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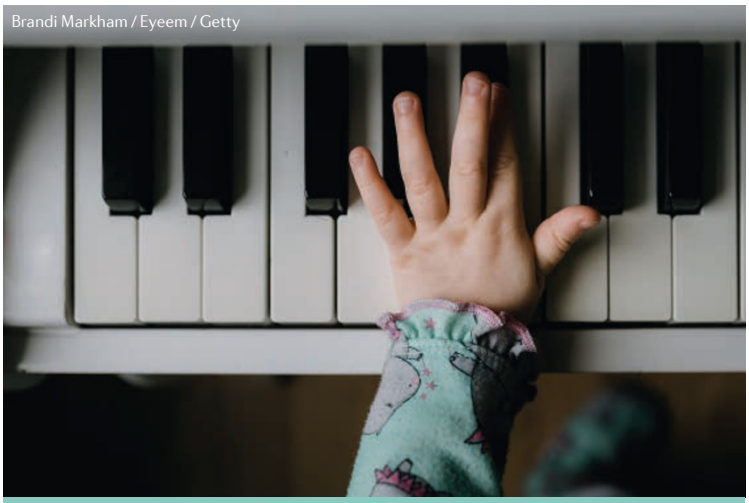
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MOTOR SYSTEMS

Mice get manual

Primates have superior manual dexterity to other mammals such as mice, possibly owing to evolution of the corticospinal system. Now, Gu *et al.* report a molecular mechanism involved in the development of the corticospinal system that may help to explain this difference in manual dexterity.

The corticospinal tract (CST) in primates descends in the ventral and lateral portions of the spinal cord, whereas in adult mice, this tract descends only in the dorsal spinal cord. Moreover, unlike adult primates, adult rodents do not show monosynaptic connections between the cortex and motor neurons (CM connections).

The authors hypothesized that, in mice, CM connections may initially form but be subsequently eliminated. Indeed, rabies virus-mediated tracing of inputs to the forelimb muscles in early postnatal mice revealed monosynaptic inputs from the motor cortex. During early postnatal development, corticospinal axons in the ventral and lateral parts of the spinal cord (vlCST projections) and in the dorsal spinal cord formed CM contacts; however, the vlCST projections were no longer detectable by postnatal day 14 (P14).

Various semaphorins and their receptors, plexins, are involved in axon guidance. Here, mice lacking plexin A1 (PLEXA1) specifically in cortical neurons exhibited vlCST projections at P38, and showed electrophysiologically functional CM contacts in adulthood. Similarly, mice lacking semaphorin 6D (SEMA6D) — one of the ligands for PLEXA1 — also retained vlCST projections in adulthood. These results suggest that PLEXA1–SEMA6D signalling in mice may mediate the elimination of vlCST projections and the loss of CM connections.

Given the importance of CM connections for manual dexterity in primates, the authors tested this ability in adult mice in which one or both copies of *Plexa1* were knocked out from motor cortical neurons at P2. Mice completely lacking cortical PLEXA1 handled and ate a fine pasta much more quickly and showed greater grasping skills than mice lacking one copy of *Plexa1* or control mice. Thus, in mice, the retention of the CM connections leads to improved fine manual dexterity.

> “in mice, the retention of the CM connections leads to improved fine manual dexterity”

The authors found that layer 5 of the developing human cortex, where corticospinal neurons are located, showed much lower levels of PLEXA1 expression than did layer 6, suggesting that PLEXA1 expression is regulated. Indeed, the authors identified a putative enhancer region in human *PLEXA1* that contains 28 binding sites for the zinc-finger transcription factor FEZF2. Only 5 of these sites also exist in mouse *Plexa1*, and FEZF2 binds to *PLEXA1* more strongly than it does to *Plexa1*. Transgenic mice expressing green fluorescent protein under the control of the human FEZF2 *cis*-regulatory elements showed lower fluorescence in layer 5 than in layer 6, mimicking the expression of PLEXA1 in the developing human cortex. Therefore, in primates, FEZF2 may repress *PLEXA1* expression, enabling retention of CM connections.

Overall, this study suggests that in primates, but not in mice, PLEXA1 expression and its signalling are repressed, allowing CM synapses that form during development to be maintained and conferring superior manual dexterity. Why these connections are eliminated in mice is unclear.

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ORIGINAL ARTICLE Gu, Z. *et al.* Control of species-dependent cortico-motoneuronal connections underlying manual dexterity. *Science* **357**, 400–457 (2017)