Corticospinal Modulation of Precision Movements

Francesca Marino[1], Yunuen Moreno-López[2] and Edmund Hollis[2,3]

[1]University of California, San Francisco, CA, USA. [2]Burke Neurological Institute, White Plains, NY, USA. [3]Feil Family Brain and Mind Research Institute, Weill Cornell Medicine, New York, NY, USA.

Neuroscience Insights
Volume 19: 1–3

DOI: 10.1177/26331055241249497
Sage

ABSTRACT: Recently we demonstrated a critical role for temporal coding of corticospinal activity in a prehension movement requiring precise forelimb control. Learning of precision isometric pull drives large-scale remodeling of corticospinal motor networks. Optogenetic modulation of corticospinal activity and full transection of the corticospinal tract disrupted critical functions of the network in expert animals resulting in impaired modulation of precise movements. In contrast, we observed more widespread corticospinal co-activation and limited temporal coding on a similar, yet more simplistic prehension task, adaptive isometric pull. Disrupting corticospinal neuron activity had much more limited effects on adaptive isometric pull, which was found to be corticospinal independent by transection of the corticospinal tract. Here we discuss these results in context of known roles for corticospinal and corticostriatal neurons in motor control, as well as some of the questions our study raised.

KEYWORDS: Corticospinal, motor control, motor cortex, motor learning

RECEIVED: October 31, 2023. **ACCEPTED:** April 9, 2024.

TYPE: Commentary

FUNDING: The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the Burke Foundation, the National Institutes of Health DP2 NS106663 and R01 NS105725 to EH, and the Craig H. Neilsen Foundation 891396 to YM-L.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

CORRESPONDING AUTHOR: Edmund Hollis, Burke Neurological Institute, 785 Mamaroneck Ave, White Plains, NY 10605, USA. Email: edh3001@med.cornell.edu

Corticospinal Control Over Precise Prehension Movements

Motor cortex corticospinal neurons provide essential output for the modulation of movements in dexterous motor control. During the learning of a dexterous prehension task, there is a selective induction of dendritic spine formation in relevant corticospinal neurons which could serve to amplify salient task specific information.[1] These structural changes are also reflected in an increase in newly formed task-related spines on excitatory layer 2/3 neurons.[2] Our recent study (Serradj et al)[3] sought to define the role of corticospinal neuron activity during the learning of a prehension task that requires precise movement modulation.

To determine the response of corticospinal neurons during precise prehension learning, we recorded calcium transients from cervical level 7/8 (C7/8) projecting, layer 5, corticospinal neurons in mouse primary motor cortex (M1). We recorded *in vivo* through cranial windows during the learning of a precision forelimb isometric pull task and contrasted that to activity in animals learning an adaptive forelimb isometric pull that did not require precision control. While both tasks utilize similar prehension movements, we found that bilateral transection of the corticospinal tract selectively impaired performance on the precision task, not the adaptive task. Furthermore, acquisition of the more straightforward adaptive task occurred rapidly, and the number of corticospinal neurons showing time-locked activity during successful trials was small, decreasing from 12% to less than 7% across learning. In contrast, on the precision task, over 40% of C7/8 corticospinal neurons had activity patterns associated with successful precision trials. Optogenetically altering C7/8 corticospinal network activity patterns during prehension selectively impaired execution of precise motor control. These findings highlight the role of corticospinal neurons in dexterous forelimb movements and raise important considerations for assessing therapeutic interventions aimed at restoring function lost to disease and injury.

Distributed Cortical Motor Networks Are Involved in Motor Learning

Coordinated motor learning requires multiple distinct motor centers throughout the central nervous system. While the corticospinal tract is a primary mediator of dexterous motor movement, dynamic patterns of neuronal activity are also observed in corticostriatal neurons during the acquisition of motor skills. During learning of coordinated motor behavior on the accelerating rotarod, associative dorsomedial striatum (DMS) is rapidly engaged as naïve animals enter the early stages of skill learning while sensorimotor dorsolateral striatum (DLS) activity increases in later learning stages.[4] Medial prefrontal cortex corticostriatal connections to DMS similarly show a rapid increase in engagement from naïve to early stages of rotarod learning, followed by a rapid disengagement.[5] Sensorimotor cortex to DLS circuits show robust engagement early, with a more gradual decrease across learning.[5] In an abstract operant task, temporally precise coherence has been shown to develop between primary motor cortex and DLS during learning with selective increases in neurons controlling behavioral output.[6] These studies demonstrate that motor learning can specifically drive task-specific coherence between brain regions and provide a potential mechanism for adaptation to motor behaviors.

Emergence of the precise components in skilled prehension movements is independent of M1-DLS activity, with inactivation of DLS impacting gross trajectory components while M1 inactivation disrupts precision control.[7] With the development of expertise, the DLS encodes low level continuous kinematics of task specific movements, independent of sensory input.[8] Thus, primary motor cortex plays a complex but dissociable role in learning a skill composed of both dexterous and non-dexterous components. While activity is separable with precise movements being controlled by the corticospinal tract and gross movements by the corticostriatal tract, a population of corticospinal neurons sends collateral projections to DLS and encodes both forelimb movement activity and planning information in a lever press task.[9] This provides a potential mechanism for adjusting basal ganglia motor programs as both pathways act in concert to direct coordinated motor behaviors.

