Multisensory neural integration of chemical and mechanical signals

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Chemosensation and mechanosensation cover an enormous spectrum of processes by which animals use information from the environment to adapt their behavior. For pragmatic reasons, these sensory modalities are commonly investigated independently. Recent advances, however, have revealed numerous situations in which they function together to control animals' actions. Highlighting examples from diverse vertebrates and invertebrates, we first discuss sensory receptors and neurons that have dual roles in the detection of chemical and mechanical stimuli. Next we present cases where peripheral chemosensory and mechanosensory pathways are discrete but intimately packaged to permit coordinated reception of external cues. Finally, we consider how chemical and mechanical signals converge in central neural circuitry to enable multisensory integration. These insights demonstrate how investigation of the interplay between different sensory modalities is key to a more holistic and realistic understanding of sensory-guided behaviors.

Keywords:
behavior; chemosensation; mechanosensation; multisensory integration; neural circuit; neurogenetics; sensory receptor

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Abbreviations:
ASIC, acid-sensing ion channel; **cAMP,** cyclic adenosine monophosphate; **DEG/ENaC,** degenerin/epithelial sodium channel; **GABA,** gamma-amino butyric acid; **GPCR,** G protein-coupled receptor; **IR,** ionotropic receptor; **NOMPC,** no mechanoreceptor potential C; **OR,** odorant receptor; **OSN,** olfactory sensory neuron; **PPK,** pickpocket; **TMC,** transmembrane channel-like; **TRN,** touch receptor neuron; **TRP,** transient receptor potential channel.

Introduction

In the bewildering complexity of the nervous system, scientists tend to separate individual regions (conceptually, if not physically) for isolated analysis. This reductionist approach is powerful because, by tacitly assuming that the part under study functions largely independently of all others, it is much easier to relate the role of specific molecules, cells or circuits to particular neural processes and behaviors. This approach is notable in sensory neuroscience, where researchers frequently identify themselves as investigators of only, for example, vision or olfaction. Indeed, the ever-deepening knowledge and technical expertise required to dissect one sensory modality can constrain scientists to particular domains, sometimes for an entire career.

While experimentally practical, reductionist investigations of sensory biology contrast sharply with the normal operation of nervous systems, which seamlessly integrate diverse cues in order to make decisions about how to respond. Determining the relationships between sensory modalities is therefore essential to appreciate natural behaviors. Substantial progress in our understanding of the molecular and neural basis of individual senses makes it timely to consider this topic in detail. In this review, we explore the relationship between two broad modalities, chemosensation and mechanosensation. Recognizing that integration of chemical and mechanical stimuli occurs in a vast array of cellular and tissue contexts [1, 2], we take here an admittedly reductionist approach: our discussion is constrained to select examples, from diverse animal model systems, of sensory integration of environmental chemical and mechanical cues.

A primer on chemosensation and mechanosensation

Peripheral chemosensation encompasses olfaction and taste. Although these two senses are often associated with detection of volatile and non-volatile chemicals, respectively, the strict distinction originates in mammals [3]: odors are detected by olfactory sensory neurons (OSNs) housed within the nose to

control diverse behaviors such as foraging and social interactions [4]; tastants are sensed by non-neuronal cells in taste buds in the mouth, to control feeding [5]. For many invertebrates, this distinction is blurred. In insects, both olfaction and taste are mediated by sensory neurons, although these modalities occur in different external organs [6]. Moreover, "taste" neurons, distributed in various appendages, control a range of feeding and non-feeding related behaviors [7]. For some animals, olfaction and taste are indistinguishable: the nematode worm *C. elegans* detects both airborne chemicals and those in solution through common chemosensory neurons [8].

Peripheral mechanosensation includes the senses of hearing and touch, generally distinguished by their detection of vibrations (in air or water) or direct physical contact with external objects/substrates, respectively [9, 10]. While hearing is contained within a discrete sensory organ in most vertebrates and insects, touch receptors are broadly distributed over the body, reflecting diverse sensory functions of this modality. In this review, we will focus on mechanosensory processes that have been linked to chemosensation.

Polymodal chemosensory and mechanosensory neurons and receptors

Despite the fundamental differences in the nature of the pertinent environmental stimuli, the initial steps of chemosensation and mechanosensation are analogous: binding of a chemical ligand to, or external force on, a receptor protein – typically located in the membrane of sensory dendrites – induces conformational changes and intracellular signal transduction to lead ultimately to neuronal activation (or inhibition). Within these two modalities, almost all analyzed sensory neurons are thought to be responsive either to chemical or mechanical stimuli (although this has only rarely been explicitly tested [11]). However, there are some examples of neurons that are responsive to both chemical and mechanical stimuli, which may integrate these sensory modalities at the interface between the environment and the nervous system.

Polymodal neurons

The best-described polymodal neurons are nociceptors, which detect stimuli that could cause tissue damage, including mechanical, chemical, and thermal cues [12]. The polymodal coding strategy for such stimuli may be because animals do not necessarily need to discriminate harmful stimuli. The clearest case of a polymodal nociceptor is in *C. elegans*, where the ASH neurons located in the nose are activated by – and mediate behavioral avoidance of – noxious chemicals and mechanosensory insult [13, 14]. Many vertebrate cutaneous C-fiber nociceptors have historically also been considered to be polymodal, based upon electrophysiological analyses demonstrating their sensitivity to chemical, mechanical and thermal stimuli [15]. However, this view has recently been countered with studies employing in vivo calcium imaging approaches, as well as behavior assays of animals lacking the functions of specific cell-types, which suggest that most C-fiber nociceptors mediate physiological and behavioral responses to unimodal stimuli [16–18]. The reasons for such discrepancies remain unclear: on the one hand, electrophysiological recordings exhibit superior sensitivity to calcium imaging; on the other, neurons analyzed in ex vivo electrophysiological preparations may display novel, potentially artefactual, response properties [16]. Such novel sensitivity could equally reflect natural, regulated plasticity of nociceptor polymodality. For example, tissue damage might enhance the sensitivity of neurons to stimuli to which they were previously unresponsive [16, 19].

Many mouse OSNs also display polymodality, responding to odors and mechanosensory stimuli caused by pressure changes [20]. Notably, both modalities appear to rely on the same cAMP-dependent second messenger signal transduction cascade [20, 21], facilitating sensory synergism: weak neuronal responses to odors can be enhanced by coincident mechanosensory stimulation [20]. These properties raise the possibility that air pressure changes in the nasal cavity during sniffing can impact odor detection, as discussed below.

A final example of potential polymodality comes from a population of neurons in the *Drosophila* antenna (the major olfactory organ) that expresses the ionotropic receptor IR40a. These cells were initially shown to respond to ammonia [22], consistent with the roles of other IR-expressing antennal neurons in detecting odors [23]. Subsequently, IR40a neurons were found also to be responsive to changes in air humidity [24, 25]. Notably, the sensory endings of these cells are housed within apparently poreless cuticular hairs, which suggests that they are not activated by direct chemical ligand/receptor interactions but potentially through indirect mechanisms such as mechanosensation (through humidity-dependent swelling/shrinkage of sensory structures) and/or thermosensation (through evaporative cooling) [26]. In this context, the "chemical" agonism by ammonia or water reveals a way in which a putative non-chemosensory neuron can still report on the presence of external chemicals through their influence on extracellular physical properties of the sensory apparatus.

In summary, although physiological studies have identified examples of neurons that respond to both chemosensory and mechanosensory stimuli, it remains unclear whether these are exceptional cases or if polymodality is more common than currently appreciated. Furthermore, caution should be applied when defining neurons as polymodal, if this is based upon evidence from physiological tuning properties alone. True mechanical/chemical polymodality necessitates demonstration that a neuron mediates behavioral responses to naturally occurring intensities of these different classes of stimuli.

