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Reaching an understanding of cortico-medullary control of forelimb behaviors

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How the neocortex modulates hindbrain and spinal circuits is of fundamental interest for understanding motor control and adaptive behaviors. New work from Yang, Kanodia, and Arber demonstrates that there is an exquisite anatomical organization and functional modulation from the anterior (motor) cortex on downstream medulla populations during forelimb behaviors in mice.

As humans, forearm and hand movements dominate our daily lives. We type on keyboards, hold utensils, shake hands, hug our loved ones, and play sports such as throwing frisbees. It all begins with a reach of the arm and a grasp of the hand. Similarly, rodents such as mice readily climb, reach for and grasp food, and groom themselves with their forelimbs. The ability of mice or humans to perform such actions requires carefully orchestrated movements, with precise activation of individual muscles in temporal sequences, allowing for the generation of both smooth and accurate movements.

Yet, we still cannot build adaptive robots with the skill and grace of a human, or even a mouse. This is, in part, due to the large gaps in our understanding of the fundamental principles underlying neural circuits that enable such forelimb behaviors. Now, a new paper in *Cell* by Yang, Kanodia, and Arber provides new understanding to a critical piece of the puzzle: how the anterior cortex (M1 and M2) exquisitely orchestrates movements via a hindbrain region called the lateral rostral medulla (latRM).[1] The latRM has been shown to be critical for the motor execution of forelimb movements,[2] but how goal-directed intentions shape its output was unclear.

Thus, to better understand the role of “top-down” influences on latRM, in an elegant series of experiments, Yang and colleagues labeled neurons projecting from different subregions of the anterior cortex to the latRM (Figure 1). This revealed a striking topography in their axonal termination patterns: neurons in the lateral anterior cortex terminated in the dorsal latRM, whereas medial anterior cortex neurons made their synaptic connections more ventrally.

To understand the functional contribution of these projections, they individually silenced two cortical subregions with muscimol during a pellet-reaching task. In this task, a mouse extended its forelimb to retrieve and consume a food pellet (a process that required bimanual manipulation to eat the food). This experiment revealed that the observed topography in motor cortical projections played distinct roles in the behavior: silencing the medial anterior cortex resulted in the mouse being unable to extend its forelimb, while silencing the lateral anterior cortex rendered the mouse unable to maintain its grasp around the food pellet, dropping it on the floor. These combined observations suggested that these cortical projections might target distinct functional populations within the latRM.

To test this hypothesis, the authors combined *in vivo* electrophysiological recordings of medullary neurons with cortical stimulation via optogenetics. The authors could thus decipher which latRM neurons were receiving input from lateral or medial cortical neurons. Recording from these neurons while the mouse performed the food pellet retrieval task showed that these medullary neurons were behaviorally tuned to either extension of the forelimb or handling of the pellet, complementing their perceived roles during silencing. Together, these results demonstrate that the anterior cortex acts as a high-level controller, recruiting different hindbrain neurons in a temporal sequence and driving distinct phases of forelimb movement.

