A Path to Understanding How Motor Cortex Influences Muscle Activity

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The influence of motor cortex on muscles during different behaviors is incompletely understood. In this issue of *Neuron*, Miri et al. (2017) show that the population activity patterns produced by motor cortex during different behaviors determine the selective routing of signals along different pathways between motor cortex and muscles.

Imagine that you are heading to the mall (Figure 1A). If you are planning to buy a television at the mall, you will need to take your car, and the fastest way to the mall is along the highway. However, if you are planning to buy just an article of clothing, you might prefer to take your bike. A bike cannot be taken on the highway, but can instead be taken on a slower trail to the mall through a park. Thus, your mode of transportation determines whether or not you can take the fastest path to the mall.

Similarly, in motor control, there are multiple pathways between the motor cortex and muscles (Lemon, 2008). For example, there are pathways from motor cortex to the spinal cord, then to the muscles. There are other pathways that involve the brainstem, subcortical areas, and possibly even other cortical areas. For different behaviors, it is often unclear whether the same or different pathways are engaged. If different pathways are engaged, it is unknown what neural mechanisms are responsible for the selective routing of signals along different pathways. In particular, is there an explicit gate that blocks signals from traveling along certain pathways or is another mechanism at play?

In this issue of *Neuron*, Miri et al. (2017) address these questions in mice during two different behaviors, a precision pull task (termed "reaching") and treadmill walking. Previous studies have shown that lesions and pharmacological inhibition of neural activity in motor cortex lead to deficits in reaching and grasping, but leave treadmill walking largely unaltered. This was confirmed by Miri et al. (2017) and suggests that different pathways between motor cortex and muscles are engaged during these two types of behaviors. However, the timescale of these manipulations allows other brain areas to compensate, so they do not provide a clear picture of the role of motor cortex in driving movements on a timescale of tens to hundreds of milliseconds.

To avoid compensation from other brain areas, Miri et al. (2017) used optogenetic stimulation to rapidly silence motor cortical activity and examined its immediate effect on muscle activity during reaching and walking. The purpose of the stimulation was to eliminate spikes that would normally have been produced in motor cortex, rather than to create new spikes. They found that the optogenetic silencing influenced muscle activity at short latency (10 ms) during reaching and longer latency (35 ms) during walking. This key result has the following important implications. First, the fastest path between motor cortex and muscles is 10 ms, as determined by electrical microstimulation. Thus, motor cortex influences muscles along short latency pathways during reaching. Second, this result implies that motor cortex *does* influence muscles during walking, in apparent contradiction to lesion and pharmacological inactivation studies that demonstrate that motor cortex is not necessary for walking. These results can be reconciled by the fact that, in the lesion and pharmacological inactivation studies, there is enough time for other brain areas to compensate for the loss of motor cortical function.

A central question is why the short latency pathways are not engaged during walking. In other words, motor cortex is active during walking—what prevents the motor cortical signals from traveling down the short latency pathways during walking? One possibility is that there is an explicit gate downstream of motor cortex. By applying electrical microstimulation during walking, Miri et al. (2017) were able to influence behavior with 10 ms latency, implying that there is not a gate downstream that prevents signals from descending the short latency pathways during walking. In other words, it appears that the short latency pathways are capable of being engaged during walking, but are not engaged by motor cortex.

