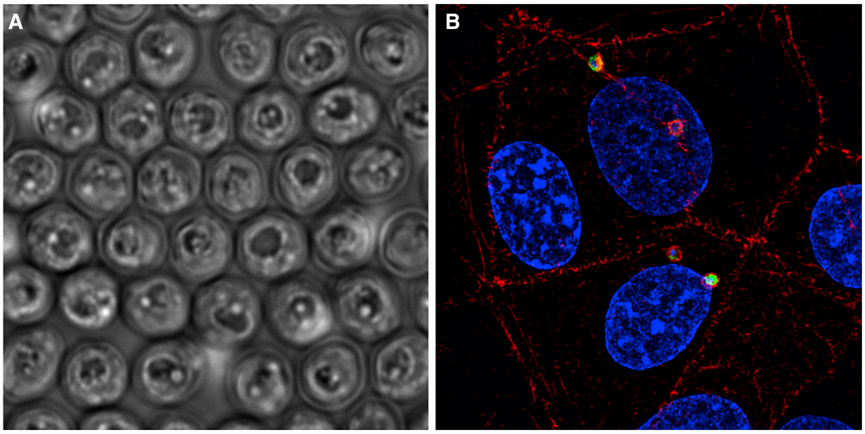


Figure 1. The apicomplexan parasite *Cryptosporidium parvum*.
(A) Infection occurs by ingestion of oocysts, meiotic spores that contain four invasive parasites and are resistant to water chlorination. (B) Crypto (green) induces actin polymerization (red, phalloidin) in the host cell at the site of infection. Blue, DNA. Images: M. Kandasmy and B. Striepen.

with pathogens like Crypto shape the composition of the bacterial community, and at the same time malnutrition keeps the microbiota in an immature state that provides an opening for pathogens.

Could immunity to Crypto be harnessed? Growing up under high exposure conditions, children are frequently diagnosed with cryptosporidiosis between the ages of 6–24 months — after that Crypto is rare. This observation suggests a protective role for adaptive immunity and offers hope for a vaccine. But robust immunity often takes more than a single infection. Our knowledge of immunity to Crypto infection is limited, but production of IFNγ and $CD4^+$ T cells are critical to positive outcomes. We recently developed a natural mouse model using Crypto strains isolated from wild mice and adapted to a life in the lab. Infection with these parasites does not require immunosuppression, but immunosuppressed mice are more susceptible, mimicking what is seen in human infections. Repeated infection yields protection, allowing the study of host factors that control infection and the parasite factors that help to outrun immunity. Such model systems will help elucidate the mechanisms of immunity and provide correlates of protection, hopefully paving the way to prevention.

DECLARATION OF INTERESTS

B.S. is an author on a patent for the methodology used for *Cryptosporidium* transfection, submitted by the University of Georgia.

Where can I find out more?

Checkley, W., White, A.C., Jr., Jaganath, D., Arrowood, M.J., Chalmers, R.M., Chen, X.M., Fayer, R., Griffiths, J.K., Guerrant, R.L., Hedstrom, L., *et al*. (2015). A review of the global burden, novel diagnostics, therapeutics, and vaccine targets for *Cryptosporidium*. Lancet Infect. Dis. *15*, 85–94.
Kane, A.V., Dinh, D.M., and Ward, H.D. (2015). Childhood malnutrition and the intestinal microbiome. Pediatr. Res. *77*, 256–262.
Kotloff, K.L., Nataro, J.P., Blackwelder, W.C., Nasrin, D., Farag, T.H., Panchalingam, S., Wu, Y., Sow, S.O., Sur, D., Breiman, R.F., *et al*. (2013). Burden and aetiology of diarrhoeal disease in infants and young children in developing countries (the Global Enteric Multicenter Study, GEMS): a prospective, case-control study. Lancet *382*, 209–222.
Lendner, M., and Daugschies, A. (2014). *Cryptosporidium* infections: molecular advances. Parasitology *141*, 1511–1532.
Mac Kenzie, W.R., Hoxie, N.J., Proctor, M.E., Gradus, M.S., Blair, K.A., Peterson, D.E., Kazmierczak, J.J., Addiss, D.G., Fox, K.R., Rose, J.B., *et al*. (1994). A massive outbreak in Milwaukee of *Cryptosporidium* infection transmitted through the public water supply. N. Engl. J. Med. *331*, 161–167.
Manjunatha, U.H., Vinayak, S., Zambriski, J.A., Chao, A.T., Sy, T., Noble, C.G., Bonamy, G.M.C., Kondreddi, R.R., Zou, B., Gedeck, P., *et al*. (2017). A *Cryptosporidium* PI(4)K inhibitor is a drug candidate for cryptosporidiosis. Nature *546*, 376–380.
Mondal, D., Minak, J., Alam, M., Liu, Y., Dai, J., Korpe, P., Liu, L., Haque, R., and Petri, W.A., Jr. (2012). Contribution of enteric infection, altered intestinal barrier function, and maternal malnutrition to infant malnutrition in Bangladesh. Clin. Infect. Dis. *54*, 185–192.
Striepen, B. (2013). Parasitic infections: Time to tackle cryptosporidiosis. Nature *503*, 189–191.
Vinayak, S., Pawlowic, M.C., Sateriale, A., Brooks, C.F., Studstill, C.J., Bar-Peled, Y., Cipriano, M.J., and Striepen, B. (2015). Genetic modification of the diarrhoeal pathogen *Cryptosporidium parvum*. Nature *523*, 477–480.

Department of Pathobiology, School of Veterinary Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA.
E-mail: algi@upenn.edu (A.R.G.); striepen@upenn.edu (B.S.)

Primer

Proprioception

John C. Tuthill[1] and Eiman Azim[2]

Although familiar to each of us, the sensation of inhabiting a body is ineffable. Traditional senses like vision and hearing monitor the external environment, allowing humans to have shared sensory experiences. But proprioception, the sensation of body position and movement, is fundamentally personal and typically absent from conscious perception. Nonetheless, this ‘sixth sense’ remains critical to human experience, a fact that is most apparent when one considers those who have lost it. Take, for example, the case of Ian Waterman who, at the age of 19, suffered a rare autoimmune response to a flu infection that attacked the sensory neurons from his neck down. This infection deprived him of the sense of position, movement and touch in his body. With this loss of feedback came a complete inability to coordinate his movements. While he could compel his muscles to contract, he lost the ability to orchestrate these actions into purposeful behaviors, in essence leaving him immobile, unable to stand, walk, or use his body to interact with the world. Only after years of dedicated training was he able to re-learn to move his body entirely under visual control.

Proprioception relies on populations of mechanosensory neurons distributed throughout the body, which are collectively referred to as *proprioceptors*. Physiologists of the 19th century, unaware of the existence of specialized proprioceptors, debated the origin of ‘muscle sense’, a term attributed to Charles Bell, the first to distinguish motor from sensory nerves. Some German physiologists of the time argued that this ‘*Muskelsinn*’ is purely central in origin, with the brain monitoring body position through careful accounting of motor commands. In the late 19th and early 20th centuries, Charles Sherrington provided definitive evidence for a peripheral source of sensory afferents and their influence on muscle contraction. Coining the term *proprioception*, which he defined as the sensation of stimuli that “are traceable to actions of the organism itself”, Sherrington distinguished this sensory modality from what he termed *exteroception*, sensation of stimuli originating outside of the body, and *interoception*, sensory signals from the organs, such as the gut. Although Kühne, Ruffini, and others had described proprioceptor organs many years earlier (Figure 1A), Sherrington was the first to demonstrate the influence of sensory neurons that innervate these proprioceptive organs on posture and movement control (Figure 1B). Today, the study of sensorimotor control continues to rely on Sherrington's initial conception of the proprioceptive system, in particular his emphasis on so-called 'reflex' pathways that translate proprioceptive feedback into motor output.

