsynaptic to few neurons (AVL, DVB; [50]), but is likely involved in more systemic regulation of behavior through asynaptic secretion of neuropeptides. INS-11 [83] or PDF-2 [84] influences food choice through neuronal signaling pathways that control learning behavior and locomotion, while NLP-40 activates DVB during evacuation [85]. INS-7 is another intestinal insulin-like peptide with potential targets on neurons to regulate lifespan [86]. Recently, gut-resident bacteria were shown to produce precursor of the neuromodulators octopamine [87], which influences food preference through chemosensory neurons (Figure 3). Because intestinal cells reportedly express pezo-1 [82], it is interesting to speculate though if the secretion of neuropeptides or neuromodulators is also initiated mechanically through gut filling or visceral morphodynamics as in the fly [88].

Mechanotransduction in the reproductive system

The timing of the egg-laying events follows a tightly regulated sequence [89] and is subjected to mechanical [90], humoral and proprioceptive [71] control. Even though the absence or the presence of food [89] and external forces [91] determine the extent of egg-laying, internal mechanical signals prevent premature dispersal of the eggs. As such, almost all components of the egg-laying circuit, including command interneurons, motor neurons as well as uterine and vulvas muscles were proposed to be mechanosensitive [90,72]. The uv1 cells of the egg-laying circuit are mechanosensitive cells that become mechanically deformed during the passage of an egg through the vulva. A few molecules that have been attributed for this mechanosensitive process are heteromers of the TRPV ion channels OCR-1,2 and 4 [92], although neither of these have been shown to be intrinsically mechanosensitive [93]. The mechanical activation of the uv1 cells as a result of eggs passing through vulva, triggers the release of tyramine, which in turn suppresses the egg-laying command interneuron HSN through the chloride channel LGC-55 [72]. This mechanical, negative feedback ensures that only mature eggs pass at a given time and this prevents immature release of progeny. HSN, on the other hand, also expresses high amounts of PEZO-1 and MEC-4 (Figure 1c, [82]), but it is still not clear if these neurons possess a cell-autonomous mechanical activity. Interestingly, egg-filling of the uterus has been proposed to sustain a burst-like activity in HSN egg laying neurons, probably through the volume-changes associated with egg accumulation [72]. In this scenario, stretch of the uterine muscles would activate vulval Ca^{2+} dynamics that in turn stimulates HSN activity by an unknown mechanism [94]. Likewise, PEZO-1 is strongly upregulated in vulval muscles (vm) [80], providing a molecular correlate for mechanosensitive activity in vm. HSN is central to integrate egg-laying with other systemic behaviors and is responsible for promoting gusts of forward movement through direct synaptic contacts with AVF. HSN also provides synaptic input into ASH sensory neurons and was shown to influence pharyngeal pumping through serotonin [95], a possible mechanism to sensitize chemoreceptors for search of optimal oviposition environment as found in *Drosophila* [96].

Figure 3



Interoceptive and proprioceptive functions and their mutual interactions. **i**) Pharyngeal food uptake is sensed mechanically by PEZO-1 in the enteric neuron NSM and directs systemic responses through serotonin (5-HT) and its various receptors (MOD-1,SER-5,SER-7) on downstream neurons (AIY, ASH, pharyngeal motor neurons). The neuromodulator represses crawling [81], and increases pharyngeal pumping [112] and the response to nose touch [113]. **ii**) Serotonin also modulates egg laying through HSN and is subjected to an elaborate mechanical feedback mechanism (possibly involving mechanosensitivity in uterine muscles (um), vulval muscles (vm), VC motor neurons and neuroendocrine cells (uv1) [90]). This also includes egg laying events that are phased with motor state and body curvature, suggesting an underlying proprioceptive fingerprint through PDE [72,71]. **iii**) Due to the coexistence of positive and negative curvatures during forward crawling, information is processed locally and confined in structural or electrical compartments, such as in PVD and DVA respectively. **iv**) No direct mechanosensitive function was shown for the gut, but intestinal release of octopamine (OA) and neuropeptides regulates diverse metabolic functions [84] and neuronal decisions through INS-11 and OA on ASH [87,83], and evacuation motor program through NLP-40 [85] on DVB.

