Motor systems

Zhou, Kuikui; Wolpert, Daniel M; De Zeeuw, Chris I

published in
Current Biology
2014

DOI (link to publisher)
10.1016/j.cub.2014.02.048

document version
Publisher's PDF, also known as Version of record

9. Charmantier, A., Brommer, J.E., and Nussey, D.H. (2014). The quantitative genetics of senescence in wild animals. In Quantitative Genetics in the Wild, A. Charmantier, D. Garant, and L.E.B. Kruuk, eds. (Oxford University Press), pp. 68–83.
10. Wilson, A.J., Nussey, D.H., Pemberton, J.M., Pilkington, J.G., Morris, A., Pelletier, F., Clutton-Brock, T.H., and Kruuk, L.E.B. (2007). Evidence for a genetic basis of aging in two wild vertebrate populations. Curr. Biol. *17*, 2136–2142.
11. Lanner, R.M., and Connor, K.F. (2001). Does bristlecone pine senesce? Exp. Gerontol. *36*, 675–685.
12. Caswell, H., and Salguero-Gómez, R. (2013). Age, stage and senescence in plants. J. Ecol. *101*, 585–595.
13. Silvertown, J., Franco, M., and Perez-Ishiwara, R. (2001). Evolution of senescence in iteroparous perennial plants. Evol. Ecol. Res. *3*, 393–412.
14. Baudisch, A., Salguero-G_omez, R., Jones, O.R., Wrycza, T., Mbeau-Ache, C., Franco, M., and Colchero, F. (2013). The pace and shape of senescence in angiosperms. J. Ecol. *101*, 596–606.
15. Roach, D.A. (2003). Evolutionary and demographic approaches to the study of whole plant senescence. In Plant Cell Death Processes, L.D. Nooden, ed. (San Diego: Academic Press), pp. 331–348.
16. Salguero-Gómez, R., Shefferson, R.P., and Hutchings, M.J. (2013). Plants do not count… or do they? New perspectives on the universality of senescence. J. Ecol. *101*, 545–554.
17. Kenyon, C.J. (2010). The genetics of ageing. Nature *467*, 622–622.
18. Reznick, D.N., Bryant, M.J., Roff, D., Ghalambor, C.K., and Ghalambor, D.E. (2004). Effect of extrinsic mortality on the evolution of senescence in guppies. Nature *431*, 1095–1099.
19. Promislow, D.E.L., Fedorka, K.M., and Burger, J.M.S. (2006). Evolutionary biology of aging: future directions. In Handbook of the Biology of Aging, E.J. Masoro and S.N. Austad, eds. (Burlington, MA: Academic Press), pp. 217–242.
20. Wilson, A.J., Charmantier, A., and Hadfield, J.D. (2008). Evolutionary genetics of ageing in the wild: empirical patterns and future perspectives. Funct. Ecol. *22*, 431–442.

Department of Biology, University Hill, 20014 University of Turku, Turku, Finland.
E-mail: jon.brommer@utu.fi

http://dx.doi.org/10.1016/j.cub.2014.02.045

Motor Systems: Reaching Out and Grasping the Molecular Tools

Two recent studies provide important insights into the organization of premotor circuitries, showing that control of highly-specific skilled forelimb movements, such as reaching and grasping, requires activation of specific subpopulations of neurons in the brainstem and spinal cord.

Kuikui Zhou[1], Daniel M. Wolpert[2], and Chris I. De Zeeuw[1,3]

The control of fine finger movements underlying skilled motor behavior has been shown to arise from the development of direct connections from the motor cortex to spinal motor neurons, while more global forelimb tasks are generally considered to depend on the evolutionarily conserved descending pathways mediated by more indirect routes through the brainstem and spinal cord [1,2]. The cerebellum, which is superimposed on these systems, receives internal copies of the motor commands and is required for the precise timing of motor functions, including that of the forelimbs and fingers. To what extent specific forms of forelimb movements are embedded in specific brainstem and spinal cord nuclei has remained elusive because of the technical difficulties of cell and nuclei specific targeting in these regions. Taking advantage of the advent of new viral and optogenetic techniques, two exciting studies from the labs of Silvia Arber [3] and Thomas Jessell [4] provide strong evidence that specific subpopulations of neurons in brainstem and spinal cord of mice are required for voluntary control of reaching and grasping movements.