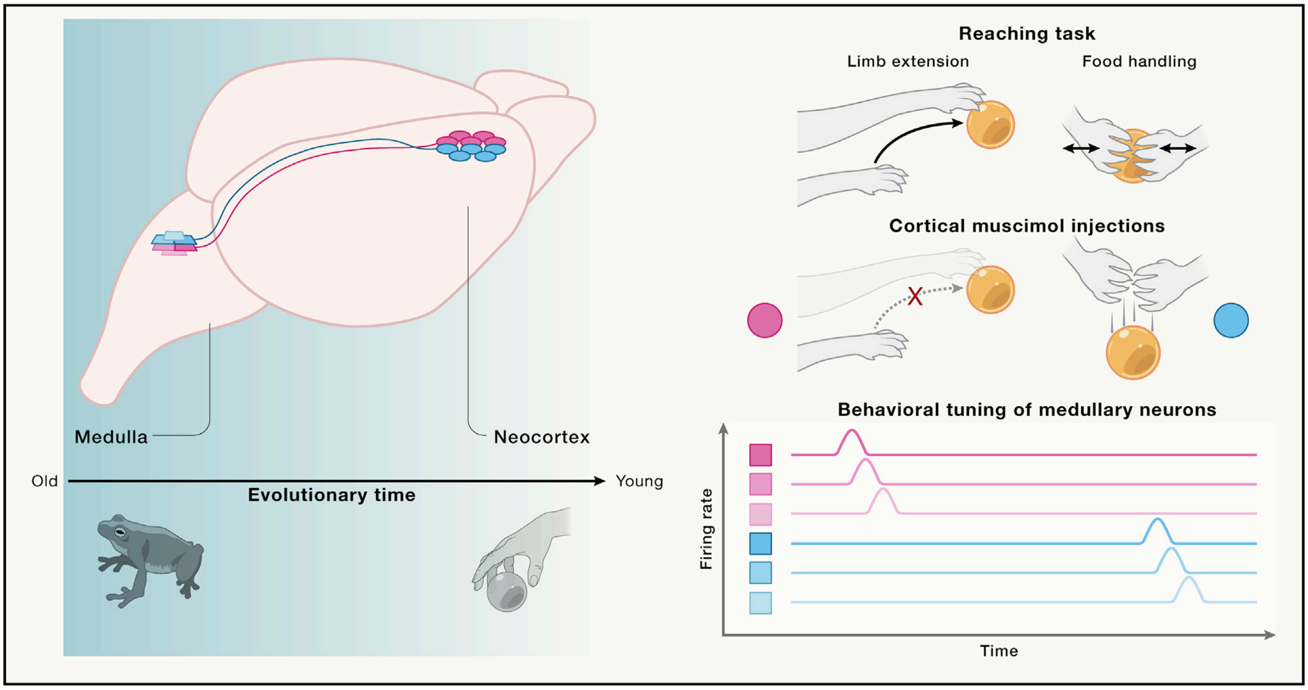

Figure 1. Cortical input to the medulla allows for flexible control of skilled forelimb movements
From the lens of evolution, the medulla can produce rather sophisticated forelimb behaviors, yet the neocortical expansion allows for fine-grained control and learning. Yang and colleagues demonstrate that there is a functional and anatomical topography to this hierarchical circuit motif. This topography corresponds to circuits that control different phases of forelimb movement during a pellet retrieval task, namely forelimb extension and food handling. Silencing neural activity using muscimol injections in the medial cortex (pink circles) results in the mouse being unable to extend its forelimb. Injections into the lateral cortex (blue circles), on the other hand, render the mouse unable to maintain its grip around the food pellet, dropping it to the floor. These two cortical populations synapse onto neurons in the medulla maintaining their topography across the dorsal-ventral axis (pink and blue squares). Recordings from the medulla show that these neurons fire at the same distinct phases of the reaching behavior, mirroring their cortical input.

This work not only highlights the orchestration of cortex onto latRM;[1] it also provides an important clue into the evolutionary role of this circuit. Namely, when the cortex arose and could control downstream hindbrain regions, this likely allowed for more skilled, learned, and dexterous behaviors. Reaching in rodents is remarkably similar to primates, suggesting that the neural architecture controlling goal-directed forelimb movements may be conserved among mammals.[3–6]

However, even non-mammalian taxa display a range of forelimb movements, suggesting that their specific use predates the mammalian neocortex. For example, frogs have been found to wipe their faces and “scoop” up prey with their hands.[7] This has led to the suggestion that frogs’ forelimb movements may be a primitive evolutionary precursor to the skilled use of forelimbs observed across many mammalian species.[8] Yet, frogs lack many of the areas associated with mammalian control of movement, including the cortex and corticospinal tract, but they do have a medulla. The medulla is an ancient (over 500 million years old) region of the hindbrain that is found throughout vertebrate species. While the role of the latRM in forelimb movements of frogs remains unclear,[9] its descending connectivity suggests that it is well positioned as a conserved region for the control of forelimbs. In mice, neurons within the latRM have been found to be recruited specifically during forelimb movements but not locomotion.[2] Optogenetic activations of different populations of excitatory latRM neurons stratified by axonal targets can produce equally diverse forelimb movements such as reaching followed by grasping, movements of the hand to mouth, and grooming.

Thus, while it’s clear that humans are more dexterous than mice, and mice more so than frogs, it is less obvious how the neocortex controls these actions. Undoubtedly, the unrivaled ability of mammals to perform the skilled manipulation of objects with their hands and forelimbs began with the cortical expansion and the newest additions to the motor system. Studies have shown that the anterior cortex is critical for dexterous behaviors of the hand involved in motor learning, yet oftentimes gross movements are spared with lesions.[10] Despite its regular neocortical columnar structure, the anterior cortex shows modularity in its function, and the work by Yang and colleagues further solidifies and extends our understanding of these circuit principles.

Looking forward, it will be of great interest to study the circuit during adaptive learning. It will also be important to consider a global perspective of the cortico-medullary circuit and how it integrates its modulation alongside the cerebellum and basal ganglia.[11] Neurons in the anterior cortex send collaterals to the basal ganglia; therefore, direct and indirect pathways may also have influence over medullary circuits, particularly during learned versus novel skills. For example, there could be rules that govern engagement: the cortical circuits could have the largest influence in shaping flexible adaptive movements, while more habitual forelimb and hand movements could be governed by the basal ganglia. Moreover, how the cerebellar circuits in both smooth movements and rapid learning influence populations of neurons in the hindbrain remains a critical open question. Collectively, studying how hierarchical circuits across the neocortex, basal ganglia, and cerebellum work in concert with the hindbrain to orchestrate learning of actions remains one of the crucial steps toward fully understanding how the old and newly emerged hierarchical circuits enable goal-directed, fine-grained forelimb movements.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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