Given its fundamental role in coordinating movement, it should come as no surprise that the sense of proprioception is not limited to higher mammals. Indeed, we now know that nearly all motile animals rely on proprioceptive feedback to control their bodies. Although entomologists had already described the anatomy of insect proprioceptors by the mid-19th century (Figure 1C), it was not understood that these organs served a proprioceptive function for many decades. In 1938, J.W.S. Pringle published a series of groundbreaking papers that described the physiology and function of two classes of proprioceptors (Figure 1D). In these studies, Pringle drew attention to the similarities in sensitivity, stimulus tuning, and adaptation of insect proprioceptors with those recorded by B.H.C. Matthews in mammals. Comparative studies over the last 80 years have corroborated Pringle's initial observations, showing that limbed animals face many common constraints and may have arrived at similar solutions to the problems of mechanosensation and proprioceptive neural coding.

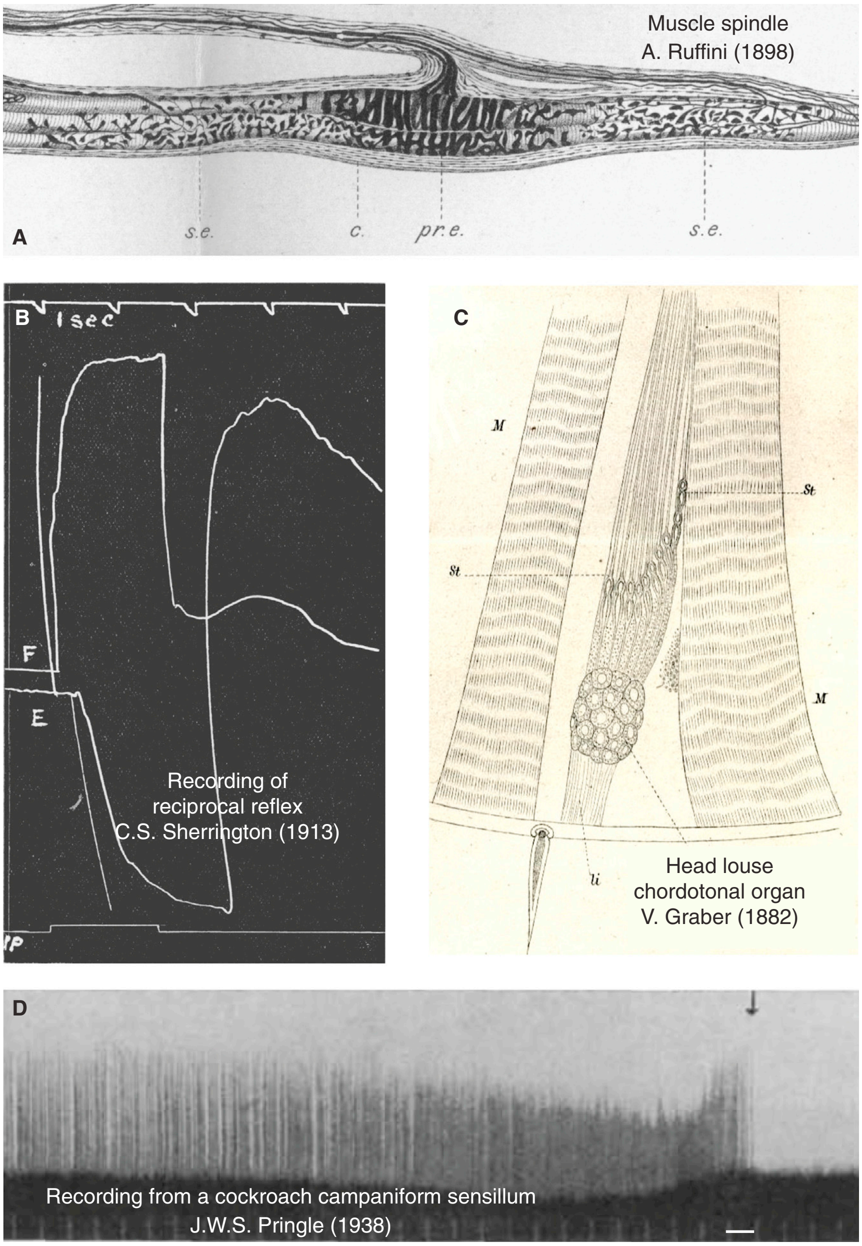


Figure 1. A historical view of proprioception.
(A) Sketch of a muscle spindle and its sensory afferent innervation in the adult cat by Angelo Ruffini (1898). pr.e., primary ending; s.e., secondary ending; c., capsule. (See Figure 2C). (B) Electrophysiological recording of the reciprocal reflex of antagonist muscles in the knee of a decerebrate cat by Charles Sherrington (1913). Traces show recordings from the semitendinosus, knee flexor (F), and vastocrureus, knee extensor (E). Signal on the bottom indicates stimulation of the ipsilateral popliteal nerve (IP), evoking flexor contraction and extensor inhibition. Inhibition of the extensor is followed by a rebound contraction and a simultaneous relaxation of the flexor. (See Figure 2B for circuit schematic). (C) Sketch of a femoral chordotonal organ from the leg of a head louse *(Pediculus capitis)* by Vitus Graber (1882), reprinted by permission from Springer Nature © 1881. M, muscle fibers; St, pin region; li, chordotonal ligament. (See Figure 2K). (D) Electrophysiological recording from the afferent of a campaniform sensillum on the maxillary palp of the cockroach in response to pressure on the cuticle (at arrow), by J.W.S. Pringle (1938), reproduced with permission from Journal of Experimental Biology jeb.biologists.org. The trace reads from right to left, and scale bar indicates 100 ms.

In this Primer, we will draw attention to these analogous solutions by discussing proprioceptive sensing of the limbs in two well-studied animal groups: mammals and insects. Comparing how such diverse nervous systems solve common behavioral challenges should provide insight into the evolutionary constraints and computational demands that have shaped proprioceptive systems. Our major goals are: to describe the key proprioceptive organs and the mechanical parameters they detect; to outline some of the major ethological contributions of proprioceptive feedback; and to point out the considerable gaps in our understanding of proprioception, particularly within the central nervous system, with an eye toward progress ahead.

Proprioceptive hardware

Body movement and position are reflected by the activity of diverse sensory neuron types. For example, the retina can monitor where the limbs are in space, and tactile feedback from the skin can provide information about body conformation, skin deformation during movement, and points of contact with an object. For the purposes of this Primer, however, we will focus primarily on classically defined proprioceptors: mechanosensory neurons located within muscles, tendons, and joints (Figure 2).

Muscle spindles and chordotonal organs

Embedded deep within mammalian skeletal muscles are muscle spindles: capsules of connective tissue that contain specialized intrafusal muscle fibers (Figure 2B,C) positioned in parallel with the extrafusal muscle fibers innervated by alpha motor neurons. The projections of primary sensory neurons, known as group Ia afferents, spiral around the central portion of intrafusal fibers, and respond to muscle stretch with brief bursts of action potentials. Group Ia neurons encode both muscle length and the rate of change (velocity) of muscle length. To the sides of the Ia fibers, at the edge of the spindle, are the sensory endings of secondary or group II afferents, which linearly encode static muscle length. A potential advantage of velocity sensitivity in Ia afferents is that it enables rapid detection of postural perturbations (before large changes in the magnitude of position occur and are detected by group II afferents). Muscle spindles receive efferent innervation from gamma motor neurons, which regulate the tension on the spindle, and thus fine-tune the gain of these sensory afferents.

