ESSAY

NEUROSCIENCE

Shortcuts and checkpoints on the road to skilled movement

Coordinating intricate motor circuits

By **Eiman Azim**

A split second late or a few inches off the mark, and few would remember. Instead, running with his back to the ball, Willie Mays extended his arm and placed his glove squarely under the 420-foot center field drive. The New York Giants win Game 1 of the 1954 World Series, and Mays, his glove, and "The Catch" earn their place in history.

Few of our limb movements will ever gain such immortality, but what we accomplish every day is remarkable, nonetheless. When we catch a tipped wineglass or launch a dart toward a bullseye, hardly a second thought is given to the intricacy of neural circuits that orchestrate such precise movements.

How do these circuits control skilled behaviors? Because rodent limb movements are strikingly similar to those of primates (*1*), and mice provide a means of manipulating neuronal subtypes selectively (*2*), as a postdoc with Tom Jessell I reasoned that a detailed quantification of mouse reaching, together with a genetic dissection of spinal circuits, might help disentangle core features of mammalian skilled motor control (*3*).

Reaching appears simple, but deceptively so. Motor neurons fire, propelling the arm to target. Yet reaching does not arise from an isolated burst of motor output; rather, motor neuron activity is continually tweaked to shape appropriate limb kinematics (*4*–*6*). One strategy for updating motor output is to use proprioceptive feedback from muscles to evaluate outcome and correct course. But sensory information is slow in its trek from the periphery to the brain, creating at least two challenges for motor systems: how to achieve faster feedback for rapid movements, and how to prevent sensory feedback delays from destabilizing the limb (*7*) (see the figure, panel A).

INTERNAL COPIES PROVIDE FEEDBACK. Rapid movements unfold before sensory information arrives (*8*), implying the need for a faster source of information to refine motor output. One long-held idea argues that when motor commands direct arm movement, internal copies of these commands are conveyed to the cerebellum and help predict movement outcome to permit rapid course correction (*7*–*9*). Nevertheless, it is unclear whether putative internal copy pathways have any influence on motor output. Traditional experimental approaches such as electrical stimulation tend to perturb command and copy simultaneously, emphasizing the need for more-selective access to internal copy circuits.

Propriospinal neurons (PNs) in the cervical spinal cord have been implicated in the control of reaching in cats and primates and have the potential to transmit both motor and internal copy signals. They receive descending motor input and extend bifurcating axonal branches both to forelimb motor neurons and to the lateral reticular nucleus (LRN), a major input to the cerebellum (*10*) (see the figure, panel B). Manipulating the LRN-directed branch could therefore provide insight into the contribution of internal feedback to skilled movement.

We first needed to resolve whether PNs exist in mice. Collaborating with Bror Alstermark, we combined in vivo electrophysiology with viral labeling to show that PNs are present and, more tellingly, that they represent a subpopulation of V2a neurons (*11*), one of the cardinal interneuron subtypes involved in motor control (*2*). This genetic insight made it possible to ablate cervical V2a interneurons, revealing a severe and behaviorally selective perturbation of reaching movements. The similarity of these reaching deficits across species (*10*) supports the view that PNs have evolved to direct specific features of mammalian forelimb movement (*12*).

But ablating PNs does not resolve whether the internal copy branch alone can influence

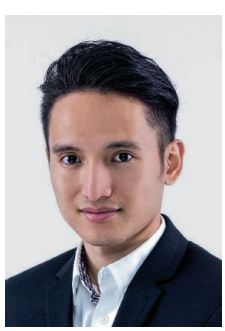
Grand Prize Winner: Eiman Azim

Eiman Azim received undergraduate degrees from Stanford University and a Ph.D. from Harvard University. As a postdoctoral fellow at Columbia University, Dr. Azim has been exploring the neural basis of skilled movement using molecular, electrophysiological, and behavioral approaches in the mouse to identify and characterize feedback pathways that control goal-directed reaching.