Another possibility is that certain population activity patterns in motor cortex are more effective at driving downstream neurons than other activity patterns. This concept was first introduced by Shenoy and colleagues in the context of understanding how the same motor cortical neurons can be active during movement planning and execution, but not drive arm movements during movement planning (Kaufman et al., 2014). The key idea can be illustrated by considering a downstream neuron (Y), which reads out the activity of two upstream neurons (X_1 and X_2) according to $Y = X_1 + X_2$. Suppose that the activity of the two upstream neurons is positively correlated (e.g., $X_1 = X_2$). In this case, coordinated changes in the activity of the two upstream neurons will influence the activity of the downstream neuron. However, if the activity of the two upstream neurons is negatively correlated (e.g., X_1 increases by the same amount that X_2 decreases), coordinated changes in the activity of the two upstream neurons will not influence the activity of the downstream neuron. Thus,
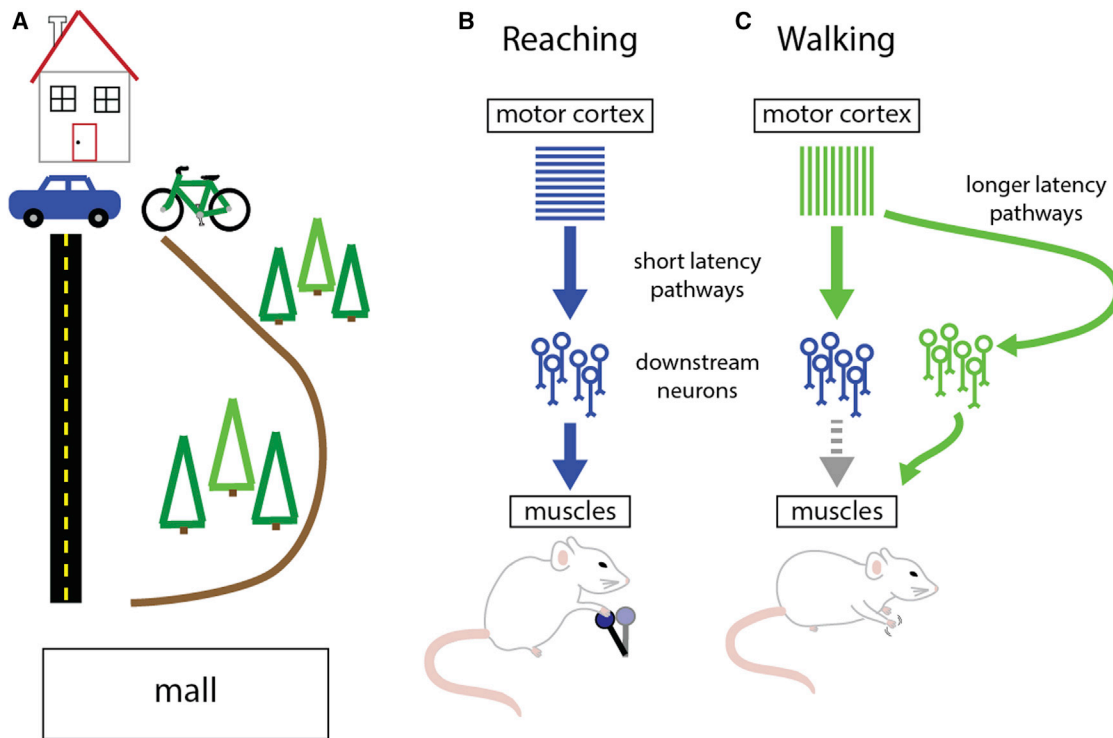
Figure 1. Selective Routing of Traffic and Neural Activity along Different Pathways
(A) There are two possible paths from home to the mall. The fastest way to the mall is by driving a car on the highway. If one instead rides a bike, which cannot be taken on the highway, a slower trail through a park is taken.
(B) During reaching, motor cortex influences muscles via short latency pathways. Blue stripes denote population activity patterns produced by motor cortex during reaching.
(C) During walking, motor cortex does not engage short latency pathways, but instead influences muscles via longer latency pathways. Green stripes denote population activity patterns produced by motor cortex during walking, which are not compatible with the short latency pathways.

whether upstream neurons influence the output of a downstream neuron is determined by the correlation of the upstream neurons, and not by an explicit gate or modulatory effect. A similar idea holds for upstream populations of more than two neurons. Rather than considering the correlation between a pair of neurons, we will need to consider how the entire population co-varies (referred to as "population activity patterns") (Cunningham and Yu, 2014).