Where Do We Come From and How to Move Forward?

In the 1960s, Lawrence and Kuypers [5,6] showed that the lateral descending brainstem pathways in both cats and monkeys mediate the capacity for independent use of the extremities, particularly of the monkey hand, while the corticospinal pathways, in addition to controlling the brainstem, allow the fractionation of movements exemplified by the ability to independently control the fingers. In contrast, the ventromedial brainstem pathway forms the basic system by which the brain maintains posture and integrates body–limb movements, such as during locomotion.

Since the discovery of this overall division of the descending brainstem pathways more than half a century ago, many anatomical details have been uncovered (Figure 1), including the identification of neurotransmitters involved [7,8]. The precise topography in these systems has been elusive, as many groups of neurons in the brainstem and spinal cord are difficult to identify by their cyto-architecture, and it has been hard to specifically target them using cell-specific promoters. However, following the revolution in molecular biology, over the last decade new expression patterns of proteins and gene regulating processes have been discovered [9], and, equally important, new technical approaches to exploit these discoveries have been invented. For example, viruses that travel trans-synaptically at single synapses can be transfected into transgenic animals and be turned on and off at will in specific cell groups, marking and/or ablating them by driving expressions of fluorescent and/or toxic probes [2,10]. Moreover, optogenetics can now be used to simultaneously stimulate and/or inhibit multiple specific cell groups with different wavelengths of light, as well as independently control the dendritic tree and remote axon terminals [11].

The Arber and Jessell labs [3,4], which are at the forefront of discovering genes and proteins relevant for the development and function of brainstem and spinal cord, have now exploited this knowledge by applying state-of-the-art viral and optogenetic techniques to advance our understanding of the precise functional topography of the lower motor systems.

Role of MdV in Grasping Types of Movements

Esposito *et al.* [3] demonstrate that the brainstem nucleus medullary reticular formation ventral part (MdV), which is probably part of the lateral system described by Kuypers (Figure 1), specifically targets a subgroup of forelimb-related spinal interneurons and motor neurons that mainly control

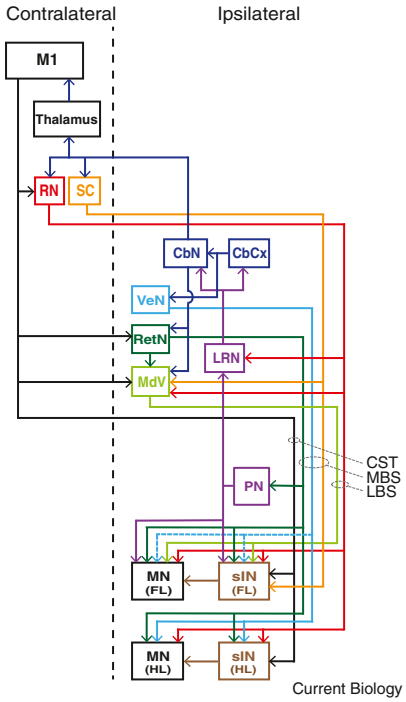

Figure 1. Pathways involved in skilled forelimb movements.