Polymodal receptors and receptor families

Although most neurons are probably either chemosensory or mechanosensory, knowledge of the receptors underlying these modalities has revealed intertwined identities and/or functional properties of chemical and mechanical molecular sensors (Fig. 1). One repertoire of ion channels with roles in both chemosensation and mechanosensation is the

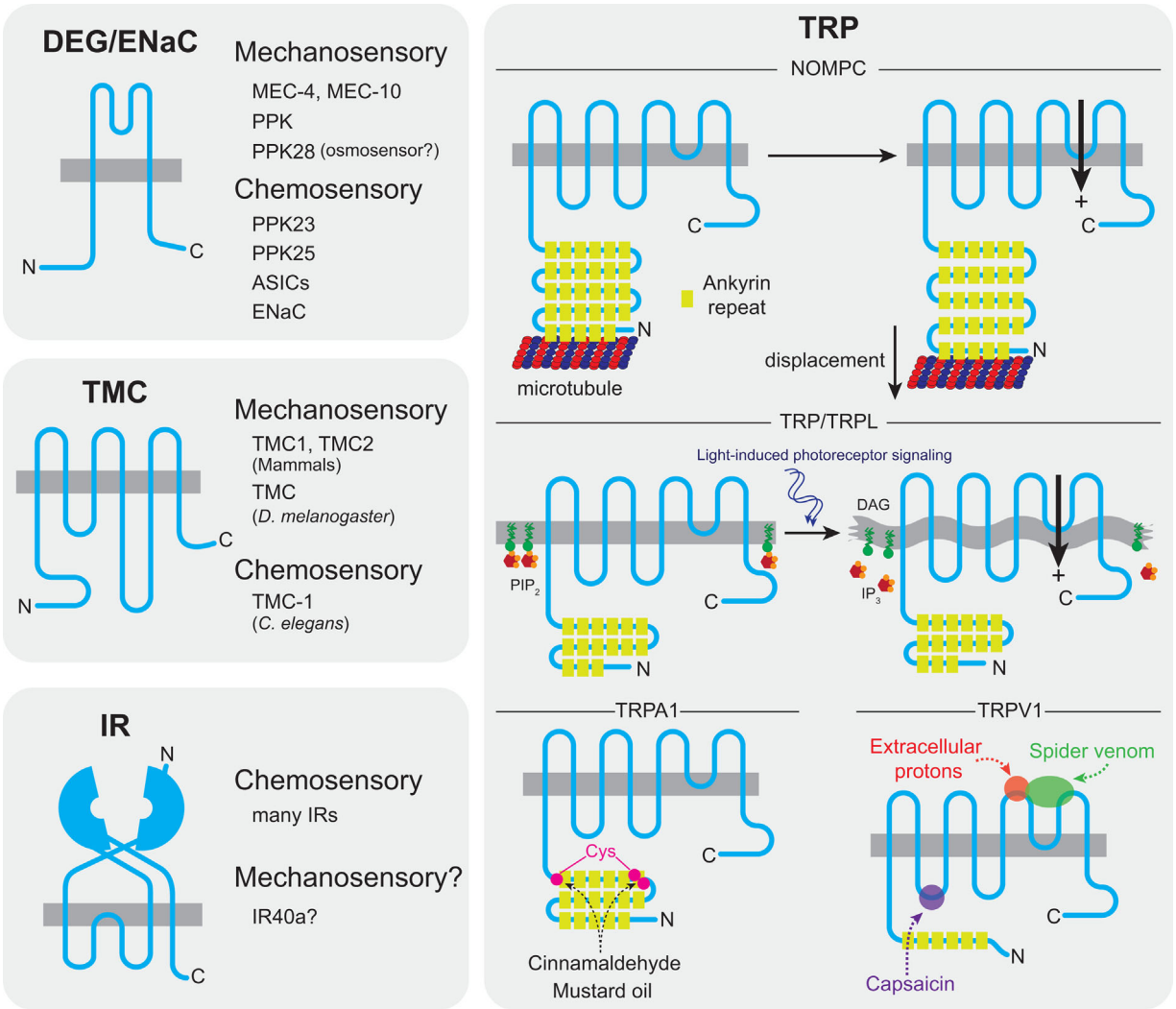

Figure 1. Sensory receptor families with chemosensory and mechanosensory functions. **Left:** Schematic structure of different families of neurosensory receptors (Degenerin/Epithelial Sodium Channels (DEG/ENaC), Transmembrane Channel-Like proteins (TMC) and Ionotropic Receptors (IR)), each of which contain members known or suspected to function as chemosensory and/or mechanosensory receptors (see text for details). **Right:** Schematic of proposed gating mechanisms of members of the Transient Receptor Potential (TRP) family of receptors by mechanical and chemical stimuli. For some channels, mechanical (NOMPC) or chemical (TRPA1) signals are mediated via the N-terminal domain, raising the possibility of similar activation mechanisms, but in other chemosensory TRPs (e.g. TRPV1), chemical agonists bind to distinct regions. TRP/TRPL channels are thought to function in visual transduction through gating by light signal-dependent changes in the sensory membrane's mechanical properties, but how this leads to channel opening is unclear.

Degenerin/Epithelial Sodium Channel (DEG/ENaC) family. In mammals, different family members have been related to gustatory sensing of salt [27] and nociceptive detection of acids (by the proton-gated Acid-Sensing Ion Channel (ASIC) subfamily) (Fig. 1) [28]. Distinct DEG/ENaC family members are implicated in mechanosensation, but it is not yet clear whether they are peripheral sensors [29]. By contrast, invertebrate DEG/ENaC homologs – including *C. elegans* MEC-4 and MEC-10 [30, 31], and *Drosophila* Pickpocket (PPK) [32, 33] – are key components of the mechanosensory transduction machinery. Other PPK family members in *Drosophila*, however, function in gustatory detection of contact pheromones [34–37], although proof that these are the ligand-activated chemosensory receptors awaits. Yet another homolog, PPK28, is a gustatory water sensor [38, 39]. Interestingly, this channel confers osmosensitivity when expressed in heterologous cells [39], raising the possibility that, like the mammalian osmosensor TRPV4 [40, 41], PPK28 detects water through an indirect, mechanosensory mechanism. On-going structural and biophysical dissection of DEG/ENaC channels [31, 42] should help illuminate how different family members can be activated by distinct types of stimuli.

A second class of polymodal receptors is the Transient Receptor Potential (TRP) family of ion channels, which are widely appreciated for their diverse roles in chemosensation and mechanosensation, as well as thermosensation and visual transduction [43, 44]. Structural information has begun to reveal the molecular basis of their polymodality. Mechanical

activation in some members of the family, such as the *Drosophila* TRPN channel NOMPC, depends on the cytoplasmic N-terminal domain [45, 46]. This domain, which contains multiple ankyrin repeats, is tethered to the microtubule cytoskeleton and transmits forces exerted through mechanically-evoked cell deformation (Fig. 1) [47]. Intriguingly, other *Drosophila* family members, TRP and TRPL, which function downstream of rhodopsin photoreceptors in the visual transduction cascade, are thought to be mechanically gated by second messenger-dependent changes in membrane tension (Fig. 1) [48]. This finding has led to a hypothesis that mechanical gating is a unifying activation mechanism for this family [47]. Indeed, some chemical agonists of mammalian TRPA1 covalently modify cysteines within the N-terminal region of this channel (Fig. 1) [49], raising the possibility that this chemical reaction leads to conformational changes that open this channel in a similar way as mechanical force gates NOMPC. However, TRPA1, as well as TRPV1, are rather promiscuous chemical nociceptors (as well as critical thermosensors), with binding sites for different ligands mapped to various intracellular and extracellular regions (Fig. 1) [44]. These observations suggest that chemical activation of TRP channels may occur through multiple mechanisms that are not necessarily related to mechanosensory-mediated gating.

Do the known cases of polymodal neurons rely on polymodal receptors? Ironically, for the clearest example, *C. elegans* ASH neurons, the receptors for most agonists are unknown. Like many sensory neurons in the *C. elegans* nervous system, ASH expresses multiple candidate receptor genes [8], so it is possible that different modalities are mediated by distinct receptors. The best characterized is Transmembrane Channel Like-1 (TMC-1) (Fig. 1), which was initially proposed to be a sensor of high salt concentrations [50]. However, a later study could not reproduce these observations and provided evidence that TMC-1 mediates noxious alkali detection instead [51]. Interestingly, the sole TMC homolog in *Drosophila* has been implicated in mechanosensation ([52, 53]; see below) and two of the eight mammalian homologs form part of the mechanosensory transduction machinery in the auditory system [54–56]. It remains to be determined whether TMC proteins are polymodal receptors, or simply have species/isoform-specific properties.

In mammalian OSNs, both chemosensitivity and mechanosensitivity depends upon the Odorant Receptor (OR) they express [21]. While odor-dependent activation of these G protein-coupled receptors (GPCRs) is, at least partly, understood [57, 58], the molecular basis of their mechanosensitivity is less clear. One hypothesis is that mechanical stimuli deform OSN membranes to modulate the spontaneous (i.e. ligand-independent) transition of ORs between inactive and active conformations to stimulate neurons [21], similar to proposed (but unproven) mechanisms for stretch-activated GPCRs [59, 60].