Insect proprioceptors also encode position and velocity. In the insect femur, for example, a large chordotonal organ contains up to several hundred mechanosensory neurons connected to the tibia by a stiff tendon (Figure 2I,K). The dendrites of femoral chordotonal neurons detect mechanical stretch as the tibia moves relative to the femur. Different chordotonal neurons are sensitive to distinct parameters of tibia movement, including position, velocity, and acceleration. Thus, insects have arrived at a mechanically distinct solution to encoding kinematic information, with chordotonal organs signaling joint displacement, as opposed to muscle spindles that signal muscle stretch.

Interestingly, some insects also possess muscle spindle-like receptors known as muscle receptor organs, complete with efferent innervation and length/velocity encoding. One reason why chordotonal neurons may be more common is that muscle receptor organs are simply too large to squeeze into most tiny insect muscles. On the other hand, there may be advantages to directly monitoring joint position, such as the ability to attach many sensory neurons, with diverse intrinsic properties, to the same tendon. Another advantage may be that chordotonal organs can monitor net changes in position and movement produced by a number of muscles. This may simplify motor control for insects, in comparison to vertebrates. However, like muscle spindles, chordotonal organs have nonlinear response properties (such as hysteresis) that compromise encoding of joint position. One compelling idea is that sensory hysteresis compensates for the nonlinear properties of muscle.

Golgi tendon organs and campaniform sensilla

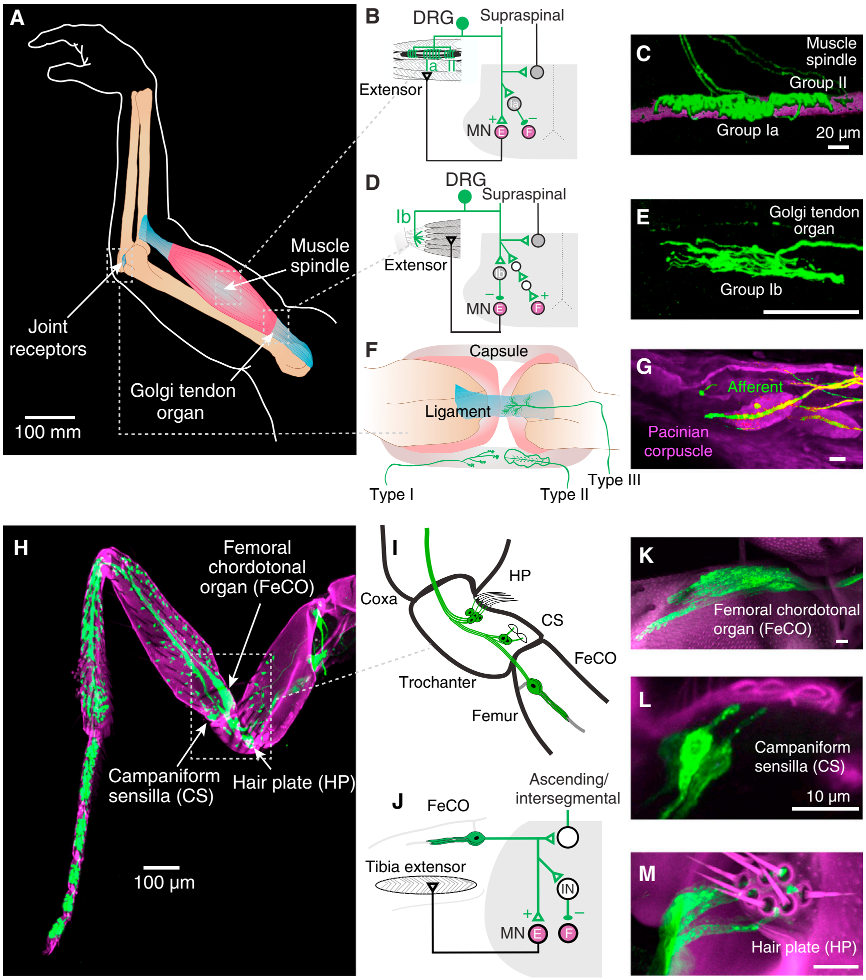
In mammals, the load on a limb is detected by Golgi tendon organs, proprioceptors that lie at the interface between muscles and tendons (Figure 2D,E). Each tendon organ contains the sensory endings of a single mechanosensory neuron wrapped around strands of collagen, which are attached to individual muscle fibers. These group Ib afferents innervate tendon organs and encode muscle force — they are silent at rest, and increase their firing frequency as tension in the muscle rises, such as during resisted movements.

Insects detect mechanical load of the limbs with campaniform sensilla, small dome-like structures that are sensitive to strain in the cuticle (Figure 2I,L). Campaniform sensilla usually occur in groups clustered close to joints. Each sensillum is innervated by one sensory neuron, whose dendrites span the length of the dome. The shape of the dome endows some campaniform sensilla with direction selectivity. Like Golgi tendon organs, campaniform sensilla may be silent at rest or when a joint is passively moved, and respond only when a movement is resisted. For both proprioceptor types, this is achieved by encoding load as the resistance to muscle contraction. Golgi tendon organs take advantage of the high levels of stress at the junction between a muscle and the internal skeleton, while campaniform sensilla take advantage of the predictable distribution of strain in the exoskeleton. Monitoring strain in the cuticle, rather than the forces produced by individual muscles, may help simplify motor control for the miniaturized insect nervous system.

Joint receptors and hair plates

In addition to position-tuned signaling from muscle spindles and chordotonal organs, insects and mammals both possess proprioceptive organs that detect when a joint reaches a certain threshold. In mammals, this system consists of sensory neurons typically associated with the tactile system: low-threshold mechanoreceptors such as Ruffini endings and Pacinian corpuscles, which are embedded in the joint (Figure 2F,G). These joint mechanoreceptors are generally considered to belong to three major types: type I, slowly adapting receptors in the outer layers of the fibrous joint capsule; type II, rapidly adapting receptors in the deeper layers of the joint capsule; and type III, slowly adapting receptors embedded in the ligaments and terminal regions of the tendons near the joint capsule. These receptor classes are distinguished from the type IV free nerve ending nociceptors distributed throughout the joint capsule, which have a higher mechanical threshold and contribute to the sensation of pain. The responses of joint receptors can often peak at the extremes of joint position, suggesting that one role may be to function as ‘limit detectors’.