Spinal motor circuits involved in limb movements can be activated directly by the corticospinal tract (CST; black) or indirectly by the lateral brainstem system (LBS) and medial brainstem system (MBS). The LBS comprises, for example, descending fibers from neurons in the red nucleus (RN; red) and the ventral part of the nucleus medullary reticular formation (MdV; green), whereas the MBS includes descending reticulospinal (dark green), tectospinal (orange) and vestibulospinal (cyan blue) fibers. Neurons in the MdV receive input from the motor cortex (M1), RN, superior colliculus (SC), cerebellar nuclei (CbN) and reticular formation (RetN), and in turn project mainly directly to forelimb (FL)-associated motor neurons (MN) and segmental interneurons (sIN) in the spinal cord [3]. In contrast, neurons in the lateral vestibular nuclei (VeN) innervate predominantly, but not exclusively, hindlimb (HL)-related MNs and sINs. The MNs and sINs controlling forelimb movements also receive prominent input from cervical propriospinal neurons (PNs), either directly or indirectly via a relay in the lateral reticular nucleus (LRN), cerebellar cortex (CbCx) and CbN [4]. Note that input from the contralateral fastigial nucleus to MdV as well as the peripheral proprioceptive input to PNs are not shown.

muscles, such as the biceps and extensor carpi radialis, that are particularly involved in grasping types of movement. In contrast to other descending pathways, such as vestibular projections, this descending projection from the MdV turns out to be highly specific, in that it only minimally projects to motor neurons innervating other forelimb muscles, such as the triceps, or to the hindlimb regions of the spinal cord. Behavioral studies following viral-genetic ablation or silencing of MdV activity confirmed that MdV has a prime role in grasping types of movement, both during locomotion and a single-pellet reaching task. Interestingly, the ability to induce acute genetic manipulations allowed the authors to show that there was no impact of motor learning preceding ablation or silencing of MdV neurons; that is, lesions equally affected the grasping phase of the single-pellet reaching task, both with and without a preceding motor learning period.

These data stand in marked contrast with the impact of motor learning preceding lesions of the cerebellar cortex. If, for example, cerebellar memories are formed with the use of eyeblink conditioning or adaptation of the vestibulo-ocular reflex just a few hours before lesioning the cerebellar cortex, the memories can still be retrieved after the lesions, presumably by engaging the cerebellar nuclei [12–14]. Together, these studies indicate that the cerebellar cortex is essential for the initial acquisition, but not later retrieval, of new motor behaviors, whereas MdV is essential for both acquisition and retrieval of motor behavior, albeit primarily for a particular set of forelimb movements.

Role of V2a-PNs in Reaching Types of Movements

Azim *et al.* [4] demonstrate that the V2a subpopulation of cervical propriospinal interneurons (V2a-PNs) specifically project to the lateral reticular nucleus, which operates as a precerebellar relay, as well as to a subgroup of forelimb related spinal motor neurons that is particularly involved in reaching types of movement (Figure 1). This bifurcating output raises the possibility that V2a-PNs serve as an anatomical substrate that allows internal copying of the premotor signals, especially as they receive their main input from reticulospinal neurons, which are known for their role in initiation and control of movement [15]. The authors go a long way towards elucidating this potential role by investigating the kinematics of different stages of forelimb movements, before and after manipulating either both outputs of V2a-PNs or solely the ascending input to the lateral reticular nucleus. In both cases, they show that the reaching phase was predominantly affected. By doing so, the authors provide an elegant example of how modern optogenetics, in contrast to classical electrophysiological stimulation, can be used to selectively perturb one branch of a neuron's output while leaving the other unaffected.

Finally, using traditional lesions, Azim *et al.* [4] show that the ascending branch of V2a-PNs, which may provide internal copy signals to the lateral reticular nucleus, operates mainly, though not exclusively, through the cerebellum. The finding that this ascending copy of a descending command is involved in generating rapid motor responses chimes with a recent computational theory termed Optimal Feedback Control (OFC), which has started to tie together previously disparate areas such as planning, on-line control, coordination and the interaction of effort and noise [16]. An elegant aspect of OFC is that it avoids the need to specify hard constraints on task goals or specify a desired trajectory. Instead, OFC suggests that the central nervous system sets up time-varying feedback controllers that continuously convert sensory inputs into motor outputs, and that these are optimally tuned to the goals of the task by trading off energy consumption with accuracy constraints. Central to such a system is the monitoring of the outgoing motor command that is used to estimate the current state of the body [17,18]. The benefits of using copies of the motor command rather than just sensory input is two-fold: it makes state estimates more reliable by combining sensory inputs with copies of motor outputs, which both carry information about state, and it does so in a timely manner by using commands before sensory feedback could inform the CNS of movement, thereby mitigating time delays.