Physiological responses of *Drosophila* humidity-sensing neurons depend upon IR40a [22, 24, 25], which is distantly related to ionotropic glutamate receptors, a family of ligand-gated ion channels [23]. However, if, as discussed above, these neurons are not directly accessible to chemicals, it is conceivable that IR40a is activated in a ligand-independent manner. Another family member, IR21a, functions in thermosensation [61], which provides a potential precedent for such an activation mechanism.

In conclusion, growing evidence indicates that nearly all families of neurosensory receptors contain members that respond to either chemosensory or mechanosensory stimuli. There are also several examples of receptors activated by both types of cues. Study of such polymodal receptors, as well as structure/function analysis of unimodal receptors, may help to clarify the similarities and differences in chemical and mechanical stimulus-dependent activation mechanisms.

Polymodal chemosensory and mechanosensory organs

While potentially only a small fraction of peripheral sensory neurons encode both chemosensory and mechanosensory cues, modality-specific neuron populations are often found in common sensory organs. In most cases, it is unclear if and how this co-packaging serves a beneficial function in sensory integration (as opposed to a simple consequence of evolution and development). However, investigations in two areas – food texture detection and the impact of fluid dynamics on olfaction – have begun to reveal how the intimate grouping of different sensors can facilitate integration of chemical and mechanical stimuli.

Taste and texture sensing

Studies of the sensory control of feeding behavior in animals have largely focused upon the chemical constituents of food. Essential nutrients, such as sugars and amino acids, are detected by sensory pathways that promote feeding, whereas noxious chemicals, such as products of pathogenic microbes or plant defense compounds, are sensed by distinct channels that suppress feeding [5, 62]. Mechanical properties of food (e.g. hardness, viscosity, stickiness) – collectively referred to as texture [63] – provide additional critical information on food quality, such as its state of ripeness or decay, and how easy something will be to masticate, swallow and digest. Despite its importance, the neurobiological basis of texture detection and its integration with chemosensory-guided feeding responses is only now being defined, mainly through work in *Drosophila* [53, 64, 65].

As in other insects, the main sensory organ involved in food assessment and ingestion in *Drosophila* is the labellum of the proboscis (Fig. 2). The surface of this appendage bears a number of cuticular sensory hairs, or sensilla, each of which houses a cluster of sensory neurons (Fig. 2B) [66]. Most of these neurons are chemosensory, tuned to specific classes of tastant (e.g. sugars or bitter/toxic compounds). One of these neurons is, however, mechanosensory, and expresses the TRP channels NOMPC [65] and, probably, Nanchung [64] (Fig. 2B). Genetic manipulations of these neurons and channels demonstrate their importance to allow flies to distinguish preferred softer food from less attractive, harder substrates [64, 65]. Notably, harder food is less appealing even if it contains higher concentrations of sugars [64, 65],

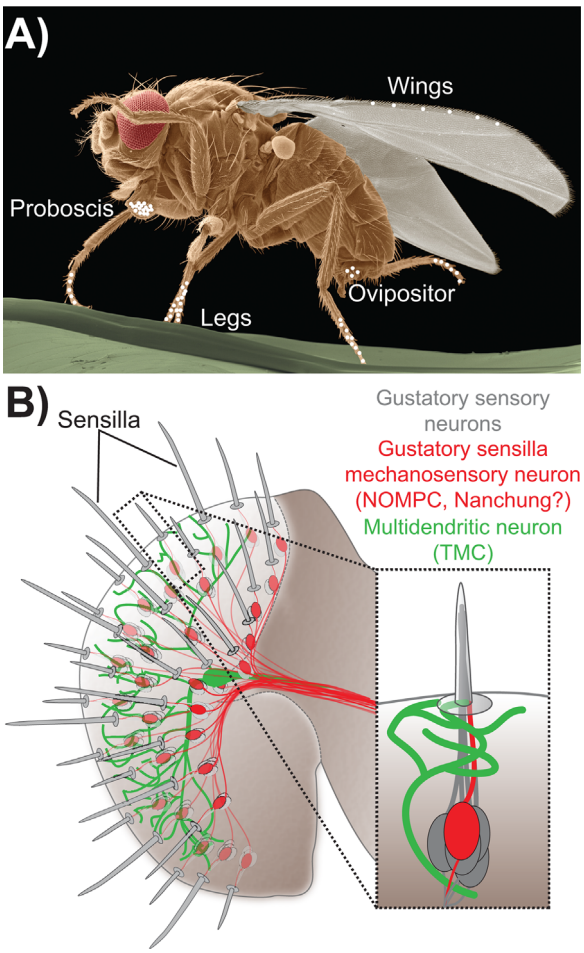

Figure 2. Texture sensing by a *Drosophila* gustatory organ. **A**: Taste sensory hairs (sensilla; white dots) are found on various appendages in *Drosophila melanogaster* (false-colored scanning electron micrograph image courtesy of Jürgen Berger, Max Planck Institute for Developmental Biology). **B**: Schematic of the labellum (the distal end of the proboscis) depicting the distribution of taste sensilla, with a close-up view of a single sensillum on the right. Each sensillum contains 2–4 gustatory sensory neurons (grey), and one mechanosensory neuron (red) (expressing the TRP channels NOMPC, and possibly Nanchung) [64, 65]. In addition, a single multidendritic mechanosensory neuron expressing TMC (green) on each side of the labellum extends highly-elaborate dendritic arborisations under the cuticle [53]. Gustatory sensory neuron dendrites project into the hair; the sensillum mechanosensory neuron projects to the base of the hair and is sensitive to bending of the hair upon contact with a substrate. The multidendritic mechanosensory neuron makes multiple contacts with the inner surface of the labellum cuticle, allowing it to sense external pressure on this appendage.

implying that these animals integrate chemosensory and mechanosensory signals when deciding what to eat. How are these signals integrated? One possibility is that the gustatory and mechanosensory neurons housed within a common sensillum exhibit non-synaptic communication (e.g. ephaptic coupling), as observed in compartmentalized OSNs [67]. Alternatively and/or additionally, sensory integration may occur in the subesophageal zone in the brain, where both gustatory and mechanosensory neurons project [64, 65]. In support of this possibility, artificial activation of the mechanosensory neurons decreases sugar-evoked calcium responses in the terminal of sweet-sensing gustatory neurons, with evidence that this may be mediated via the inhibitory neurotransmitter GABA [64]. The extent of direct (synaptic) contact between mechanosensory and sugar-sensing neuron axon terminals is unclear [64, 65], so it is possible that this effect is mediated primarily via interneurons.

In addition to the mechanosensory neurons within each sensillum, the labellum also contains a pair of force-activated multidendritic neurons, whose processes contact the internal surface at many points of the labellar cuticle (Fig. 2B) [53]. These neurons express a TMC homolog (see previous section), which is important for flies' feeding preferences on solid and liquid food of different textures. Interestingly, calibrated artificial activation of these neurons suggests that they encode textural properties in an intensity-dependent manner: weak activation leads to extension of the proboscis (a behavior reflecting engagement to feed), while strong activation suppresses proboscis extension, even when flies are also presented with sugar [53]. The neuronal mechanism by which these neurons interact with sugar-sensing pathways is unknown, as is their anatomical and functional relationship with sensillar mechanosensory neurons.

Together, these studies define a promising model to understand how chemical and mechanical stimuli are integrated within a common feeding organ. Morphologically (and probably functionally) related sensilla are found on other appendages, including the legs, wing margins and ovipositor (Fig. 2A) [7]. It seems very likely that similar coincident detection of chemical and mechanical cues occurs when *Drosophila* (or other insects) walk on substrates [68], exhibit sexual/social interactions [69, 70] and lay eggs [71, 72]. Compartmentalized mechanosensory and chemosensory neurons are also observed in highly specialized sensory organs of other species, such as the skin piercing stylet at the tip of the proboscis of mosquitoes [73], or the stinger of the parasitoid jewel wasp. In the latter, appropriate mechanosensory input is important for dictating the persistence of the stinging behavior [74].