Perspective: *C. elegans* as a model for interoception

Mechanoelectrical transduction channels fulfil many functions in various physiological contexts, in which the receptive processes are subjected to different strain tensors, compression, shear, torsion and extension. Different activation modes have been proposed that includes the application of membrane tension gradients [97], cell compression [18,98], normal stress [16] and friction [99]. On one hand, it was shown that the same ion channel, Piezo1, responds to different stresses, such as pressure [22], tension [100] and fluid shear [101], depending on the cellular context. On the other hand, it is plausible that different ion channels do not act alone, but in conjunction with auxiliary proteins that select and funnel a dominating force transmission pathway. Cadherins, for example, were shown to be necessary for cytoskeleton-mediated gating of Piezo1 [102]. Likewise, an unstructured domain on the intracellular side is important for force-from-filament activation during mechanical stimulation [103]. NOMPC requires microtubules [104], TMC-1 require ankyrins [30] and at least partially, DEG/ENaCs in *C. elegans* TRNs require the spectrin cytoskeleton for full touch sensitivity [105]. Because *pezo-1* is expressed in nearly every cell in *C. elegans* (Figure 1c), collaboration with cell-specific auxiliary molecules might be important to select cell specific functions. In addition, there is increasing evidence that some ion channels conspire with different partners depending on the physiological context [106,93,107,45] and thus select alternative mechanotransducion pathways, even in the same cell. Given the coexpression of *pezo-1* with *mec-4* in various *C. elegans* cells with presumptive mechanoresponsive features (Figure 1c), it is plausible to speculate a more general principle.

The simple wiring pattern and powerful genetics provide unrivaled opportunities to unravel the endogenous mechanotransduction pathways within the natural environment of the mechanoreceptors. The combination of super-resolution microscopy [67], precision genetics, force measurements and advanced mathematical modeling [108,18,59] enables *C. elegans* as a premier model to investigate axonal stability and transmission of mechanical stresses leading to MeT activity during intero- and proprioception (Figure 3). Cells can be studied *in situ* by optical recording of neuronal activity in freely behaving animals, but also *in vitro* to map specific force transmission pathways. Importantly, the timescales and frequencies of the periodic deformations of mammalian receptors during rhythmic organ morphodynamics matches well with the proprioceptive dynamics of *C. elegans* locomotion [3]. In future, not the forces applied through elastic substrates, glass pipettes or optical tweezers, but the endogenous force transmission pathways leading to MeT channel gating need to be charted. The knowledge of the sensory processing and integration promises advances in the development of non-invasive body–brain devices to treat medical conditions as diverse as rheuma, anxiety and stress disorders [109]. We thus argue that *C. elegans* provides an integrative model to study the most fundamental questions that could culminate in the formulation of a conceptual framework of how stress transmission pathways traverse the interoceptive sensory landscape.

Conflict of interest statement

Nothing declared.

Acknowledgements

Work related to the review is supported by the ERC (MechanoSystems, 715243), HFSP (CDA00023/2018), Spanish Ministry of Economy and Competitiveness through the Plan Nacional (PGC2018-097882-A-I00), FEDER (EQC2018-005048-P), CEX2019-000910-S [MCIN/ AEI/ 10.13039/501100011033], Fundació Cellex, Fundació Mir-Puig, and Generalitat de Catalunya (CERCA, 2017 SGR 1012) and H2020 Marie Skłodowska-Curie Actions (754510).

Appendix A.

Table S1

Mechanoreceptor cells indicated in Figure 1a. According to the origin of the sensory stimulus, exteroceptive, proprioceptive and other interoceptive mechanosensors are classified. This view is not exhaustive, and many more cells have been proposed to be mechanosensitive, but are omitted from Figure 1a and this table, awaiting more complete and sufficient characterization of their cell autonomous and functional sensitivity. For more details see reviews on touch sensation and general mechanosensation [119,121].

Exteroceptive		
Function	Neurons	Reference
Gentle body touch	TRNs	[114]
Harsh body touch	ALA, PVD	[77,44]
Nose touch	FLP, OLQ, ASH, IL1	[115,116]
Nictation	IL2	[117]
Tail touch	PHA, PHB, PHC	[118,76]
Surface texture	CEP, ADE, PDE	[79]
Male tail sensors	Many, e.g. HOB, SPC	see [119]
Proprioceptive		
Function	Neurons	Reference
Forward locomotion	DVA	[39,18]
Reverse locomotion	DVC	[35]
Head bending	SMD	[62]
Swimming	ALM	[120]
Forward locomotion	PVD	[44,45]
Body bending	B, (D?, A?)	[28,29,36]
Interoceptive		
Function	Neurons	Reference
Egg laying	uv1	[72]
Egg laying	HSN	[94]
Egg laying	VC	[90]
Osmosensation	CAN (?)	[75]
Food ingestion	NSM	[80]

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* of special interest
** of outstanding interest

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