Although the idea of using a copy of the descending motor command for state estimation is consistent with the current study [4], there are now a range of possible computational uses of such a copy, including as a signal to cancel re-afference, thereby filtering sensory inputs or as a signal that can drive learning. While disrupting any of these uses is likely to affect motor control, these new molecular techniques are promising in being able to dissect not only anatomical and functional

pathways, but when combined with electrophysiological recordings, potentially also the computations that these pathways embody.

Future Research on Forelimb Movements

The new studies on the role of MdV in grasping [3] and on that of V2a-PN in reaching types of movements [4] beautifully highlight how deeply functional topographical principles are embedded in the brain, even when these are not directly evident from the cyto-architecture and even when they are studied in lower mammals like mice. As these building blocks are now becoming more apparent, the obvious question that arises is how these different phases of forelimb movements, resulting from different muscle activities and different control centers in the brainstem and spinal cord, are coordinated over time. Undoubtedly, the olivocerebellar system, which is readily accessible with genetic approaches using cell-specific promoters, plays a pivotal role in this coordination [19,20]. By showing the diverse viral and optogenetic applications as well as the precise functional topography for forelimb movements, the Arber and Jessell labs are acting as guides to the main functional questions on coordination control, both in terms of technical approaches and the concrete neuro-anatomical targets in the brainstem and spinal cord that need to be investigated.

References

1. Alstermark, B., and Isa, T. (2012). Circuits for skilled reaching and grasping. Annu. Rev. Neurosci. *35*, 559–578.
2. Kinoshita, M., Matsui, R., Kato, S., Hasegawa, T., Kasahara, H., Isa, K., Watakabe, A., Yamamori, T., Nishimura, Y., Alstermark, B., *et al*. (2012). Genetic dissection of the circuit for hand dexterity in primates. Nature *487*, 235–238.
3. Esposito, M.S., Capelli, P., and Arber, S. (2014). Brainstem nucleus MdV mediates skilled forelimb motor tasks. Nature, February 2. http://dx.doi.org/10.1038/nature13023. [Epub ahead of print].
4. Azim, E., Jiang, J., Alstermark, B., and Jessell, T.M. (2014). Skilled reaching relies on a V2a propriospinal internal copy circuit. Nature, February 2. http://dx.doi.org/10.1038/nature13021. [Epub ahead of print].
5. Lawrence, D.G., and Kuypers, H.G. (1968). The functional organization of the motor system in the monkey. II. The effects of lesions of the descending brain-stem pathways. Brain *91*, 15–36.
6. Lawrence, D.G., and Kuypers, H.G. (1968). The functional organization of the motor system in the monkey. I. The effects of bilateral pyramidal lesions. Brain *91*, 1–14.
7. Holstege, J.C. (1996). The ventro-medial medullary projections to spinal motoneurons: ultrastructure, transmitters and functional aspects. Prog. Brain Res. *107*, 159–181.
8. Lemon, R.N., Landau, W., Tutssel, D., and Lawrence, D.G. (2012). Lawrence and Kuypers (1968a, b) revisited: copies of the original filmed material from their classic papers in Brain. Brain *135*, 2290–2295.
9. Goulding, M. (2009). Circuits controlling vertebrate locomotion: moving in a new direction. Nat. Rev. Neurosci. *10*, 507–518.
10. Stepien, A.E., Tripodi, M., and Arber, S. (2010). Monosynaptic rabies virus reveals premotor network organization and synaptic specificity of cholinergic partition cells. Neuron *68*, 456–472.
11. Klapoetke, N.C., Murata, Y., Kim, S.S., Pulver, S.R., Birdsey-Benson, A., Cho, Y.K., Morimoto, T.K., Chuong, A.S., Carpenter, E.J., Tian, Z., *et al*. (2014). Independent optical excitation of distinct neural populations. Nat. Methods *11*, 338–346.
12. Kassardjian, C.D., Tan, Y.F., Chung, J.Y., Heskin, R., Peterson, M.J., and Broussard, D.M. (2005). The site of a motor memory shifts with consolidation. J. Neurosci. *25*, 7979–7985.
13. Shutoh, F., Ohki, M., Kitazawa, H., Itohara, S., and Nagao, S. (2006). Memory trace of motor learning shifts transsynaptically from cerebellar cortex to nuclei for consolidation. Neuroscience *139*, 767–777.
14. Perrett, S.P., Ruiz, B.P., and Mauk, M.D. (1993). Cerebellar cortex lesions disrupt learning-dependent timing of conditioned eyelid responses. J. Neurosci. *13*, 1708–1718.
15. Perreault, M.C., and Glover, J.C. (2013). Glutamatergic reticulospinal neurons in the mouse: developmental origins, axon projections, and functional connectivity. Ann. NY Acad. Sci. *1279*, 80–89.
16. Todorov, E. (2004). Optimality principles in sensorimotor control. Nat. Neurosci. *7*, 907–915.
17. Wolpert, D.M., and Miall, R.C. (1996). Forward models for physiological motor control. Neural Networks *9*, 1265–1279.
18. Wolpert, D.M., Ghahramani, Z., and Jordan, M.I. (1995). An internal model for sensorimotor integration. Science *269*, 1880–1882.
19. De Zeeuw, C.I., Hoebeek, F.E., Bosman, L.W., Schonewille, M., Witter, L., and Koekkoek, S.K. (2011). Spatiotemporal firing patterns in the cerebellum. Nat. Rev. Neurosci. *12*, 327–344.
20. Gao, Z., van Beugen, B.J., and De Zeeuw, C.I. (2012). Distributed synergistic plasticity and cerebellar learning. Nat. Rev. Neurosci. *13*, 619–635.