In humans, food texture has high aesthetic value [63], and is of consequent importance for the food industry [75]. Convergence of sensory representations of taste and textural stimuli has been documented through electrophysiological recordings in the primary taste cortex (anterior insular/frontal opercular) of primates [76] but the peripheral mechanisms of texture detection are essentially unknown. One candidate neural substrate for texture assessment is the trigeminal nerve, as its dual role in sensation and control of motor actions such as biting make it well-placed to coordinate detection of mechanical properties of food with mastication and swallowing [77]. Ultrastructural and/or electrophysiological analyses have identified mechanosensory neurons in the palate of birds [78] and mammals [79–82], as well as mechanosensitive fibers in the tongue [83–85]. However, determination of the role of any these mechanosensors in texture detection awaits.

Olfaction and mechanosensory detection of fluid dynamics

Olfactory organs do not come into direct contact with sources of chemical stimuli. Nevertheless, they are exposed to mechanical stimuli through the aerodynamic (or, for aquatic animals, hydrodynamic) properties of the odor plumes that carry chemicals from the source to OSNs. For small animals, such as flying insects, aquatic crustaceans and fish, these plumes – created by wind or water turbulence – comprise unpredictable spatiotemporal patterns of odor filaments, which result in intermittent reception of chemical stimuli by olfactory receptors [86, 87]. Fluid dynamics are further complicated by the influence of the sensing animal itself on the local environment, for example, by insect wing beating, and by crustacean or insect antennal "flicking" (a behavior that is thought to remove boundary layers to enhance odor exposure [87] and/or to facilitate odor localization [88]). Together these properties render tracking of the source of an odor stimulus much more difficult than in a uniform chemical gradient.

Evidence from aquatic and terrestrial invertebrates has revealed several ways in which mechanosensory signals might play a role in facilitating odor detection and tracking. In flying insects, air movement provides key information for navigation [89]. Although airflow detection is mediated by a purely mechanosensory structure (the Johnston's organ), this is located in the insect antenna adjacent to the segment(s) that mediate odor detection [90, 91]. Analogously, in molluscs, there is behavioral evidence for the integration of chemical and water flow signals [92] and presumed olfactory and mechanosensory subsystems are both housed in the rhinophore, the most prominent head sensory organ [93]. In these cases it remains unclear whether the close apposition of olfactory and mechanosensory structures in invertebrates has any significance for peripheral sensory processing.

More intimate interactions between olfactory sensory detection and fluid dynamic-dependent mechanosensory input have been implied through the ultrastructural and/or electrophysiological identification of mechanosensory neurons within olfactory organs themselves. Such interactions have been most extensively explored in crustaceans [94, 95]. Notably, recordings from olfactory interneurons in crayfish have revealed an influence of both odor and hydrodynamic stimuli on the temporal dynamics and magnitude of their responses [96]. These observations suggest that central perception of odor stimuli reflects not only chemical identity and intensity, but also the stimulus in the context of water flow across the olfactory structures. In insects, mechanosensory neurons have been observed in the olfactory organ sensilla of many species [97–99]. The functional significance of their input is, however, unclear. In the moth, *Manduca sexta*, air currents can suppress the activity of many second order interneurons in the olfactory circuitry [100]. Although it was not formally established that this suppression is due to the input of mechanosensory afferents from the antennae, these data raise the possibility that olfactory organs integrate odor and mechanical stimuli to produce central representations of specific stimuli. The impact of such integration on odor-guided behavior remains to be determined.

The complex relationship between olfaction and fluid dynamics in small animals – in which the entire organism or external olfactory sensory organ moves through the odiferous environment – poses the question of how olfactory cues integrate with aerodynamic signals in larger animals. In vertebrates, odors are actively sampled by sniffing, in which respiratory centers regulate inhalation of air by internally located olfactory organs. Electrophysiological studies in mice have revealed that the phase of the "sniff cycle" can strongly influence the activity patterns of both OSNs and second-order interneurons [101, 102]. Such modulation is likely to be due to many factors, including both the number of odor molecules carried to olfactory receptors in the airflow and sensory input-independent central circuit dynamics [102]. However, analogous to the impact of texture on gustatory perception of food, it is also interesting to consider to what extent sniffing-dependent pressure changes in the nasal cavity contribute to modulation of neural representations of odor stimuli. To determine the influence of external mechanical input, identifying the underlying sensory basis of pressure detection will be necessary. As this capacity may reside in the mechanosensitivity of many OSNs themselves [20, 21] (see previous section), it may be very challenging to separate the contributions of chemosensory and mechanosensory pathways. Furthermore, while sniffing influences odor stimulus discrimination in experimental assays [101], the behavioral significance of mechanosensory input to the olfactory system in natural situations is likely to be harder to ascertain.

Neural circuit integration of chemosensory and mechanosensory stimuli

Many behaviors rely on the central integration of chemical and mechanical signals that are detected by distinct peripheral sensory organs to create a unified perception of the source of a stimulus. This capacity is particularly important during interactions of an individual with other animals, such as potential mates, kin, competitors or predators, whose reliable discrimination may only come from a combination of sensory cues. The best-understood examples of this type of integration are in *Drosophila*, where high-resolution behavioral analyses, circuit mapping and functional interventions have provided some of the first insights into the mechanisms of polymodal integration at the level of neural circuits.

Sensory integration during inter- and intra-specific interactions

Recent work in the *Drosophila* larva has started to reveal how mechanosensory and nociceptive information is integrated to mediate escape behaviors from predators (Fig. 3A). In the presence of a mild mechanical stimulus alone – which might occur in diverse, harmless situations in nature – larvae typically respond with a fast-crawling movement [103]. By contrast, when multiple mechanical and chemical or thermal nociceptive cues are presented – which may resemble the