Insect hair plates may serve a similar purpose; these are tightly-packed arrays of sensory hairs positioned on the cuticle so that they are deflected when the joint is at a particular position (Figure 2 I,M). As in mammals, this is typically at the edges of the joint range, which could



Current Biology

Figure 2. Proprioceptive hardware.
(A) Location of proprioceptive organs in a mammalian limb. (B) Schematic of muscle spindle afferent spinal connectivity, highlighting homonymous motor pool activation and antagonist inhibition, via Ia inhibitory interneurons (also see Figure 1B). MN, motor neuron; E, extensor; F, flexor; DRG, dorsal root ganglion. (C) GFP expression in group Ia (central) and group II (lateral) afferents innervating an intrafusal fiber (magenta autofluorescence) in a mouse plantaris muscle spindle. (D) Schematic of Golgi tendon organ group Ib afferent connectivity in the spinal cord. Note the opposite effects on extensor and flexor activity as compared to muscle spindle afferents, in part mediated by inhibitory Ib interneurons that innervate homonymous motor neurons. (E) GFP expression in a group Ib afferent innervating a mouse gluteus Golgi tendon organ. (F) Schematic of receptor types in the joint capsule and ligament that could convey proprioceptive information. (G) GFP expression in an afferent innervating a nonmyelinating Schwann cell of a Pacinian corpuscle (S100 immunostaining, magenta) in mouse interosseous membrane. (H) Distribution of mechanosensory neurons on the *Drosophila* leg. Image shows ChAT-Gal4 driving UAS-GFP. (I) Schematic of proprioceptor distribution on proximal regions of the *Drosophila* leg. For clarity, only a subset of proprioceptors are shown. (J) Example wiring schematic of sensory neuron targets in the insect VNC, based on data from the locust (note that not all connections are shown). Flexion-sensitive proprioceptors from the femoral chordotonal organ directly excite tibial extensor motor neurons, and indirectly inhibit flexor motor neurons. FeCO neurons also synapse on intersegmental and ascending interneurons. (Note the similarity to muscle spindle afferent connectivity in Figure 2B.) (K) GFP expression in neurons of the FeCO of *Drosophila*. Magenta is cuticle autofluorescence. (L) Campaniform sensilla from the *Drosophila* trochanter. (M) Hair plate neurons from the coxa of *Drosophila*. Panels (B–E,G) courtesy of Joriene de Nooij; images in (H,K–M) are from Tuthill and Wilson (2016).

provide a mechanism for anticipating phase changes in walking, such as the swing to stance transition. Each hair within the array is innervated by a single sensory neuron, and may be either slowly or rapidly adapting.

Central projections of proprioceptor axons

In both mammals and insects, the axonal projections of limb proprioceptors are systematically organized depending on proprioceptor type and body location. In mammals, the cell bodies of proprioceptive afferents from the limbs reside in dorsal root ganglia, where they intermingle with neurons dedicated to other sensory modalities (such as pain and touch). These afferents project through dorsal roots into the central nervous system, where some proprioceptive axons extend into the ventral spinal cord toward motor neuron pools.

Different afferent types assemble into specialized and stereotyped circuit motifs that can affect muscle activity in different ways. For example, muscle spindle group Ia afferents directly excite alpha motor neurons that innervate the same (homonymous) and synergist (heteronymous) muscles, while also recruiting inhibitory neurons that innervate the antagonist motor pools (Figure 2B). In contrast, Golgi tendon organ group Ib afferents synapse onto excitatory and inhibitory interneurons that ultimately inhibit alpha motor neurons of homonymous muscles and excite those of antagonist muscles (Figure 2D). Joint mechanoreceptors have been shown to affect motor neuron activity as well as the flow of nociceptive information, though less is known about the spinal circuits involved. Together, these ‘basic’ spinal reflex pathways represent only the best-described circuit connectivity; proprioceptive feedback is also transmitted directly, by the afferents themselves, or indirectly, via interneurons, to local circuits, to other spinal segments, and to the brain. Moreover, these circuit rules are not rigid in a functional sense; effects on muscle activity have mostly been defined in anesthetized animals and can change during behavior, as discussed below.

The ventral nerve cord (VNC), the insect analog of the spinal cord, follows a similar logic: the VNC neuropil is organized by leg segment, and within each segment, motor neurons arborize dorsally, touch receptor axons project ventrally, and proprioceptor axons terminate in intermediate layers. As in the mammalian spinal cord, many proprioceptor axons project to multiple segments of the VNC, but only a small fraction have collaterals that ascend to the central brain. Most proprioceptive afferents form synapses with multiple postsynaptic partners, including motor neurons, local interneurons, and long-range ascending and intersegmental neurons (Figure 2J). Although not completely understood, the spatial and modality-specific organization of proprioceptive afferents provides a substrate for sensorimotor integration in central circuits. In the next section, we review how proprioceptive signals are used by the central nervous system, with a focus on contributions to motor control.

Ethological uses of proprioception

Stability, protection, and locomotion

The most elementary function of proprioceptive feedback is to stabilize and protect the body. A human stuck on a swaying bus or a grasshopper crouched on a wind-blown leaf must fine-tune muscle activity to maintain posture and stay upright. One way stability is achieved is through direct feedback from proprioceptors onto motor neurons. For example, when the quadriceps is stretched, Ia afferents from this muscle group directly excite quadriceps motor neurons and indirectly inhibit the antagonist hamstring flexor motor neurons, a phenomenon termed reciprocal inhibition (Figure 1B and 2B). Together, these two feedback pathways protect the muscle from being pulled with excessive force or moving beyond its normal range, and ensure stable extension of the knee joint. Equivalent mono- and di-synaptic feedback pathways exist in the local leg circuitry of insects. When a grasshopper's tibia is flexed, proprioceptors in the femoral chordotonal organ directly excite extensor motor neurons and indirectly inhibit flexor motor neurons, so that the position of the femur/tibia joint is stabilized and posture is maintained (Figure 2J).

What is the role of proprioceptive feedback in generating more complex movement sequences? Rhythmic behaviors like walking, running, swimming, and scratching are thought to be driven by central pattern generators (CPGs): neural networks capable of generating organized patterns of flexor/extensor and left/right alternating activity independently of sensory input or descending control. Although some CPG circuits might be capable of generating rudimentary locomotor rhythms in a purely feedforward manner, motor circuits rarely operate independently of proprioceptive feedback. One extreme case is that of the quick-legged cockroach, which runs so fast (>20 steps per second) that within-step stabilization cannot rely on delayed sensory feedback (~20 milliseconds minimum latency from sensory neuron spike to muscle response). Thus, feedforward central commands appear to dominate. At the opposite extreme is the unhurried stick insect, where proprioceptive feedback signals from hair plates and campaniform sensilla are required to produce a normal walking gait. Most ambulatory animals appear to operate somewhere between these two extremes. Many animals rely on ballistic (feedforward) control to execute explosive movements, like jumping or kicking; however, skilled limb movements (imagine a mountain goat navigating a precarious ledge) typically last hundreds of milliseconds, providing time for proprioceptive feedback to refine locomotor output.

During locomotion, a major role of proprioceptive feedback is to modulate the magnitude and timing of CPG-driven muscle activity to ensure robust motor output. For example, proprioception corrects limb targeting when a perturbation occurs, and can ensure appropriate timing of phase transitions (for example, swing to stance), or the timing of individual muscle activation. The role of proprioception for a given animal can also change as a function of context. When a cockroach is running on unpredictable terrain, it has to slow down, and intersegmental proprioceptive feedback sets the firing phase of leg motor neurons. Overall, central commands from CPGs can be thought of as predictions that are readily refined by sensory updates from the proprioceptive system. Under predictable circumstances, modification of this pattern may be minimal, but in most situations, the animal must adapt its movements to accommodate the vagaries of the natural environment.

Flexible tuning of proprioceptive feedback

Proprioceptive signaling is not immutable — its effects on motor output can vary dramatically. This raises the question of how feedback is 'tuned' during different behavioral contexts. Like many engineered systems, a key control parameter is feedback gain: the ratio between the motor output and sensory input of the system. In some cases, proprioceptive feedback gain should be high to maximize sensitivity to useful peripheral information. Imagine a tennis player fine-tuning her limb position before striking the ball, or a stick insect stiffening her posture to mimic a motionless twig. In other cases, peripheral feedback gain needs to be tuned down — for example, when an animal needs to co-contract antagonist muscles that reciprocally inhibit each other under normal conditions.