To assess whether this population readout mechanism might be at play, Miri et al. (2017) examined the population activity patterns in motor cortex during the two behaviors. They found that population activity patterns for reaching were distinct from those for walking. This result is consistent with the following picture: population activity patterns in motor cortex for reaching are effective at driving downstream neurons along short latency pathways (Figure 1B). However, population activity patterns for walking (which

are distinct from those for reaching) are not effective at driving downstream neurons along short latency pathways (Figure 1C). This provides a compelling explanation for why motor cortical activity present during walking does not engage the short latency pathways, thereby yielding a behaviorally selective engagement of the short latency pathways.

The analogy in Figure 1A demonstrates a behaviorally selective engagement of a short latency pathway. Buying a television at the mall (the behavior) requires a car (akin to population activity patterns), which can travel along the highway (short latency pathway). In contrast, when buying an article of clothing at the mall (a different behavior), a bike (akin to a different set of population activity patterns) cannot travel along the highway (short latency pathway), but can instead travel along a trail through a park (longer latency pathway).

The current study can be extended in several ways. First, Miri et al. (2017) have

shown that the population activity patterns produced by motor cortex during reaching are distinct from those during walking. To solidify the claim that the population readout mechanism is responsible for the selective engagement of the short latency pathways, it will be necessary to demonstrate more directly that the population activity patterns for reaching are more effective than other patterns at driving downstream neurons along the short latency pathways. With ongoing technological developments, it may soon be possible to write in specified population activity patterns to test this hypothesis (Szabo et al., 2014).

Second, the short latency pathways likely involve the most direct routes between motor cortex and the muscles. In rodents, these are disynaptic pathways connecting corticospinal neurons with motor neurons (Lemon, 2008). However, it is unclear what the longer latency pathways correspond to anatomically, as they could involve the brainstem, subcortical

structures, or other cortical areas. Future work in dissecting these longer latency pathways can help to further clarify the role of motor cortex during walking and other behaviors.

Third, it is unknown whether the results of the current study also apply to primates. There are important anatomical differences between primates and rodents in the pathways between motor cortex and muscles (Lemon, 2008). Current optogenetic tools are better developed for rodents, enabling the current study. With the continued development of optogenetic technologies, it may soon be possible to perform similar experiments in primates (Yazdan-Shahmorad et al., 2016).

Overall, the work by Miri et al. (2017) is important for the following reasons. First, it clarifies the role of motor cortex during different behaviors. This study demonstrates that short latency pathways between motor cortex and muscles are engaged during reaching. However, during walking, motor cortex fails to engage the short latency pathways and instead influences muscles along longer latency pathways. By combining these results with previous lesion and pharmacological inactivation studies of motor cortex that allow other brain areas to compensate, the following picture emerges: the brain appears to be able to compensate for the loss of motor cortical signals that travel down long latency pathways, but

not for the loss of signals that travel down short latency pathways.

Second, a fundamental question in systems neuroscience is how signals are selectively routed in the brain. A much-studied mechanism is communication through coherence, whereby brain areas selectively communicate by synchronizing their oscillations (Fries, 2005). An emerging alternative is the idea of selective readout of population activity (Kaufman et al., 2014; Elsayed et al., 2016; Semedo et al., 2014). Downstream areas can read out different aspects of the activity of an upstream area by taking different combinations of the upstream activity. For example, one downstream area might read out $Y_1 = X_1 + X_2$, whereas another downstream area might read out $Y_2 = X_1 - X_2$. As a result, certain upstream population activity patterns will be effective at driving one downstream area, but not the other downstream area. Thus, the selective routing of signals can be achieved by producing different population activity patterns in the upstream area. The Miri et al. (2017) study provides support for this population-level mechanism.

Third, the approach used by Miri et al. (2017) can be extended to dissect how signals are routed in the brain along pathways with different latencies. In particular, by optogenetically silencing a brain area while recording from another brain area, the pathways by which one brain area influences another brain area can be char-

acterized (e.g., Guo et al., 2017). Just as we can map out traffic conditions in a city at various times of day, we may one day be able to map out how the brain controls flexible behaviors by routing neural activity along different pathways.

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