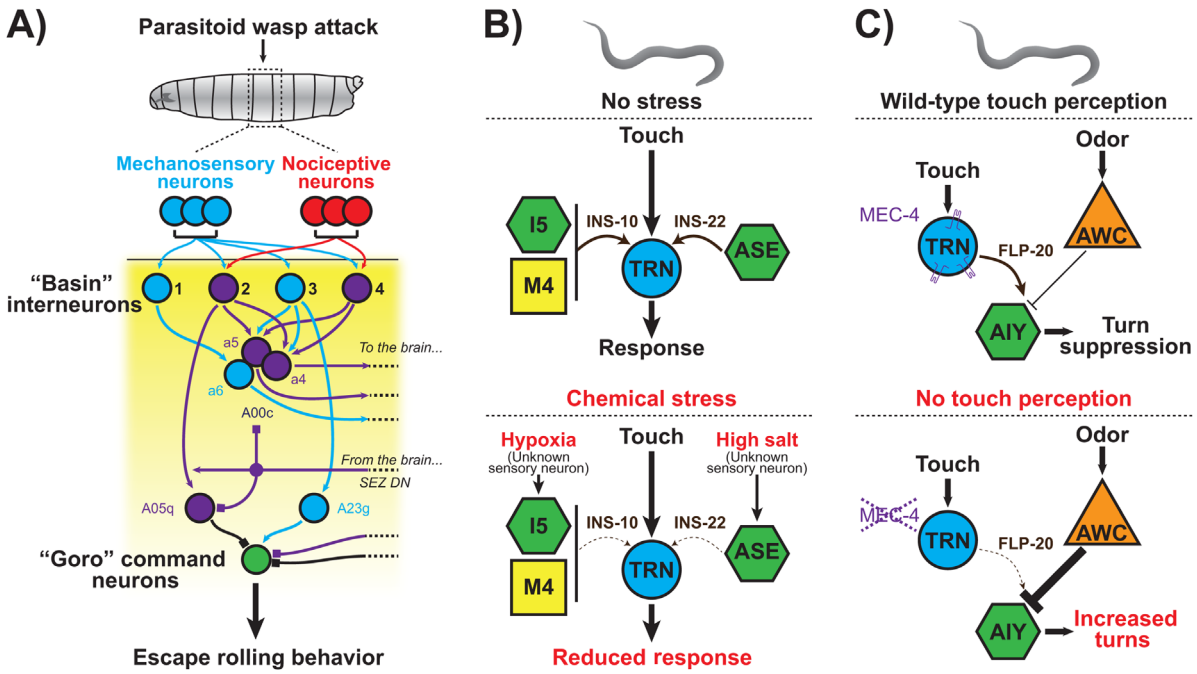

Figure 3. Neural circuit motifs underlying chemosensory and mechanosensory integration. **A**: Schematic representing multimodal connectivity of escape behavior circuitry in the ventral nerve cord of the *D. melanogaster* larva. Co-ordinate reception of mechanical and nociceptive signals – as might occur during attack by a parasitoid wasp – by discrete sensory pathways (blue and red, respectively) are transmitted to first-order "Basin" interneurons; multimodal integration already occurs within some of these neurons (purple). Successive transmission and integration occurs in higher-order interneurons, ultimately connecting to "Goro" command neurons, which induce rolling, a stereotyped escape behavior [108]. Arrows indicate excitatory connections; squares indicate connections of unknown sign. **B**: Chemosensory regulation of touch sensitivity in *C. elegans*. Top: Upon continuous touch stimulation (vibration), touch receptor neurons (TRNs) quickly habituate. If the stimulus is prolonged, those neurons become sensitized. Bottom: In the presence of stressors such as high salt or hypoxia (detected through unknown chemosensory pathways), TRN sensitivity is decreased. This is due to the decreased release of insulin-like peptides (INS) controlled by ASE interneurons (in high salt conditions) or I5 interneurons/M4 motoneurons (in hypoxic conditions) [124]. **C**: Cross-modal plasticity of mechanosensation and chemosensation in *C. elegans*. Top: AWC chemosensory neurons inhibit AIY interneurons, which normally suppress turns and reversals of the animal. AWC is activated in the absence of food odors [129], and the consequent inhibition of AIY promotes these behaviors to facilitate relocation of an odor source. Bottom: In the absence of sensory input from TRNs (due to loss of the mechanosensory receptor MEC-4), AWC more strongly inhibits AIY, through the reduced production of the FMRFamide neuropeptide FLP-20 by the TRNs. Thus, without this touch response, the increased propensity of animals to turn/reverse in the absence of olfactory cues enhances their ability to relocate odor sources [123].

interaction with a parasitoid wasp – larvae exhibit a more elaborate, "rolling" escape behavior [104–106]. These stimuli are detected by discrete peripheral sensors: mechanical stimuli by neurons in the chordotonal organs within each segment, and nociceptive chemical and thermal cues by multidendritic neurons that tile the larval body wall [103, 105–107]. Electron microscopic reconstruction of the interneuron network downstream of these peripheral sensors revealed that integration of mechanical and nociceptive signals occurs at several levels in the circuitry, including first, second and third order interneurons as well as command neurons that trigger rolling (Fig. 3A) [108]. Optogenetic activation experiments indicated that individual nodes within this network of multi-level convergent projections have distinct roles in inducing or facilitating particular actions. Thus, even an apparently simple (albeit vital) innate behavior can rely on complex integration mechanisms that begin near the sensory periphery.

In adult *Drosophila*, courting males and females rely on numerous chemical and mechanical signals to determine each other's presence and suitability as mating partners [69, 109]. Pheromone cues can be both volatile and non-volatile, produced by males and/or females (reviewed recently in Refs. [69, 110]), while acoustic cues comprise male courtship song (produced by vibration of one wing) [111], as well as acoustic or seismic cues produced by moving female flies [112]. Although the precise mechanism by which this polymodal information is integrated is still unclear, anatomical and functional studies point to the P1 neurons in the brain as candidates for mediating sensory integration and behavioral action selection [69, 113, 114]. A related, sexually-dimorphic social behavior, aggression, is also modulated by chemical and auditory signals [115, 116]. Interestingly, integration of these cues may also occur in P1 neurons [117], raising the question of how these central neurons are differentially regulated to trigger alternative behaviors. Study of this problem in the relatively compact *Drosophila* brain may help us to address conceptually similar processes in rodents, where multisensory integration of chemical and auditory signals (from vocalizations) may control both mating and fighting behaviors [118, 119].

Even "simple" single stimulus-evoked behaviors are subject to modulation upon additional sensory input emanating from other animals. For example, in adult *Drosophila*, avoidance of an aversive odorant is strongly enhanced by increasing group density [120]. This effect depends upon tactile interactions between individuals, where activation of mechanosensory neurons in the appendages during inter-individual encounters provides a spatial cue that influences the collective movement of the group of flies. How chemical and mechanical inputs are integrated centrally is unknown. However, the observation that these tactile interactions can, at least in part, promote movement away from the odor in animals that are anosmic to the stimulus, suggests that the circuits underlying mechanosensory-directed locomotor responses are partially independent of those mediating odor-evoked avoidance [120].

Cross-modal plasticity

Integration of mechanosensory and chemosensory pathways may also occur in other contexts, where excessive activation or loss of one type of input results in changes in how another is perceived. While this phenomenon is well-appreciated in humans [121, 122], studies in *C. elegans* have provided the most detailed insights into underlying neuronal and molecular mechanisms of cross-modal plasticitiy [123, 124]. As the worm navigates through the environment, it relies on touch receptor neurons (TRNs) to detect gentle mechanical stimuli. TRN sensitivity is, however, plastic: worms exposed to continuous vibrations have increased TRN responses, while animals grown under high salt concentrations or hypoxia display reduced touch responses [124]. Although the sensory pathways signaling these chemical stressors have not been determined, the cross-modal modulation occurs via chemosensory-dependent control of the expression of insulin-like peptides in neurohormonal cells, which directly control TRN sensitivity (Fig. 3B). The adaptive advantage of this modulation might be to focus the worm on the immediate sensory challenges so that it is not distracted by less relevant mechanosensory input while it tries to escape adverse conditions. In a similar type of study with *Drosophila* larvae, mechanosensory disturbance – in the form of high frequency "buzzes," perhaps reminiscent of the sound of parasitoid wasps – reduced behavioral responses to attractive odors [125].

A complementary investigation in *C. elegans* investigated the impact of the loss of functional TRNs on chemosensory detection [123]. In these mechanosensory-deprived animals, behavioral responses to food odors mediated by one chemosensory neuron type, AWC, were enhanced. The cross-modal plasticity again appears to be mediated by neurohormonal signaling: inactive TRNs release reduced levels of an FMRFamide-related neuropeptide, FLP-20, which leads to a strengthening of the synaptic connections between AWC and a downstream interneuron, AIY, to promote enhanced food odor-seeking (Fig. 3C).

In summary, while research on circuit integration of chemosensory and mechanosensory stimuli is still in a nascent phase, early insights illustrate how peripherally segregated sensory inputs may rapidly (and repeatedly) converge within downstream interneurons. Moreover, neurochemical communication between neurons that are not directly connected can underlie another mechanism of cross-talk between these sensory modalities.

Conclusions

Animal behaviors in nature depend upon the constant detection and integration of myriad environmental cues. Yet, in an effort to derive causal relationships between genes, circuits and behaviors, many laboratory studies strive to simplify sensory input, often to a degree where it can be debated how natural the resulting behaviors are. With advances in our understanding of different modalities, neuroscientists are becoming more attuned to the limitations of reductionist approaches to sensory-evoked behaviors [126, 127]. By surveying in this review how animals' responses to the environment depend upon the integration of just two different types of stimuli – chemical and mechanical – we reveal a complex relationship between these modalities at the molecular, circuit and behavioral level. It is clear that we have only just started to understand multisensory integration in a meaningful mechanistic way. Notably, many of the recent advances have come from invertebrate genetic models, where the deep knowledge of sensory biology and experimental accessibility allows us to approach the substantial challenge of reconstructing a holistic picture of nervous system function. However, it is likely that principles established in such models will help guide dissection of the integration of these (and other) sensory modalities in more complex nervous systems. Moreover, continued exploration of non-traditional model species [128] will undoubtedly offer unexpected insights into how nervous systems exploit the wealth of information in the environment.

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References

1. **Mao Q, Lecuit T.** 2016. Mechanochemical interplay drives polarization in cellular and developmental systems. *Curr Top Dev Biol* **116**: 633–57.
2. **Williams EK, Chang RB, Strochlic DE, Umans BD**, et al. 2016. Sensory neurons that detect stretch and nutrients in the digestive system. *Cell* **166**: 209–21.
3. **Wyatt TD.** 2003. *Pheromones and Animal Behaviour: Communication by Smell and Taste* Oxford: Oxford University Press.
4. **Su CY, Menuz K, Carlson JR.** 2009. Olfactory perception: receptors, cells, and circuits. *Cell* **139**: 45–59.