In some contexts, proprioceptive feedback gain can completely invert from negative to positive, a phenomenon referred to as 'reflex reversal', suggesting the existence of flexible systems for tuning peripheral feedback. For example, during locomotion in mammals and insects, the effects of proprioceptive feedback on motor neuron activity can reverse in sign to ensure timely transition from stance to swing. At a circuit level, this flexible reversal in cats is thought to be mediated by a transition from inhibitory to excitatory reflex pathways recruited by Ib Golgi tendon organ afferents during locomotion (Figure 3A). In insects, descending signals from the brain and intersegmental signals from other legs play an important role in modulating proprioceptive feedback signals during different behaviors (Figure 3B).

The first site of gain control within the proprioceptive system occurs in the periphery, through adaptation in the excitability of sensory neurons. Specific classes of proprioceptor neurons exhibit different degrees and time courses of adaptation. These adaptive properties can arise from mechanisms intrinsic or extrinsic to the sensory neuron, such as active membrane conductances or viscoelastic behavior of the receptor organ. An important function of sensory adaptation is to adjust the dynamic range of the neuron, either by reducing overall sensitivity or by shifting stimulus tuning. Gain may also be actively tuned by efferent modulation, as in the case of gamma motor neurons that control proprioceptive sensitivity by adjusting tension on the muscle spindle.

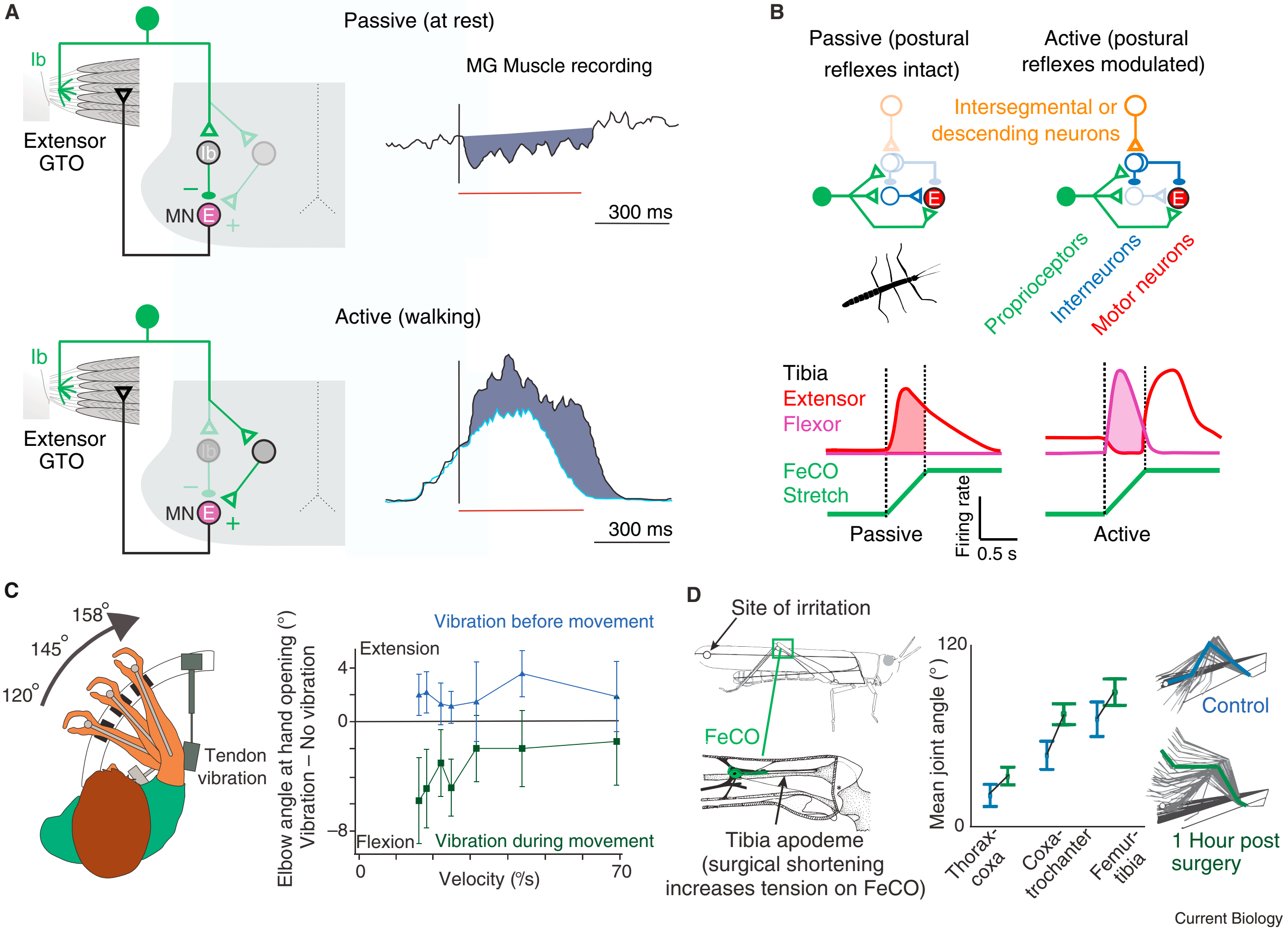


Figure 3. Proprioceptive function.

(A) Reversal of the reflex actions of Ib afferents from Golgi tendon organs (GTO) onto motor neurons occurs during locomotion. (Top) At rest, Ib afferents inhibit homonymous extensor (E) motor neurons (MN) via a disynaptic inhibitory pathway (as shown in Fig. 2D). Plot shows rectified and averaged electromyography (EMG) recording during stretch of the medial gastrocnemius (MG) muscle in cat. During stimulation of the plantaris nerve (red line), stretch-evoked activity is reduced (shaded area). (Bottom) During locomotion, Ib afferents recruit a disynaptic excitatory pathway to excite homonymous motor neurons. Stimulation of the plantaris nerve (red line) increases the magnitude of MG bursts (shaded area), as compared to MG activity in the absence of nerve stimulation (light blue trace). EMG panels adapted from Pearson and Collins (1993) and Pearson (1995), reprinted by permission from Springer Nature ©1995). (B) Reflex reversal in leg sensorimotor loops. (Top) Hypothetical architectures of a circuit in which descending or intersegmental input modifies the sign of a proprioceptive feedback signal. (Bottom) In a quiescent insect, flexion-sensitive proprioceptors drive tibia extension. During an active state such as locomotion, the sign of this reflex reverses, and flexion-sensitive proprioceptors assist flexion. Bottom traces adapted from Bässler and Büschges (1998). (C) Tendon vibration preferentially excites Ia afferents and perturbs voluntary limb movements. (Left) Subjects were asked to open their hand at a target angle (145° or 158°) as their elbow was rotated passively in the direction of extension. To ensure proprioception was the only information that could be used for the task, vision of the arm was occluded and rotational velocity was changed randomly from trial to trial. In randomly occurring trials, the tendon of the biceps brachii muscle was vibrated (40 Hz), perturbing Ia proprioceptive feedback. (Right) When vibration is applied before movement onset, the subject overshoots the target; when applied during the movement, the subject undershoots. Plots indicate elbow angle at which the hand is opened during vibration minus elbow angle during control conditions across rotation velocities. Adapted from Cordo *et al*. (1995). (D) Locusts accurately scratch a spot on their back using a hindleg. Increasing tension on the femoral chordotonal organ, by surgical shortening of the tendon (left), leads to consistent reaching errors produced by changes at each leg joint angle (right). Republished with permission of the Society for Neuroscience, adapted from Page and Matheson (2009).