Sensory Shaping of Precise Movements

While corticospinal and corticostriatal pathways control different aspects of movement, external inputs to motor cortex carry sensory information necessary for forelimb behaviors. Integration of sensory information (proprioceptive, tactile, and visual) and motor signals occurs throughout the central nervous system and is fundamental for motor learning. Within the cortex, a reciprocal loop between S1 and M1 in mice has been shown to facilitate the integration of sensory input with motor output.[10] Lemnisco-cortical sensory information is transmitted from ventral posterolateral thalamus to S1 layers 2/3 and 4. Subsequently, these sensory signals are transmitted to M1 layer 2/3 and 5, influencing motor cortex output.[10] This sensorimotor integration is conserved across species. In cats, *in vivo* intracellular recordings have shown that high frequency S1 stimulation can drive long-term potentiation (LTP) in M1 layer 2/3, implicating a role for S1-M1 corticocortical connections in motor learning.[11] Whereas, in non-human primates, lesioning S1 results in impairments in learning new motor skills, but not in executing previously learned ones.[12] In rodents, single pellet reach training drives increases in PKMζ (an atypical isoform of PKC necessary for LTP) in S1 and M1 layers 2/3 and 5 .[13] The increase in M1 expression of PKMζ in layer 5 neurons is stable and persists over several weeks without continued training or reinforcement. In addition to S1-M1 corticocortical connectivity, S1 and M1 motor pathways may run in parallel. Coordinated locomotor learning, which relies on the convergence of medial pre-frontal cortex to DMS and M1 projections to DLS,[5] also drives increased anatomical S1 to DLS connectivity.[14]

Adjusting trained forelimb behavior to perturbations requires sensorimotor input to correct responsive movements.[15] Silencing S1 prevents functional adaptations to correct motor movements on a prehension pull task.[15] Further study is necessary to determine how perturbation of S1 or related circuits affect the adaptive and precision tasks used in our recent study.[3] However, both tasks require the use of similar prehension movements and thus likely engage similar M1 and S1 neurons. Therefore, these two versions of the isometric pull task may prove useful in dissociating motor and sensory aspects of automated gross movement execution from precise control.

Remaining Questions on Corticospinal Control of Precise Movements

An interesting, but unexplored, question is whether corticospinal neurons are spatially organized by task specific activity. In our precision task, corticospinal neurons exhibited patterned temporal activity during successful trials. However, whether corticospinal neurons with activity locked to the same phase of prehension behavior are spatially clustered remains unanswered. A recent study using *in vivo* 2-photon calcium imaging of layer 2/3 motor cortex revealed direction selective activity while mice reached for water droplets in multiple directions. These task related neurons in motor cortex were spatially intermingled.[16] That is, neurons coding different directional selectivity were not clustered by the direction they encode. *In vivo* recordings of corticospinal neurons during a pellet retrieval, prehension task show large-scale spatial organization based on different movement phases, with the rostral forelimb area containing more neurons encoding pre-grasping patterns and caudal forelimb area containing more corticospinal neurons encoding pre-reaching or post-grasping activity.[17] These results indicate that there is at least some large-scale clustering of corticospinal neurons activated at temporally distinct periods of prehension movements. A further analysis examining task-related neurons within each time point could determine if corticospinal neurons necessary for precision isometric pull execution are spatially organized or stochastically intermingled and add to the understanding of motor circuit organization during dexterous movement.

Another aspect of corticospinal activity that remains unexplored is the activity of individual neurons over learning. That is, do neurons maintain their select temporal specificity over learning or do their activity patterns change over time? *In vivo* 2-photon imaging of apical dendrites of layer 5 corticospinal neurons during a lever press task identified a subset of neurons active during movement but a larger number active while the animal was not engaged in the task. Furthermore, cells could switch between these classifications across days.[18] Similarly, during an alternative push/pull lever task, small populations of layer 5B projection neurons displayed movement-specific activity. However, movement-invariant responses dominated layer 5B population dynamics and different corticospinal neurons had differing activity between trials.[19] While we did not directly quantify the activity of individual neurons across learning, our analysis of corticospinal activity opens further avenues worth exploring. For example, the majority of corticospinal neurons did not exhibit temporally patterned activity during our precision task regardless of trial outcome. This result is consistent with the previous findings that the movement specific corticospinal neurons are a small fraction during a given movement. These insights help explain why the activity correlation of our corticospinal population only slightly increased in the precision learners. The population of corticospinal neurons that develop task specific activity is small and activity can change across days and even within trials.[19] Therefore, the population activity correlation is not significantly increasing, but the activity of a particular selection of corticospinal neurons could be becoming specialized. There is likely much redundancy in the capacity for corticospinal neurons projecting to the same spinal levels and tracking individual neurons across the late phase of learning may reveal how much of this population is task specific and whether a sub-network of the population is consistent across time in our precise isometric forelimb task. Additionally, selectively inactivating task-specific neurons could determine if these neurons are specifically required for dexterous behavior or if the network can compensate without them. Further study could lead to important insights into how individual corticospinal neurons contribute to population activity and control of dexterous movements.

