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Author

Montell, Craig

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Coordinated movement: watching proprioception unfold

Craig Montell

Department of Molecular, Cellular and Developmental Biology, and the Neuroscience Research Institute, University of California Santa Barbara, Santa Barbara, CA, 93106, USA

Summary

Proprioceptive neurons provide feedback about body positions and movements that are critical for coordination. Using *Drosophila* larvae, two papers use high-speed microscopy to create movies revealing sequential, direction-dependent changes in dendritic folding and activities of proprioceptive neurons in freely-moving animals.

Proprioception is what allows us to make coordinated movements. This is accomplished through neurons that sense both the static and dynamic positions of body parts. Every time an animal moves, proprioceptive neurons send out signals that are received by the central nervous system, ultimately modifying commands to muscles that control movements. This process, called proprioceptive feedback, is essential so that muscle activity can adjust under a variety of changing situations, such as occurs during planned motor sequences or when body position shifts suddenly in response to an unpredictable perturbation. Proprioception helps animals accomplish basic survival tasks including defense, navigation to food sources, migration away from noxious environments and mating. Despite the critical role for proprioception, our understanding of how proprioceptive neurons are activated and how they coordinate their activities in real time during different types of movements is understood poorly. An impediment to solving this problem is that it is very difficult to monitor dynamic changes in the shape and activities of proprioceptive neurons in freely-moving animals. Two papers in this issue of *Current Biology* use high-speed video microscopy in *Drosophila* larvae to reveal sequential changes in the folding of dendrites of proprioceptive neurons and neuronal activity patterns that correlate with these shape changes in untethered, moving animals [1, 2]. The studies by He and colleagues and Vaadia and colleagues represent major accomplishments, which set the stage for testing new models underlying proprioception.

Illuminating how proprioceptive neurons detect body position and movements entails overcoming a special challenge that is not incurred when studying most other senses. How sensory cells are activated by stimuli such as light, odorants, tastants and thermal input is largely resolved once the signaling molecules and the cellular architecture of the receptor cells are known. In the case of proprioceptive neurons, this sort of information is insufficient. Since proprioceptors sense movement or mechanical cues, it is not possible to clarify how these neurons are activated, and how this activation impacts motor function,

cmontell@ucsb.edu; phone, (805) 893-3634.

without examining the dynamic changes in the flexing of their dendrites, and their activity in untethered, exploring animals.

This is where *Drosophila* larvae come to the rescue. Larvae have two missions in life—to eat and avoid being eaten. These vital objectives require forward and backward locomotion, turning, burrowing and occasionally rolling perpendicular to their body axis [3]. The forward and backward movements are accomplished through repetitive, rhythmic strides [4, 5]. These strides remain relatively constant at a variety of speeds [5]. During forward locomotion the muscles within the body wall of each of the 8 abdominal segments undergo peristaltic waves of posterior-to-anterior contractions. When larvae reverse direction to move backward, the contractions now initiate from the anterior. These waves of contractions are coordinated within and between segments to enable smooth movement.

Acting presynaptic to the motor neurons that control the muscles are several multidendritic (md) sensory neurons that tile the body wall of each abdominal segment [6]. These include three class I md neurons (dorsal ddaD, ddaE; ventral, vpda) with relatively large, non-overlapping receptive fields, and dorsal and ventral md bipolar neurons (dbd and vbd), which extend processes in the anterior to posterior direction (Figure 1). Inactivation of all md neurons disrupts locomotion, suggesting that they are proprioceptors providing important information about body position [7, 8]. Previous work using a dissected larval preparation and a genetically encoded Ca^{2+} sensor, GCaMP, demonstrate that md neurons respond to muscle contractions [9]. It has been proposed that upon segment contraction, the md proprioceptive neurons in the peripheral nervous system send a “mission accomplished” signal to the central nervous system, allowing the muscles in one segment to relax, thereby promoting rapid propagation of the peristaltic wave to the adjacent segment during locomotion [8].