Within the central nervous system, an important mechanism for adjusting feedback gains is through presynaptic inhibition of sensory afferents. In both mammals and insects, specialized classes of GABAergic interneurons make inhibitory synapses on the central axon terminals of sensory neurons, reducing sensory transmission. This form of sensory gain control has been most closely studied at the synapses between Ia proprioceptive afferents and motor neurons in the mammalian spinal cord, and between femoral chordotonal afferents and nonspiking interneurons in the locust. An essential function of presynaptic inhibition in these systems is to stabilize the dynamics of sensorimotor feedback loops. Faced with the temporal delays inherent in proprioceptive feedback, the antagonist neurons and muscles in a sensorimotor loop will oscillate at high feedback gains. This effect can also be induced experimentally through elimination of presynaptic inhibition or introduction of artificial feedback delays. Overall, it appears that regulatory circuits have evolved to deal with the physiological delays inherent in the proprioceptive system and adjust feedback gains to prevent tremor and maintain stability.

The selectivity of presynaptic inhibition allows the central nervous system to flexibly regulate neurotransmitter release from specific sensory afferents without directly affecting their postsynaptic targets. Target-specific connections between presynaptic inhibitory interneurons and sensory neurons could, in principle, provide an anatomical substrate for selective regulation of parallel feedback channels. Indeed, anatomical, electrophysiological, and molecular evidence hints at a fine-grained circuit logic to modulating sensory feedback, with discrete classes of presynaptic inhibitory neurons targeting: sensory neurons that convey different modalities of sensory information (for example, tactile versus proprioceptive); sensory neurons within the same modality (for example, joint flexion versus extension); and distinct collaterals of the same sensory afferent (though this has only been shown in mammals so far).

Target specificity can provide flexibility, enabling afferents to be tuned in different directions during the same movement. For example, tactile feedback gain may be reduced and proprioceptive feedback gain increased during active (but not passive) wrist movements in primates. In other contexts, high tactile feedback gains can be essential for detecting perturbations to handheld objects and rapidly correcting movements. In many cases, gain modulation can be thought of as predictive: motor pathways suppress expected sensory inputs, while unexpected (and therefore informative) sensory information is transmitted into the central nervous system. Thus, dynamic adjustment of feedback pathways, at least in part through presynaptic inhibition of sensory afferents, can ensure that feedback gains are high when the information is helpful, and low when it is disruptive.

State estimation for planning and refining movements

We have seen that proprioceptive signals play a critical role in shaping basic rhythmic locomotor patterns. But how do motor circuits take advantage of proprioceptive information to plan and adapt more complex, non-rhythmic movements, like capturing moving prey or threading a needle? A particularly useful framework for approaching this question is optimal feedback control. This set of control engineering principles has been applied to movement, positing that the motor system attempts to minimize a set of cost functions — for example, movement effort, sloppiness, and instability. The role of proprioception in this framework is to help generate an accurate state estimate of the body, which can be used to plan movements and predict the outcome of future actions. One simple way to illustrate the utility of optimal feedback control is to examine three phases of a goal-directed limb movement.

First: before a reach is initiated, the brain must select a control policy — basically a set of motor commands that will propel the limb toward a desired position. What constitutes an appropriate strategy will depend on a state estimate of the limb, which can be provided by visual and proprioceptive feedback, and the context within which those states arise. Perturbing these initial state estimates can lead to predictable errors in motor planning and execution. For example, stimulating muscle spindle Ia afferents by tendon vibration produces systematic errors in human voluntary limb movements (Figure 3C). Similarly, artificially increasing tension on the femoral chordotonal tendon leads to systematic over-reaching in the locust (Figure 3D).

Second: as the movement proceeds, motor output is continuously refined to ensure that the limb trajectory will reach a desired end-point. During rapid movements, proprioceptive feedback delays present a challenge for these online corrections — how is it possible to maintain an accurate state estimate if peripheral feedback is outdated? One compelling idea is that the motor commands that drive movement are copied and conveyed internally to generate online predictions of movement outcome. This process of using efference copies to predict outcome, often referred to as a forward model, can compensate for sensory feedback delays by predicting a future state and adjusting the control policy when necessary. Of course, predictions are more accurate if they extrapolate from an accurate estimate of the current state. Thus, it is advantageous to combine both internal estimates and external reports of limb state by integrating forward model predictions with delayed sensory information. Indeed, estimates of limb location are more accurate during active than passive movements, suggesting a dynamic interplay between the forward model predictions (generated during active movement) and proprioceptive feedback (generated during active and passive movement). Evidence for the existence of forward models, and the importance of proprioception in their implementation, has been provided by behavioral experiments in both mammals and insects.

Third: on a longer time-scale, across many repetitions of the same movement, the motor system refines its output to achieve greater precision and accommodate changing conditions. Consider an amateur tennis player practicing a serve over the course of months, or adapting to a sore elbow over the course of a match. In both cases, it might be advantageous for the brain to compare forward model-based prediction with proprioceptive feedback that reports movement outcome. By identifying the mismatches between these signals, forward models could be calibrated, ensuring that subsequent control policies minimize the discrepancy between intent and outcome. Recent work in mice and flies has demonstrated that this process of sensorimotor adaptation, when learning a new task or recovering from injury, is critically dependent on proprioceptive feedback.

Central circuits for feedback control of movement

How and where in the nervous system are control policies implemented, and how does proprioception influence these circuits? The short answer is that we do not yet know; however, anatomical, electrophysiological, and perturbation studies have provided some initial clues.

In mammals, local and intersegmental spinal circuits recruited by proprioceptive feedback can ensure coordination between forelimbs and hindlimbs on both sides of the body. In addition, ascending proprioceptive pathways project to supraspinal structures that exert additional layers of control over motor output. One major target of ascending proprioceptive feedback is the cerebellum, a brain structure necessary for online corrections and sensorimotor adaptation, and posited as a neural substrate for implementing forward models. Proprioceptive information reaches the cerebellum via intermediate mossy fiber pathways — in particular, proprioceptive afferents directly recruit neurons that form the dorsal spinocerebellar tract for the lower extremities and the cuneocerebellar tract for the forelimbs. Proprioceptive and efference copy signals converge at individual granule cells in the cerebellar cortex, providing a potential anatomical locus for merging motor and peripheral feedback signals. Cerebellar nuclei, the output of the cerebellum, could then adjust the control policy to modify motor output.

Another potential route for ascending proprioceptive feedback is the dorsal column-medial lemniscus pathway, hypothesized to be a pathway for consciously-accessible proprioceptive information. Here, proprioceptive afferents could either directly or indirectly target the dorsal column nuclei in the brainstem, which then project to circuits in the thalamus that innervate the cerebral cortex. Proprioceptive modulation of cortical motor circuits might be important for the appropriate updating of the control policy. For example, when the limb is perturbed during a goal-directed movement, neurons in motor cortex integrate feedback across joints, suggesting they are involved in generating updated motor commands that account for the complex biomechanics of the limb.

In insects, proprioceptive information from the legs is initially processed by networks of local spiking and nonspiking interneurons in the VNC. Many of these local interneurons provide excitatory and inhibitory input to leg motor neurons, and are important for postural and leg motor control. Far less is known about the anatomy of intersegmental and ascending proprioceptive pathways, aside from a handful of putative second-order neurons, in *Drosophila* and other species, that arborize in ventral brain regions. The influence of proprioceptive feedback in these regions, and their relationship to descending motor control, is not yet clear. The central complex and one of its postsynaptic targets, the lateral accessory lobe (LAL), have been implicated in leg motor control, and are thus likely targets of ascending proprioceptive information. The activity of neurons in the central complex is predictive of walking speed and turning behavior, and electrical stimulation of these neurons can alter walking and turning. Few central complex output neurons project directly to the VNC, but many send axons to the LAL, which does contain descending neurons. Overall, these brain areas represent strong candidates for proprioceptive integration and sensorimotor feedback control, although the specific computations they implement remain to be explored.