5. **Yarmolinsky DA, Zuker CS, Ryba NJ.** 2009. Common sense about taste: from mammals to insects. *Cell* **139**: 234–44.
6. **Vosshall LB, Stocker RF.** 2007. Molecular architecture of smell and taste in *Drosophila*. *Annu Rev Neurosci* **30**: 505–33.
7. **Freeman EG, Dahanukar A.** 2015. Molecular neurobiology of *Drosophila* taste. *Curr Opin Neurobiol* **34**: 140–8.
8. **Bargmann CI.** 2006. Chemosensation in *C. elegans*. WormBook, ed. The *C. elegans* Research Community, WormBook, doi/10.1895/wormbook.1.123.1, http://www.wormbook.org
9. **Hudspeth AJ.** 2014. Integrating the active process of hair cells with cochlear function. *Nat Rev Neurosci* **15**: 600–14.
10. **Abraira VE, Ginty DD.** 2013. The sensory neurons of touch. *Neuron* **79**: 618–39.
11. **Zaslaver A, Liani I, Shtangel O, Ginzburg S**, et al. 2015. Hierarchical sparse coding in the sensory system of *Caenorhabditis elegans*. *Proc Natl Acad Sci USA* **112**: 1185–9.
12. **Woolf CJ, Ma Q.** 2007. Nociceptors-noxious stimulus detectors. *Neuron* **55**: 353–64.
13. **Kaplan JM, Horvitz HR.** 1993. A dual mechanosensory and chemosensory neuron in *Caenorhabditis elegans*. *Proc Natl Acad Sci USA* **90**: 2227–31.
14. **Hilliard MA, Apicella AJ, Kerr R, Suzuki H**, et al. 2005. In vivo imaging of *C. elegans* ASH neurons: cellular response and adaptation to chemical repellents. *EMBO J* **24**: 63–72.
15. **Perl ER.** 1996. Cutaneous polymodal receptors: characteristics and plasticity. *Prog Brain Res* **113**: 21–37.
16. **Emery EC, Luiz AP, Sikandar S, Magnusdottir R**, et al. 2016. In vivo characterization of distinct modality-specific subsets of somatosensory neurons using GCaMP. *Sci Adv* **2**: e1600990.
17. **Zhang J, Cavanaugh DJ, Nemenov MI, Basbaum AI.** 2013. The modality-specific contribution of peptidergic and non-peptidergic nociceptors is manifest at the level of dorsal horn nociresponsive neurons. *J Physiol* **591**: 1097–110.
18. **Cavanaugh DJ, Lee H, Lo L, Shields SD**, et al. 2009. Distinct subsets of unmyelinated primary sensory fibers mediate behavioral responses to noxious thermal and mechanical stimuli. *Proc Natl Acad Sci USA* **106**: 9075–80.
19. **Rau KK, McIlwrath SL, Wang H, Lawson JJ**, et al. 2009. Mrgprd enhances excitability in specific populations of cutaneous murine polymodal nociceptors. *J Neurosci* **29**: 8612–9.
20. **Grosmaitre X, Santarelli LC, Tan J, Luo M**, et al. 2007. Dual functions of mammalian olfactory sensory neurons as odor detectors and mechanical sensors. *Nat Neurosci* **10**: 348–54.
21. **Connelly T, Yu Y, Grosmaitre X, Wang J**, et al. 2015. G protein-coupled odorant receptors underlie mechanosensitivity in mammalian olfactory sensory neurons. *Proc Natl Acad Sci USA* **112**: 590–5.
22. **Silbering AF, Bell R, Munch D, Cruchet S**, et al. 2016. Ir40a neurons are not DEET detectors. *Nature* **534**: E5–7.
23. **Rytz R, Croset V, Benton R.** 2013. Ionotropic Receptors (IRs): Chemosensory ionotropic glutamate receptors in *Drosophila* and beyond. *Insect Biochem Mol Biol* **43**: 888–97.
24. **Knecht ZA, Silbering AF, Ni LN, Klein M**, et al. 2016. Distinct combinations of variant ionotropic glutamate receptors mediate thermosensation and hygrosensation in *Drosophila*. *eLife* **5**: e17879.
25. **Enjin A, Zaharieva EE, Frank DD, Mansourian S**, et al. 2016. Humidity sensing in *Drosophila*. *Curr Biol* **26**: 1352–8.
26. **Russell J, Vidal-Gadea AG, Makay A, Lanam C**, et al. 2014. Humidity sensation requires both mechanosensory and thermosensory pathways in *Caenorhabditis elegans*. *Proc Natl Acad Sci USA* **111**: 8269–74.
27. **Chandrashekar J, Kuhn C, Oka Y, Yarmolinsky DA**, et al. 2010. The cells and peripheral representation of sodium taste in mice. *Nature* **464**: 297–301.
28. **Boscardin E, Alijevic O, Hummler E, Frateschi S**, et al. 2016. The function and regulation of acid-sensing ion channels (ASICs) and the epithelial Na^+ channel (ENaC): IUPHAR Review 19. *Br J Pharmacol* **173**: 2671–701.
29. **Ben-Shahar Y.** 2011. Sensory functions for degenerin/epithelial sodium channels (DEG/ENaC). *Adv Genet* **76**: 1–26.
30. **O'Hagan R, Chalfie M, Goodman MB.** 2005. The MEC-4 DEG/ENaC channel of *Caenorhabditis elegans* touch receptor neurons transduces mechanical signals. *Nat Neurosci* **8**: 43–50.
31. **Eastwood AL, Goodman MB.** 2012. Insight into DEG/ENaC channel gating from genetics and structure. *Physiology (Bethesda)* **27**: 282–90.
32. **Adams CM, Anderson MG, Motto DG, Price MP**, et al. 1998. Ripped pocket and pickpocket, novel *Drosophila* DEG/ENaC subunits expressed in early development and in mechanosensory neurons. *J Cell Biol* **140**: 143–52.
33. **Zhong L, Hwang RY, Tracey WD.** 2010. Pickpocket is a DEG/ENaC protein required for mechanical nociception in *Drosophila* larvae. *Curr Biol* **20**: 429–34.
34. **Pikielny CW.** 2012. Sexy DEG/ENaC channels involved in gustatory detection of fruit fly pheromones. *Sci Signal* **5**: pe48.
35. **Lu B, Lamora A, Sun Y, Welsh MJ**, et al. 2012. *ppk23*-dependent chemosensory functions contribute to courtship behavior in *Drosophila melanogaster*. *PLoS Genet* **8**: e1002587.
36. **Toda H, Zhao X, Dickson BJ.** 2012. The *Drosophila* female aphrodisiac pheromone activates ppk23(+) sensory neurons to elicit male courtship behavior. *Cell Rep* **1**: 599–607.
37. **Thistle R, Cameron P, Ghorayshi A, Dennison L**, et al. 2012. Contact chemoreceptors mediate male-male repulsion and male-female attraction during *Drosophila* courtship. *Cell* **149**: 1140–51.
38. **Chen Z, Wang Q, Wang Z.** 2010. The amiloride-sensitive epithelial Na+ channel PPK28 is essential for *Drosophila* gustatory water reception. *J Neurosci* **30**: 6247–52.
39. **Cameron P, Hiroi M, Ngai J, Scott K.** 2010. The molecular basis for water taste in *Drosophila*. *Nature* **465**: 91–5.
40. **Liedtke W, Choe Y, Marti-Renom MA, Bell AM**, et al. 2000. Vanilloid receptor-related osmotically activated channel (VR-OAC), a candidate vertebrate osmoreceptor. *Cell* **103**: 525–35.
41. **Liedtke W.** 2008. Molecular mechanisms of TRPV4-mediated neural signaling. *Ann N Y Acad Sci* **1144**: 42–52.
42. **Kellenberger S, Schild L.** 2015. International union of basic and clinical pharmacology. XCI. structure, function, and pharmacology of acid-sensing ion channels and the epithelial Na^+ channel. *Pharmacol Rev* **67**: 1–35.
43. **Fowler MA, Montell C.** 2013. *Drosophila* TRP channels and animal behavior. *Life Sci* **92**: 394–403.
44. **Julius D.** 2013. TRP channels and pain. *Annu Rev Cell Dev Biol* **29**: 355–84.
45. **Zhang W, Cheng LE, Kittelmann M, Li J**, et al. 2015. Ankyrin repeats convey force to gate the NOMPC mechanotransduction channel. *Cell* **162**: 1391–403.
46. **Kang K, Panzano VC, Chang EC, Ni L**, et al. 2011. Modulation of TRPA1 thermal sensitivity enables sensory discrimination in *Drosophila*. *Nature* **481**: 76–80.
47. **Liu C, Montell C.** 2015. Forcing open TRP channels: mechanical gating as a unifying activation mechanism. *Biochem Biophys Res Commun* **460**: 22–5.
48. **Hardie RC, Franze K.** 2012. Photomechanical responses in *Drosophila* photoreceptors. *Science* **338**: 260–3.
49. **Macpherson LJ, Dubin AE, Evans MJ, Marr F**, et al. 2007. Noxious compounds activate TRPA1 ion channels through covalent modification of cysteines. *Nature* **445**: 541–5.
50. **Chatzigeorgiou M, Bang S, Hwang SW, Schafer WR.** 2013. *tmc-1* encodes a sodium-sensitive channel required for salt chemosensation in *C. elegans*. *Nature* **494**: 95–9.
51. **Wang X, Li G, Liu J, Liu JF**, et al. 2016. TMC-1 mediates alkaline sensation in *C. elegans* through nociceptive neurons. *Neuron* **91**: 146–54.
52. **Guo Y, Wang Y, Zhang W, Meltzer S**, et al. 2016. Transmembrane channel-like (tmc) gene regulates *Drosophila* larval locomotion. *Proc Natl Acad Sci USA* **113**: 7243–8.
53. **Zhang YV, Aikin TJ, Li Z, Montell C.** 2016. The basis of food texture sensation in *Drosophila*. *Neuron* **91**: 863–77.
54. **Kawashima Y, Geleoc GS, Kurima K, Labay V**, et al. 2011. Mechanotransduction in mouse inner ear hair cells requires transmembrane channel-like genes. *J Clin Invest* **121**: 4796–809.
55. **Vreugde S, Erven A, Kros CJ, Marcotti W**, et al. 2002. Beethoven, a mouse model for dominant, progressive hearing loss DFNA36. *Nat Genet* **30**: 257–8.
56. **Kurima K, Peters LM, Yang Y, Riazuddin S**, et al. 2002. Dominant and recessive deafness caused by mutations of a novel gene, TMC1, required for cochlear hair-cell function. *Nat Genet* **30**: 277–84.
57. **Kato A, Touhara K.** 2009. Mammalian olfactory receptors: pharmacology, G protein coupling and desensitization. *Cell Mol Life Sci* **66**: 3743–53.
58. **Baud O, Yuan S, Veya L, Filipek S**, et al. 2015. Exchanging ligand-binding specificity between a pair of mouse olfactory receptor paralogs reveals odorant recognition principles. *Sci Rep* **5**: 14948.
59. **Storch U, Mederos y Schnitzler M, Gudermann T.** 2012. G protein-mediated stretch reception. *Am J Physiol Heart Circ Physiol* **302**: H1241–9.