But the burning question is how proprioceptive neurons provide the feedback on rapidly changing body positions, endowing untethered larvae the ability to navigate through the environment. In particular, how is locomotion in different directions, such as forward and backward movement, sensed? To answer this, researchers needed to find a way to visualize changes in the ultrastructure and activity of the proprioceptive neurons in real time in freely-moving larvae. To do so, the two teams expressed fluorescent proteins in the md neurons and established rapid scanning microscopy methods to view the peripheral nervous system in a given segment 10 or more times per second, either by improving a 3-D light sheet approach, called SCAPE (Swept Confocally Aligned Planar Excitation) [2], or by employing a high-speed confocal microscope with a motor-driven objective [1].

The videos showing the real-time deformations of the dendrites in the larval body wall are beautiful and informative. The differences between videos and fixed images of md neurons are dramatic—like watching the first-ever film from 1878, which revealed all four horse’s hooves lift off the ground simultaneously during a gallop—an observation that was never caught in the early still photographs.

The movies of the *Drosophila* larvae display dynamic flexing of the dendrites of proprioceptive neurons during locomotion in different directions. During forward motion the

most posterior dendrites of the ventral class I neuron (vpda) [2] and the dorsal class I neuron, ddaE, fold inward during each contraction, followed by bending of the dendrites corresponding to the more anterior dorsal class I neuron (ddaD) [1, 2] (Figure 1). These observations highlight that the forces during contraction proceed from the posterior to the anterior part of each segment, rather than simultaneous contraction from both ends towards the middle. When the larvae move backward, the ddaD neurons are the first to fold inward (Figure 1). In addition to revealing the folding and curvature patterns of these and other md neurons during movements, the studies with the Ca^{2+} sensor, GCaMP6f, indicate that they are activated by deformations of their dendrites. Moreover, the various proprioceptive neurons are activated sequentially, and to different extents during the segment contractions that accompany movement. For example, in the forward direction maximal activation of ddaE exceeds ddaD, while during backward locomotion, ddaD shows greater activity (Figure 1). The successive and different magnitudes of activation of proprioceptors that extend dendrites over distinct regions of each segment could provide a mechanism through which different neurons code for distinct body positions and movements, including the angles of leftward and rightward turning, and head retraction.

Not all of the proprioceptive neurons are activated by contraction. Rather, the activities of morphological similar bipolar neurons on the dorsal and ventral side of each abdominal segment (dbd and vbd) are activated by stretch and contraction respectively [2, 10], highlighting that the repertoire of proprioceptors provide continuous feedback on various types of body positions. A question for the future is whether each proprioceptive neuron is activated and turned off independently or whether there is direct communication between the different proprioceptors.

Which cation channels sense the mechanical forces applied to the dendrites of the proprioceptive neurons in larvae during locomotion? Candidates include NOMPC (a TRPN channel) and TMC since mutations affecting either of these cation channels impair larval locomotion [9, 11]. Based on analyses with GCaMP sensors in dissected preparations, both channels contribute to the activities of class I md neurons [9–11]. Moreover, NOMPC and TMC have multiple mechanosensory roles in flies [9, 11–16]. In mammals, recent evidence supports the idea that TMC1 is the enigmatic auditory transduction channel, perhaps forming a dimer in association with TMC2 [17]. He et al. focused on *tmc* mutant larvae and found using GCaMP that the dynamic changes in the activities of the ddaD and ddaE dorsal proprioceptors neurons that normally accompany locomotion were eliminated [1]. The impact of the *tmc* mutation on the activities of the other class I neurons remains to be determined.

Do other mechanosensory channels also function in the md proprioceptive neurons? The mechanotransduction channel Piezo is an appealing candidate since it is required in dbd neurons that are activated by stretch [10], but mutation of *piezo* does not cause any obvious impairment in larval locomotion [18]. NOMPC is required for normal locomotion [9], so it would be of interest to examine the effect of the *nompC* mutation on the activities ddaD and ddaE and on other proprioceptive neurons in exploring larvae. Correlating alterations in specific proprioceptor activity with changes in behavior like stride length, locomotion speed, or the ability to assume certain angular positions would be informative—and it is now

possible with the high-speed microscopy. Interestingly, a role for NOMPC in locomotion is evolutionarily conserved in worms. In *C. elegans*, the NOMPC homolog is a mechanotransduction channel required in stretch-sensitive proprioceptive neurons for normal body posture during their locomotion [19, 20].