Distance estimation and navigation

A fundamental use for limbs is to move from one place to another, raising the question of how proprioception might contribute to spatial navigation. When visual cues are unavailable, animals could use proprioceptive feedback to estimate their movement history. For example, the desert ant *Cataglyphis* keeps track of its location during foraging by counting the number of steps it has taken since leaving the nest. Combining this internal pedometer with direction cues from a celestial compass allows the ant to calculate a direct route home after it finds a food source. Artificially lengthening the legs of a successful forager (with stilts) causes the ant to overshoot its homing destination. Interestingly, opposite results have been found in humans: leg lengthening, either surgically or with stilts, causes people to undershoot a target destination when walking in darkness. This difference could result from the fact that humans are conscious of the leg manipulation, and thus overcompensate by taking fewer steps. Both humans and ants quickly adapt to their new leg lengths.

Spatial navigation is not specific to desert ants and humans — the fruit fly uses path integration to systematically explore its environment after encountering a food source. Although the role of proprioception has not been established in this behavior, recordings from navigation circuits in the *Drosophila* brain suggest that proprioception helps the fly stay on course in the absence of other landmarks. When a fly is walking in the dark, an internal representation of heading is maintained within the central complex. The latency with which this heading signal is updated suggests a key role for leg proprioception. Signatures of limb proprioception have also been found in head direction cells of the rodent entorhinal cortex, suggesting a contribution to spatial navigation. In both systems, it remains unclear how integrated parameters such as distance, direction, and angular velocity are extracted from the spike trains of leg proprioceptors.

'Conscious' perception of the body: psychophysical limits and misrepresentation

Proprioception is largely subconscious, in that it does not typically require directed attention. But in some cases, humans do have conscious access to proprioceptive sensory information, and psychophysical studies have explored the perceptual limits of human limb proprioception. For example, the absolute threshold for detecting a passive movement of the elbow joint is less than 1°. Interestingly, estimates of body position and size are also subject to distortions, such as a tendency to underestimate the length of fingers and overestimate the width of hands. That these errors do not seem to impact behavioral performance suggests that either humans do not have perceptual access to the full complement of proprioceptive information, or motor planning circuits account for systematic distortions in body proprioception.

It is, of course, not possible to ask insects to report perceptual thresholds of limb proprioception. However, clever behavioral experiments have measured the accuracy with which a blindfolded locust can target a foot to scratch an itchy spot on its back. Irrespective of initial leg posture and leg joint kinematics, the targeting accuracy of locust scratching movements is within a few millimeters of the site of irritation. This error corresponds to less than 10° at the femur/tibia joint. Scratching movements remain accurate even when a substantial load (eight times the mass of the tibia) is added to the leg, revealing a critical role for proprioceptive feedback control.

While the importance of conscious proprioception for movement execution remains unclear, the potential burden of this perception is well known to many. Amputees can suffer from severe pain localized to a 'phantom limb' that is no longer present. In some cases, they also continue to perceive detailed positional information and even a sense of control over the position of the lost limb. Insects will also continue to groom a body part after it has been amputated. These perceptual remnants point to the existence of a proprioceptive 'body model' stored somewhere in the central nervous system. Current therapies for phantom limb syndrome attempt to manipulate this body model with feedback from other senses, such as through visual illusions of phantom limb position or movement.

The path forward

Sherrington's initial characterization of so-called 'reflex arcs' may have provided a sense that proprioceptive pathways are simple and stereotyped, and thus easy to dissect and understand. However, many subsequent years of anatomical and physiological study have shown that although some sensorimotor circuits may be stereotyped, they are far from simple. Below, we outline four key challenges in the field.

Dissecting the function of cell types in redundant, distributed networks

Two common features of the insect and mammalian proprioceptive systems are parallel, distributed processing and redundancy. The parallel nature of proprioceptive circuits starts at the level of the sensory axons, which can be complex and diverse. A muscle spindle afferent might synapse on local motor neurons and spinal interneurons, and send an ascending collateral to the brainstem. In insects, many chordotonal and campaniform sensilla neurons have both local and long-range intersegmental projections, which target both motor neurons and interneurons. These proprioceptive channels are also highly redundant, in that many sensory neurons monitor each joint. Perhaps for this reason, it has been challenging to assign circumscribed functional roles to specific proprioceptors or even proprioceptor classes. For the most part, ablating small numbers of proprioceptors has little effect on an animal's behavior. In fact, defining unimodal roles for different proprioceptor classes may not be the relevant goal, if meaningful positional information can only arise through their integrated activity; for example, signals from muscle spindles and Golgi tendon organs are likely both needed to infer joint position.

Techniques for artificially controlling neural activity, such as optogenetics, are beginning to reveal the contributions of specific sensory neuron types to downstream neural computations and behavior. A current bottleneck is the creation of specific genetic drivers for the abundance of unique cell types. As in other parts of the nervous system, genetic dissection of the spinal cord/VNC and the afferents that innervate motor circuits has begun to reveal harrowing levels of cell-type diversity and anatomical complexity. It is a promising sign that the extent of diversity and specialization within cardinal sensorimotor circuits, and genetic access points to discrete classes of peripheral and central neurons, are beginning to be defined.

Our knowledge of higher-order proprioceptive circuitry also lags far behind other sensory systems, such as vision, audition, and olfaction. One possible reason for this discrepancy is that proprioceptive sensing is distributed throughout the body, and lacks a single central organ such as an eye or nose. A related issue is that we have not identified central circuits in the brain specifically dedicated to the representation of body position and movement. Although proprioceptive information is present in higher-order areas, such as the mammalian cerebral cortex and insect central complex, these signals are often complex and multimodal. The absence of a clear topographic representation of body kinematics has made it challenging to analyze proprioceptive neural codes on a population level. However, new tools for synaptic tracing of neural circuits provide an opportunity to understand how proprioceptive inputs from different body regions are organized within the central brain.

Identifying sites and mechanisms of multimodal integration

Distinct sensory systems often encode overlapping information. Indeed, proprioceptors, touch receptors, and nociceptors respond to many of the same mechanical stimuli. For example, mechanoreceptors in the skin and interosseous membrane respond to skin deformation and vibration, and likely contribute to the sense of body position and movement. Furthermore, recordings have shown that touch and proprioception may already be integrated within spinal cord and VNC neurons. We currently do not know how this integration contributes to proprioceptive neural coding and feedback control of movement. Are proprioceptive signals recorded in the brain a result of integration across diverse somatosensory neuron types? Is the integration of proprioception with other sensory modalities necessary for appropriate sensorimotor control? These are partly questions of anatomy, which can be addressed with cell-type-specific anatomical and functional circuit mapping methods. But it will also require a detailed understanding of how different types of somatosensory neurons dynamically encode natural stimuli, and how these signals interact within central circuits.

At higher levels, in central motor planning centers like the cerebral cortex and central complex, proprioceptive signals must be integrated with information from the visual and balance organs. This raises the question of spatial reference frames: for example, in mammals, visual signals are encoded in eye-centered coordinates, while vestibular signals are in head-centered coordinates. Is there a common coordinate system for proprioceptive information, or does it vary from limb to limb? And how are multimodal signals in different coordinate systems combined to form a stable representation? Computational models have shown that multimodal neurons with mixed or intermediate reference frames can still provide useful information for some simple tasks, such as control of head rotation. However, it is not yet clear whether this combinatorial strategy applies to more complex, naturalistic movements, such as skilled reaching or locomotion on uneven terrain.