60. **Zou YZ, Akazawa H, Qin YJ, Sano M**, et al. 2004. Mechanical stress activates angiotensin II type 1 receptor without the involvement of angiotensin II. *Nat Cell Biol* **6**: 499–506.
61. **Ni L, Klein M, Svec KV, Budelli G**, et al. 2016. The ionotropic receptors IR21a and IR25a mediate cool sensing in *Drosophila*. *eLife* **5**: e13254.
62. **Liman ER, Zhang YV, Montell C.** 2014. Peripheral coding of taste. *Neuron* **81**: 984–1000.
63. **Szczesniak AS.** 2002. Texture is a sensory property. *Food Qual Prefer* **13**: 215–25.
64. **Jeong YT, Oh SM, Shim J, Seo JT**, et al. 2016. Mechanosensory neurons control sweet sensing in *Drosophila*. *Nat Commun* **7**: 12872.
65. **Sanchez-Alcaniz JA, Zappia G, Marion-Poll F, Benton R.** 2017. A mechanosensory receptor required for food texture detection in *Drosophila*. *Nat Commun* **8**: 14192.
66. **Shanbhag SR, Park SK, Pikielny CW, Steinbrecht RA**. 2001. Gustatory organs of *Drosophila melanogaster*: fine structure and expression of the putative odorant-binding protein PBPRP2. *Cell Tissue Res* **304**: 423–37.
67. **Su CY, Menuz K, Reisert J, Carlson JR.** 2012. Non-synaptic inhibition between grouped neurons in an olfactory circuit. *Nature* **492**: 66–71.
68. **Thoma V, Knapek S, Arai S, Hartl M**, et al. 2016. Functional dissociation in sweet taste receptor neurons between and within taste organs of *Drosophila*. *Nat Commun* **7**: 10678.
69. **Auer T, Benton R.** 2016. Sexual circuitry in *Drosophila*. *Curr Opin Neurobiol* **38**: 18–26.
70. **Raad H, Ferveur JF, Ledger N, Capovilla M**, et al. 2016. Functional gustatory role of chemoreceptors in *Drosophila* wings. *Cell Rep* **15**: 1442–54.
71. **Takamura T.** 1984. Behavior genetics of choice of oviposition sites in *Drosophila melanogaster*. IV. Differentiation of oviposition force in the *melanogaster* species sub-group. *Jpn J Genet* **59**: 71–81.
72. **Karageorgi M, Bracker LB, Lebreton S, Minervino C**, et al. 2017. Evolution of multiple sensory systems drives novel egg-laying behavior in the fruit pest *Drosophila suzukii*. *Curr Biol* **27**: 847–853.
73. **Kong XQ, Wu CW.** 2010. Mosquito proboscis: an elegant biomicroelectromechanical system. *Phys Rev E Stat Nonlin Soft Matter Phys* **82**: 011910.
74. **Gal R, Kaiser M, Haspel G, Libersat F.** 2014. Sensory arsenal on the stinger of the parasitoid jewel wasp and its possible role in identifying cockroach brains. *PLoS ONE* **9**: e89683.
75. **Barrett DM, Beaulieu JC, Shewfelt R.** 2010. Color, flavor, texture, and nutritional quality of fresh-cut fruits and vegetables: desirable levels, instrumental and sensory measurement, and the effects of processing. *Crit Rev Food Sci Nutr* **50**: 369–89.
76. **Rolls ET.** 2015. Taste, olfactory, and food reward value processing in the brain. *Prog Neurobiol* **127-128**: 64–90.
77. **Westberg KG, Kolta A.** 2011. The trigeminal circuits responsible for chewing. *Int Rev Neurobiol* **97**: 77–98.
78. **McKeegan DE.** 2004. Mechano-chemical nociceptors in the avian trigeminal mucosa. *Brain Res Brain Res Rev* **46**: 146–54.
79. **Sweazey RD, Bradley RM.** 1989. Response characteristics of lamb trigeminal neurons to stimulation of the oral cavity and epiglottis with different sensory modalities. *Brain Res Bull* **22**: 883–91.
80. **Halata Z, Cooper BY, Baumann KI, Schwegmann C**, et al. 1999. Sensory nerve endings in the hard palate and papilla incisiva of the goat. *Exp Brain Res* **129**: 218–28.
81. **Halata Z, Baumann KI.** 1999. Sensory nerve endings in the hard palate and papilla incisiva of the rhesus monkey. *Anat Embryol* **199**: 427–37.
82. **Lacour JP, Dubois D, Pisani A, Ortonne JP.** 1991. Anatomical mapping of Merkel cells in normal human adult epidermis. *Br J Dermatol* **125**: 535–42.
83. **Matsuo R, Inoue T, Masuda Y, Nakamura O**, et al. 1995. Neural activity of chorda tympani mechanosensitive fibers during licking behavior in rats. *Brain Res* **689**: 289–98.
84. **Biedenbach MA, Chan KY.** 1971. Tongue mechanoreceptors: comparison of afferent fibers in the lingual nerve and chorda tympani. *Brain Res* **35**: 584–8.
85. **Whitehead MC, Beeman CS, Kinsella BA.** 1985. Distribution of taste and general sensory nerve endings in fungiform papillae of the hamster. *Am J Anat* **173**: 185–201.
86. **Montgomery JC, Macdonald F, Baker CF, Carton AG.** 2002. Hydrodynamic contributions to multimodal guidance of prey capture behavior in fish. *Brain Behav Evol* **59**: 190–8.
87. **Koehl MA.** 2006. The fluid mechanics of arthropod sniffing in turbulent odor plumes. *Chemical Senses* **31**: 93–105.
88. **Huston SJ, Stopfer M, Cassenaer S, Aldworth ZN**, et al. 2015. Neural encoding of odors during active sampling and in turbulent plumes. *Neuron* **88**: 403–18.
89. **Carde RT, Willis MA.** 2008. Navigational strategies used by insects to find distant, wind-borne sources of odor. *J Chem Ecol* **34**: 854–66.
90. **Dieudonne A, Daniel TL, Sane SP.** 2014. Encoding properties of the mechanosensory neurons in the Johnston's organ of the hawk moth, *Manduca sexta*. *J Exp Biol* **217**: 3045–56.
91. **Sane SP, Dieudonne A, Willis MA, Daniel TL.** 2007. Antennal mechanosensors mediate flight control in moths. *Science* **315**: 863–6.
92. **Wyeth RC, Willows AO.** 2006. Odours detected by rhinophores mediate orientation to flow in the nudibranch mollusc, *Tritonia diomedea*. *J Exp Biol* **209**: 1441–53.
93. **Ierusalimsky VN, Balaban PM.** 2010. Two morphological sub-systems within the olfactory organs of a terrestrial snail. *Brain Res* **1326**: 68–74.
94. **Altner I, Hatt H, Altner H.** 1983. Structural properties of bimodal chemo- and mechanosensitive setae on the pereiopod chelae of the crayfish, *Austropotamobius torrentium*. *Cell Tissue Res* **228**: 357–74.
95. **Mellon D, Jr.** 2012. Smelling, feeling, tasting and touching: behavioral and neural integration of antennular chemosensory and mechanosensory inputs in the crayfish. *J Exp Biol* **215**: 2163–72.
96. **Mellon D, Jr.** 2005. Integration of hydrodynamic and odorant inputs by local interneurons of the crayfish deutocerebrum. *J Exp Biol* **208**: 3711–20.
97. **Lee JK, Strausfeld NJ.** 1990. Structure, distribution and number of surface sensilla and their receptor cells on the olfactory appendage of the male moth *Manduca sexta*. *J Neurocytol* **19**: 519–38.
98. **Rebora M, Tierno de Figueroa JM, Piersanti S**. 2016. Antennal sensilla of the stonefly Dinocras cephalotes (Plecoptera: Perlidae). *Arthropod Struct Dev* **45**: 552–61.
99. **Olberg RM.** 1983. Interneurons sensitive to female pheromone in the deutocerebrum of the male silkworm moth, *Bombyx mori*. *Physiol Entomol* **8**: 419–28.
100. **Kanzaki R, Arbas EA, Strausfeld NJ, Hildebrand JG.** 1989. Physiology and morphology of projection neurons in the antennal lobe of the male moth *Manduca sexta*. *J Comp Physiol A* **165**: 427–53.
101. **Smear M, Shusterman R, O'Connor R, Bozza T**, et al. 2011. Perception of sniff phase in mouse olfaction. *Nature* **479**: 397–400.
102. **Wachowiak M.** 2011. All in a sniff: olfaction as a model for active sensing. *Neuron* **71**: 962–73.
103. **Ohyama T, Jovanic T, Denisov G, Dang TC**, et al. 2013. High-throughput analysis of stimulus-evoked behaviors in *Drosophila* larva reveals multiple modality-specific escape strategies. *PLoS ONE* **8**: e71706.
104. **Hwang RY, Zhong L, Xu Y, Johnson T**, et al. 2007. Nociceptive neurons protect *Drosophila* larvae from parasitoid wasps. *Curr Biol* **17**: 2105–16.
105. **Zhang W, Yan Z, Jan LY, Jan YN.** 2013. Sound response mediated by the TRP channels NOMPC, NANCHUNG, and INACTIVE in chordotonal organs of *Drosophila* larvae. *Proc Natl Acad Sci USA* **110**: 13612–7.
106. **Robertson JL, Tsubouchi A, Tracey WD.** 2013. Larval defense against attack from parasitoid wasps requires nociceptive neurons. *PLoS ONE* **8**: e78704.
107. **Zhong L, Bellemer A, Yan H, Honjo K**, et al. 2012. Thermosensory and non-thermosensory isoforms of *Drosophila melanogaster* TRPA1 reveal heat sensor domains of a thermoTRP channel. *Cell Rep* **1**: 43–55.
108. **Ohyama T, Schneider-Mizell CM, Fetter RD, Aleman JV**, et al. 2015. A multilevel multimodal circuit enhances action selection in *Drosophila*. *Nature* **520**: 633–9.
109. **Griffith LC, Ejima A.** 2009. Multimodal sensory integration of courtship stimulating cues in *Drosophila melanogaster*. *Ann N Y Acad Sci* **1170**: 394–8.
110. **Kohl J, Huoviala P, Jefferis GS.** 2015. Pheromone processing in *Drosophila*. *Curr Opin Neurobiol* **34**: 149–57.
111. **Coen P, Murthy M.** 2016. Singing on the fly: sensorimotor integration and acoustic communication in *Drosophila*. *Curr Opin Neurobiol* **38**: 38–45.
112. **Ejima A, Griffith LC.** 2008. Courtship initiation is stimulated by acoustic signals in *Drosophila melanogaster*. *PLoS ONE* **3**: e3246.
113. **Zhou C, Franconville R, Vaughan AG, Robinett CC**, et al. 2015. Central neural circuitry mediating courtship song perception in male *Drosophila*. *eLife* **4**: e08477
114. **Coen P, Xie M, Clemens J, Murthy M.** 2016. Sensorimotor transformations underlying variability in song intensity during *Drosophila* courtship. *Neuron* **89**: 629–44.