In conclusion, the ability to monitor changes in dendritic folding and activities of proprioceptive neurons in untethered, freely-moving animals in real time is a game-changer for defining how proprioceptive neurons modulate coordinated movements. This new technical ability opens the door to analyzing the proprioceptive neurons during other behaviors, such as the rapid rolling perpendicular to the body axis in response to nociceptive stimuli. Finally, in the future it would be of interest to test models concerning the specific roles of the individual md neurons for proprioceptive feedback, by acutely activating them using optogenetics, in the absence of the proprioceptive channels.

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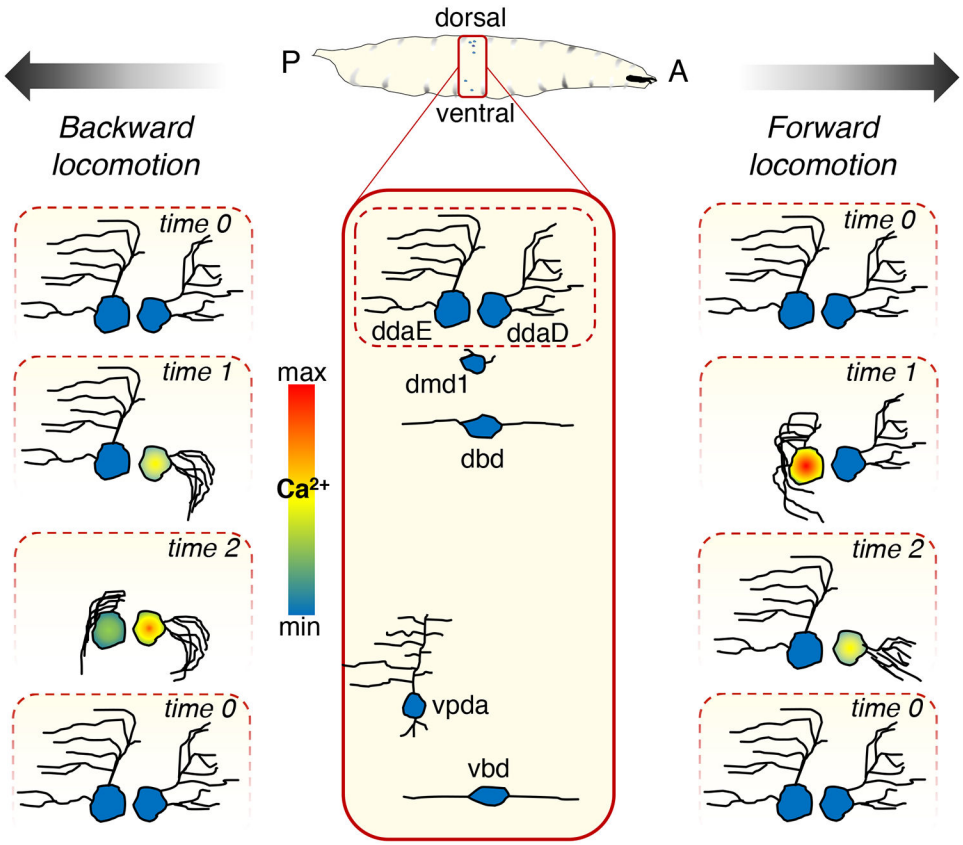

Figure 1.

Cartoons illustrating distinct, sequential folding patterns and activities exhibited by proprioceptive neurons during forward and backward movement of a *Drosophila* larva. Shown at the top is a cartoon of a larva with the anterior (A) and posterior (P) ends indicated. Directly below the larva is a cartoon of one abdominal segment with six proprioceptive neurons. The red dashed box indicates the ddaE and ddaD neurons. To the right and left are depictions of the changes in dendritic folding and neuronal activities (using a genetically encoded Ca^{2+} sensor, GCaMP6f) exhibited by ddaE and ddaD neurons during forward and backward locomotion. Time 0 indicates the relaxed state, and times 1 and 2 depict two points during a contraction wave in either the forward or backward directions. The colors of the neurons indicate the relative level of free intracellular Ca^{2+} as assessed using the GCaMP6f sensor. A relative Ca^{2+} scale is shown. This illustration was prepared by Dr. Dhananjay Thakur.