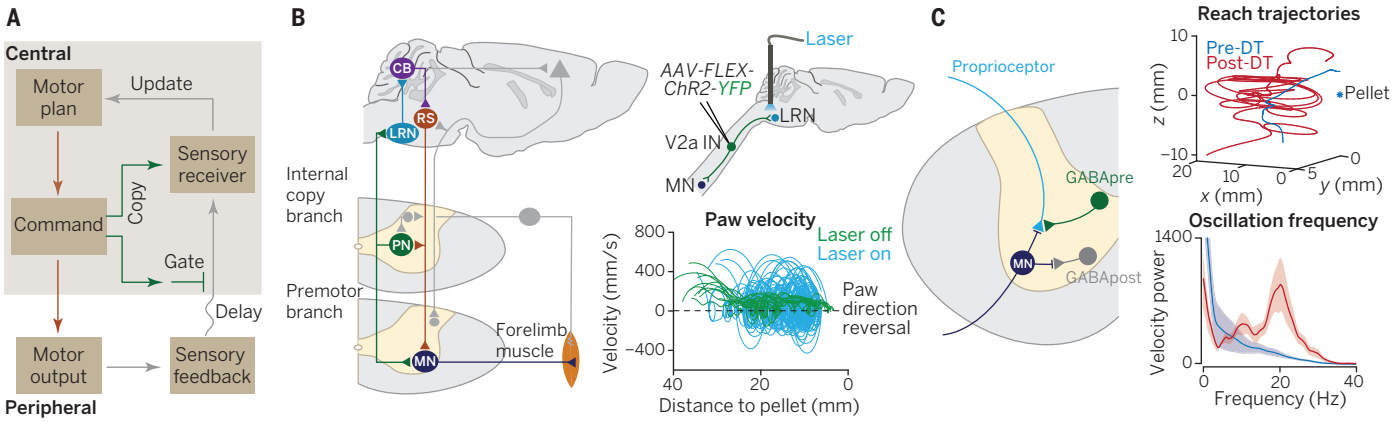
Finalist: Allyson Friedman

Allyson Friedman received her undergraduate degree from Barnard College at Columbia University and her Ph.D. from Mount Sinai School of Medicine. Dr. Friedman is currently a postdoctoral fellow at Mount Sinai where she is conducting research on the ionic and neural circuit mechanisms of susceptibility and resilience to major depressive disorder to identify novel targets for treatment.

Finalist: Ho Ko



Ho Ko received his undergraduate degree from the Chinese University of Hong Kong and a Ph.D. from University College London. He is currently pursuing clinical training while conducting research studying the neural basis of motor control and visual information processing, as well as planning collaborative work with engineers to develop novel biomedical engineering technology.



Internal copies and sensory gating in forelimb motor control. (**A**) During limb movement, motor commands elicit motor neuron activation and muscle contraction, generating proprioceptive sensory feedback. Temporal delays in peripheral feedback imply a need for i) a more rapid internal feedback mechanism (copy); and ii) a means to constrain sensory feedback gain (gate). (**B**) Cervical PNs receive input from descending pathways, including the reticulospinal (RS) tract. Bifurcating PN axons innervate forelimb motor neurons (MN; premotor branch) and the lateral reticular nucleus (LRN; internal copy branch), which projects to the cerebellum (CB). Colored neurons trace a putative cerebellar-motor loop. A conditional viral approach (*AAV-FLEX-ChR2-YFP*) was used to express ChR2 in cervical V2a interneurons, and ChR2+ PN terminals in the LRN were photostimulated to activate the PN internal copy branch selectively, resulting in a severe disruption of reaching kinematics (blue). (**C**) Presynaptic inhibitory (GABApre) neurons form axo-axonic contacts onto proprioceptive afferent terminals, in contrast to the far more abundant GABApost neurons, which form direct postsynaptic inhibitory contacts. Diphtheria toxin (DT)–mediated genetic ablation of cervical GABApre neurons uncovered severe limb oscillations during reaching of consistent ~20 Hz frequency (red). [(B) adapted from (*11*); (C) adapted from (*18*)]

reaching. To explore this issue, we expressed the light-gated cation channel ChR2 in cervical V2a interneurons and found that photostimulation of PN axon terminals within the LRN activates the internally directed PN branch without affecting the premotor branch. Intriguingly, activation of this copy pathway excites forelimb motor neurons through a rapid polysynaptic circuit, disrupting reach accuracy (figure, panel B). Moreover, these motor responses were substantially diminished by severing LRN projections to the cerebellum, implicating a fast cerebellar-motor feedback loop in forelimb control (figure, panel B). Thus, PN internal feedback, and likely motor copy circuits more generally, can serve to calibrate movement.

GAIN-CONTROL FOR SMOOTH MOVEMENT. What if Mays needed to wait for the announcer to relay the ball's location? Despite his best efforts, he would likely have undershot. By analogy, the spinal cord is similarly sensitive to outdated information. Delayed sensory feedback can push the system off equilibrium into an unstable state (*7*).

Like a volume knob adjusting feedback strength, a gating mechanism that limits the impact of delayed sensory information might maintain motor stability (*13*). For decades it has been appreciated that spinal sensory feedback can be inhibited presynaptically (*14*, *15*) (figure, panel C), yet pharmacological approaches have been unable to manipulate presynaptic and postsynaptic inhibition separately, leaving presynaptic inhibition as a phenomenon in search of a function.

> ***"Reaching appears simple, but deceptively so."***

Inhibitory neurons are not created equal, and thus molecular differences could provide a means of selective interneuron manipulation. Using the GABA-synthetic gene *Gad2* to gain selective access to neurons that contact sensory terminals (*16*, *17*), Andrew Fink combined ChR2-based activation with in vitro electrophysiology to establish that *Gad2*-expressing neurons mediate presynaptic inhibition at sensory-motor synapses (*18*). More strikingly, we found that eliminating these neurons unleashes severe limb oscillations during reaching that are absent at rest (figure, panel C), implicating proprioceptive feedback as the trigger. With Larry Abbott, we found that the core features of these reaching deficits can be accounted for by a model of the limb in which sensory feedback gain is high. Thus, a mix of molecules, manipulation, and modeling has uncovered presynaptic inhibition as a sensory gain-control mechanism critical for smooth limb movement.

Whether refined or routine, in the World Series or on backyard bases, movement defines our interaction with the world. Deciphering how intention is converted into action calls for a greater appreciation of the causal link between motor circuits and behavior. Through a reductionist approach in mice, in essence dismantling circuits one neural element at a time, plausible substrates for internal and external feedback control are emerging. Exploring how these and other motor circuits are conserved and modified across species should lead to a clearer understanding of our impressive—on occasion even Mays-like—repertoires of skilled behavior.■

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