[1]Department of Neuroscience, Erasmus MC, Rotterdam, The Netherlands. [2]Computational and Biological Learning Lab, Cambridge University, UK. [3]Netherlands Institute for Neuroscience, Amsterdam, The Netherlands.
E-mail: c.dezeeuw@erasmusmc.nl

http://dx.doi.org/10.1016/j.cub.2014.02.048

Evolution: Hidden at the End of a Very Long Branch

DNA-based methods continue to unveil the diversity and evolutionary origins of life on Earth. 'Next generation' methods have just solved a long-standing puzzle by uncovering previously unseen yet globally distributed diversity within a lineage of amitochondriate parasites affecting commercially exploited aquatic hosts. This discovery will impact both pure and applied research fields.

Cathryn L. Abbott

Mikrocytos mackini is a mysterious microbe that causes Denman Island disease in Pacific oysters (*Crassostrea gigas*) on the northwest coast of North America. The disease causes mortality in oysters as well as unsightly green lesions which result in reduced marketability [1,2]. It is perplexing to consider how a parasite described in 1988 and now known to represent a unique amitochondriate lineage completely eluded the scientific literature on eukaryotic evolution until last year [3,4]. Amitochondriate eukaryotic lineages are rare, and have been salient to empirical studies of early eukaryotic evolution since 1983 when Cavalier-Smith formalized the now defunct theory that they comprise a primitive eukaryotic group (Archezoa) that evolved before the endosymbiotic origin of the mitochondrion [5]. The fact is *M. mackini* is astoundingly elusive. It is among the tiniest eukaryotes (Figure 1), has no defining morphological features, had no known relatives (until now), occurs in only one part of the world, is not culturable, has an unknown life cycle, and disappears for part of the year because the disease it causes is temperature-dependent [6]. '*Mikrocytos*-like' organisms have been reported from various parts of the world but the identity of the parasites could not be confirmed nor the detections repeated (e.g., [7–9]).