115. **Wang L, Anderson DJ.** 2010. Identification of an aggression-promoting pheromone and its receptor neurons in *Drosophila*. *Nature* **463**: 227–31.
116. **Versteven M, Vanden Broeck L, Geurten B, Zwarts L**, et al. 2017. Hearing regulates *Drosophila* aggression. *Proc Natl Acad Sci USA* **114**: 1958–63.
117. **Hoopfer ED, Jung Y, Inagaki HK, Rubin GM**, et al. 2015. P1 interneurons promote a persistent internal state that enhances inter-male aggression in *Drosophila*. *eLife* **4**: e11346.
118. **Asaba A, Hattori T, Mogi K, Kikusui T.** 2014. Sexual attractiveness of male chemicals and vocalizations in mice. *Front Neurosci* **8**: 231.
119. **Anderson DJ.** 2016. Circuit modules linking internal states and social behaviour in flies and mice. *Nat Rev Neurosci* **17**: 692–704.
120. **Ramdya P, Lichocki P, Cruchet S, Frisch L**, et al. 2015. Mechano-sensory interactions drive collective behaviour in *Drosophila*. *Nature* **519**: 233–6.
121. **Merabet LB, Pascual-Leone A.** 2010. Neural reorganization following sensory loss: the opportunity of change. *Nat Rev Neurosci* **11**: 44–52.
122. **Murray MM, Lewkowicz DJ, Amedi A, Wallace MT.** 2016. Multisensory processes: a balancing act across the lifespan. *Trends Neurosci* **39**: 567–79.
123. **Rabinowitch I, Laurent P, Zhao B, Walker D**, et al. 2016. Neuropeptide-driven cross-modal plasticity following sensory loss in *Caenorhabditis elegans*. *PLoS Biol* **14**: e1002348.
124. **Chen XY, Chalfie M.** 2014. Modulation of *C. elegans* touch sensitivity is integrated at multiple levels. *J Neurosci* **34**: 6522–36.
125. **Saumweber T, Cano C, Klessen J, Eichler K**, et al. 2014. Immediate and punitive impact of mechanosensory disturbance on olfactory behaviour of larval *Drosophila*. *Biol Open* **3**: 1005–10.
126. **Partan SR.** 2013. Ten unanswered questions in multimodal communication. *Behav Ecol Sociobiol* **67**: 1523–39.
127. **Krakauer JW, Ghazanfar AA, Gomez-Marin A, MacIver MA**, et al. 2017. Neuroscience needs behavior: correcting a reductionist bias. *Neuron* **93**: 480–90.
128. **Catania KC.** 2017. Behavioral pieces of neuroethological puzzles. *J Comp Physiol A* **10**: 1–13.
129. **Chalasani SH, Chronis N, Tsunozaki M, Gray JM**, et al. 2007. Dissecting a circuit for olfactory behaviour in *Caenorhabditis elegans*. *Nature* **450**: 63–70.