Understanding context-dependence of proprioceptive processing

Identifying cell types and dissecting circuitry can provide a roadmap for proprioceptive information flow, but maps alone will not reveal the underlying dynamics that make proprioception such a rich and indispensable sense. Previous work in both insects and mammals has demonstrated that proprioceptive neural coding is fundamentally different when an animal is actively behaving, compared to when it experiences passive stimulation. Ultimately, a meaningful understanding of the proprioceptive system will require probing circuit function in active, behaving animals.

What does it mean to study feedback signaling during active behavior? Studies of mammalian proprioception and motor control have historically focused on a small group of behaviors: for example, rhythmic output during walking or scratching, or tightly controlled movements, such as reaching in a defined plane. The advent of genetic tools for targeted recording and optical imaging means that one can now study the same neurons across different behaviors and individuals. Moreover, recent progress in computer vision methods has made it possible to record detailed body kinematics over long periods of time in more natural environments. Given the vast space of possible behaviors that can now be studied, a judicious choice may be to expand our focus to a broad set of ethologically relevant behaviors that the proprioceptive system has evolved to regulate.

Constructing a computational framework for proprioceptive circuit function

A brief survey of the vast proprioceptive literature, whether in the mammalian spinal cord or the insect ventral nerve cord, provides one with a sense that, although many details are known, it is not clear how these details fit together into a coherent whole. This is partly due to the nature of the experimental methods; for many years, investigators used glass or tungsten electrodes to record from single neurons located within heterogeneous neural populations. Now that we are starting to record from larger numbers of genetically-defined neuron populations, a key task will be to synthesize the growing level of experimental detail into a coherent framework of proprioceptive circuit function. In particular, we will need new computational and theoretical methods that permit analysis of highly distributed, parallel networks, in contrast to the standard hierarchical models that have historically dominated sensory neuroscience. We will also need new tools to integrate physiology and behavioral data with large-scale anatomical reconstructions of neural circuits. Ultimately, models should not only describe the data being collected, but also guide experiments that perturb the proprioceptive system to test and refine model assumptions.

Conclusion

In this Primer, we have chosen to focus on two classes of animals whose last common ancestor was probably a limbless, wormlike creature (*Urbilateria*) that met a grisly end hundreds of millions of years ago. The structure and function of this extinct creature's proprioceptive system are a mystery. It likely possessed many of the core molecular pathways from which the proprioceptive systems of contemporary mammals and insects are built, such as the genes that establish the dorsal-ventral boundaries of the limbs (for example, *fringe*) and the mechanotransduction channels found in proprioceptive sensory neurons (for example, the ion channels formed by the *piezo* gene product). Over millions of years of evolution, these and other genes have been modified to produce the morphological and functional diversity of proprioceptors observed across the animal kingdom.

Despite the fact that insect and mammalian proprioception probably evolved separately for half a billion years, one observes striking functional similarities across the evolutionary gap. One example is the existence of proprioceptor classes that separately convey information about position, velocity, and load. This similarity appears to have evolved convergently in response to fundamental ethological constraints. Identifying such general and robust solutions is not only intellectually satisfying, but it can also help guide the design of artificial systems like mobile robots or brain machine interfaces. Yet characterizing a design principle as *general* requires a comparative approach with a wide scope. As some of us get to work cracking proprioceptive circuits using genetic tools in flies and mice, it is essential that others continue to seek insights throughout the weird, wet, and wild animal kingdom.

FURTHER READING

Azim, E., and Alstermark, B. (2015). Skilled forelimb movements and internal copy motor circuits. Curr. Opin. Neurobiol. *33*, 16–24.

Bässler, U., and Büschges, A. (1998). Pattern generation for stick insect walking movements - multisensory control of a locomotor program. Brain Res. Rev. *27*, 65-88.

Bidaye, S.S., Bockemuhl, T., and Büschges, A. (2017). Six-legged walking in insects: how CPGs, peripheral feedback, and descending signals generate coordinated and adaptive motor rhythms. J. Neurophysiol. http://dx.doi.org/10.1152/jn.00658.2017.

Burrows, M. (1996). Neurobiology of an Insect Brain (Oxford: Oxford University Press).

Cordo, P., Gurfinkel, V.S., Bevan, L., and Kerr, G.K. (1995). Proprioceptive consequences of tendon vibration during movement. J. Neurophysiol. *74*, 1675–1688.

Dietz, V. (2002). Proprioception and locomotor disorders. Nat. Rev. Neurosci. *3*, 781–790.

Field, L.H., and Matheson, T. (1998). Chordotonal organs of insects. In Advances in Insect Physiology, Volume 27, P.D. Evans, ed. (San Diego: Academic Press Inc.), pp. 1–228.

Franklin, D.W., and Wolpert, D.M. (2011). Computational mechanisms of sensorimotor control. Neuron *72*, 425–442.

Graber, V. (1882). Die chordotonalen sinnesorgane und das gehör der insecten. Archiv. Mikroskop. Anat. *20*, 506–640.

Page, K.L., and Matheson, T. (2009). Functional recovery of aimed scratching movements after a graded proprioceptive manipulation. J. Neurosci. *29*, 3897–3907.

Pearson, K.G., and Collins, D.F. (1993). Reversal of the influence of group Ib afferents from plantaris on activity in medial gastrocnemius muscle during locomotor activity. J. Neurophysiol. *70*, 1009–1017.

Pearson, K.G. (1995). Reflex reversal in the walking systems of mammals and arthropods. In Neural Control of Movement, W.R. Ferrell and U. Proske, eds. (Boston, MA: Springer US), pp. 135–141.

Pringle, J.W.S. (1938). Proprioception in insects II. The action of the campaniform sensilla on the legs. J. Exp. Biol. *15*, 114–131.

Proske, U., and Gandevia, S.C. (2012). The proprioceptive senses: their roles in signaling body shape, body position and movement, and muscle force. Physiol. Rev. *92*, 1651–1697.

Rothwell, J.C. (1987). Proprioceptors in muscle, joint and skin. In Control of Human Voluntary Movement. (Boston, MA: Springer US), pp. 74–104.

Rudomin, P., and Schmidt, R.F. (1999). Presynaptic inhibition in the vertebrate spinal cord revisited. Exp. Brain Res. *129*, 1–37.

Ruffini, A. (1898). On the minute anatomy of the neuromuscular spindles of the cat, and on their physiological significance. J. Physiol. *23*, 190–208.e3.

Scott, S.H. (2004). Optimal feedback control and the neural basis of volitional motor control. Nat. Rev. Neurosci. *5*, 532–546.

Shadmehr, R., and Krakauer, J.W. (2008). A computational neuroanatomy for motor control. Exp. Brain Res. *185*, 359–381.

Sherrington, C.S. (1913). Reflex inhibition as a factor in the co-ordination of movements and postures. Quart. J. Exp. Physiol. *6*, 251–310.

Sherrington, C.S. (1906). The Integrative Action of the Nervous System (C Scribner's sons).

Tuthill, J.C., and Wilson, R.I. (2016). Mechanosensation and adaptive motor control in insects. Curr. Biol. *26*, R1022–R1038.

Windhorst, U. (2007). Muscle proprioceptive feedback and spinal networks. Brain Res. Bull. *73*, 155–202.

[1]Department of Physiology and Biophysics, University of Washington, 1705 NE Pacific St, Seattle, WA 91895, USA. [2]Molecular Neurobiology Laboratory, Salk Institute for Biological Studies, 10010 N. Torrey Pines Road, La Jolla, CA 92037, USA.
E-mail: tuthill@uw.edu (J.C.T.); eazim@salk.edu (E.A.)