One final unanswered question is how disrupting corticospinal circuits during different phases of learning affects task acquisition. Physical dissection of the corticospinal tract through pyramidotomy and transient disruption of corticospinal networks through optogenetics demonstrated the importance of these neurons for precision prehension performance in expert animals after learning. Recent work has shown that mossy fiber activity adapts to optogenetic stimulation during repeated stimulation every trial.[20] This could explain the weak impairment we observed during repeated optogenetic silencing and could indicate an interesting adaptation potential for corticospinal neurons. Further experiments would be required to assess whether earlier stages of learning show a greater dependence on the fidelity of corticospinal activity. Future studies could introduce transient inactivation or disruption of corticospinal networks during different phases of learning to dissect the effects of corticospinal activity on motor modulation and acquisition of dexterous forelimb behavior.

Author Contributions

FM, YML, and EH wrote and edited the manuscript.

ORCID iD

Edmund Hollis https://orcid.org/0000-0002-4535-4668

REFERENCES

1. Wang L, Conner JM, Rickert J, Tuszynski MH. Structural plasticity within highly specific neuronal populations identifies a unique parcellation of motor learning in the adult brain. *Proc Natl Acad Sci USA*. 2011;108:2545-2550.
2. Peters AJ, Chen SX, Komiyama T. Emergence of reproducible spatiotemporal activity during motor learning. *Nature*. 2014;510:263-267.
3. Serradj N, Marino F, Moreno-López Y, et al. Task-specific modulation of corticospinal neuron activity during motor learning in mice. *Nat Commun*. 2023;14:2708.
4. Yin HH, Mulcare SP, Hilário MR, et al. Dynamic reorganization of striatal circuits during the acquisition and consolidation of a skill. *Nat Neurosci*. 2009;12:333-341.
5. Kupferschmidt DA, Juczewski K, Cui G, Johnson KA, Lovinger DM. Parallel, but dissociable, processing in discrete corticostriatal inputs encodes skill learning. *Neuron*. 2017;96:476-489.e5.
6. Koralek AC, Costa RM, Carmena JM. Temporally precise cell-specific coherence develops in corticostriatal networks during learning. *Neuron*. 2013;79:865-872.
7. Lemke SM, Ramanathan DS, Guo L, Won SJ, Ganguly K. Emergent modular neural control drives coordinated motor actions. *Nat Neurosci*. 2019;22:1122-1131.
8. Mizes KGC, Lindsey J, Escola GS, Ölveczky BP. Dissociating the contributions of sensorimotor striatum to automatic and visually guided motor sequences. *Nat Neurosci*. 2023;26:1791-1804.
9. Nelson A, Abdelmesih B, Costa RM. Corticospinal populations broadcast complex motor signals to coordinated spinal and striatal circuits. *Nat Neurosci*. 2021;24:1721-1732.
10. Yamawaki N, Raineri Tapies MG, Stults A, Smith GA, Shepherd GM. Circuit organization of the excitatory sensorimotor loop through hand/forelimb S1 and M1. *eLife*. 2021;10:10.
11. Keller A, Iriki A, Asanuma H. Identification of neurons producing long-term potentiation in the cat motor cortex: Intracellular recordings and labeling. *J Comp Neurol*. 1990;300:47-60.
12. Pavlides C, Miyashita E, Asanuma H. Projection from the sensory to the motor cortex is important in learning motor skills in the monkey. *J Neurophysiol*. 1993;70:733-741.
13. Gao PP, Goodman JH, Sacktor TC, Francis JT. Persistent increases of PKMζ in sensorimotor cortex maintain procedural long-term memory storage. *Işç*. 2018;5:90-98.
14. Badreddine N, Zalcman G, Appaix F, et al. Spatiotemporal reorganization of corticostriatal networks encodes motor skill learning. *Cell Rep*. 2022;39:110623.
15. Mathis MW, Mathis A, Uchida N. Somatosensory cortex plays an essential role in forelimb motor adaptation in mice. *Neuron*. 2017;93:1493-1503.e6.
16. Galiñanes GL, Bonardi C, Huber D. Directional reaching for water as a cortex-dependent behavioral framework for Mice. *Cell Rep*. 2018;22:2767-2783.
17. Wang X, Liu Y, Li X, et al. Deconstruction of corticospinal circuits for goal-directed motor skills. *Cell*. 2017;171:440-455.e14.
18. Peters AJ, Lee J, Hedrick NG, O'Neil K, Komiyama T. Reorganization of corticospinal output during motor learning. *Nat Neurosci*. 2017;20:1133-1141.
19. Currie SP, Ammer JJ, Premchand B, et al. Movement-specific signaling is differentially distributed across motor cortex layer 5 projection neuron classes. *Cell Rep*. 2022;39:110801.
20. Calame DJ, Becker MI, Person AL. Cerebellar associative learning underlies skilled reach adaptation. *Nat Neurosci*. 2023;26:1068-1079.