Stalling for Time: It's Not the Magnitude, but the Way Neurons Fire that Matters

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In this issue of *Neuron*, Stavisky et al. (2017) demonstrate that visual feedback in M1 during reaching initially reflects a specific pattern of neural activity that does not generate motor output and then is altered to a pattern that does generate motor output. This switch likely provides time for the motor system to consider various behavioral factors when specifying the appropriate motor response during voluntary motor actions.

Sensory signals are essential for motor function, providing information that helps plan and guide our body movements to interact in a complex world. Sensory signals are rapidly transmitted to motor regions in the CNS, such as motor cortex and the ventral horn of the spinal cord. However, there is a clear difference in how these two motor regions process and use sensory information for motor action. At the spinal level, motor responses to a mechanical disturbance of the arm are rather fixed and stereotyped, but are extremely fast, on the order of 15 ms; this time is almost entirely due to transmission times to and from the spinal cord.

In contrast, motor cortical processing provides a more flexible feedback response. Transmission times through primary motor cortex (M1) are longer, on the order of 30 ms. However, neurophysiological studies in awake, behaving monkeys highlight that these task-dependent motor responses take ~60 ms, twice as long as transmission delays. For example, classic work by Tanji and Evarts (1976) highlights that when a limb disturbance instructed a monkey to generate a movement (push or pull), there was a fast default response in M1 at ~20 ms following the disturbance reflecting features of the sensory disturbance (flexor or extensor disturbance), followed by a second task-dependent response at ~50 ms that reflected the upcoming motor action (move in the same or opposite direction as the disturbance). Correspondingly, muscle activity to generate the instructed movement begins soon after the task-dependent response at ~60 ms. Why two separate responses in M1?

Further, in reaction time tasks, neural activity in M1 begins ~100 ms before muscle activity that initiates the movement (Cheney and Fetz, 1980). Why such long delays between M1 activity and muscle activity, given that the transmission time from M1 to muscles can be as little as 10 ms?

In the present issue of *Neuron*, Stavisky et al. (2017) may have resolved these issues by exploring how visual feedback of the limb influences motor cortical activity during reaching. Previous work from this lab addressed a related problem: why does preparatory activity during a delayed reaching task not generate muscle activity? That study found that the pattern of activity in the preparatory period before a cue signal was unrelated to the pattern of activity during movement (Kaufman et al., 2014). The neural trick is that the pattern of activity across the population of neurons is strategically quite different when preparing versus when controlling limb movements (see also Vigneswaran et al., 2013). For example, two cells that both increase their activity before a movement display a reciprocal pattern of activity during the preparatory period. In other words, it's not the magnitude, but the pattern, of activity that matters.

The basic principle can be understood with a very simplified model of the motor system containing two motoneurons, each innervating a muscle with opposite actions at a joint (flexor and extensor), two inhibitory interneurons in the spinal cord, and two motor cortex neurons (Figure 1). The flexor M1 neuron (CF) synapses onto the flexor motoneuron and onto an inhibitory interneuron, which, in turn, synapses onto the extensor motoneuron. Correspondingly, the extensor M1 neuron (CE) synapses onto the extensor motoneuron and an inhibitory interneuron. A flexor movement is generated by increasing activity in the flexor M1 neuron and decreasing activity in the extensor M1 neuron. This leads to increases in flexor and decreases in extensor motoneuron activities, leading to joint flexion. An extensor movement generates the opposite pattern of activity in M1 and motoneurons. Thus, M1 activity follows a specific pattern of activity across the two M1 neurons to generate a range of flexor and extension movements, something the target article termed the "output-potent" dimension or solution space.

What's important to note is the presence of other patterns of activity by M1 neurons that generate no movement at all. This "output-null" dimension involves combined increases or decreases in activity by the two M1 neurons. In this case, changes in excitatory and inhibitory input onto each motoneuron are balanced, leading to no change in motoneuron activity. The simple example shown in Figure 1 includes only two M1 neurons. However, with more M1 neurons, the output-null solution space grows quickly, providing computational capacity without influencing motor output.

Stavisky et al. (2017) explore whether initial sensory feedback during reaching reflects output-potent or output-null dimensions. In the first experiment, they develop

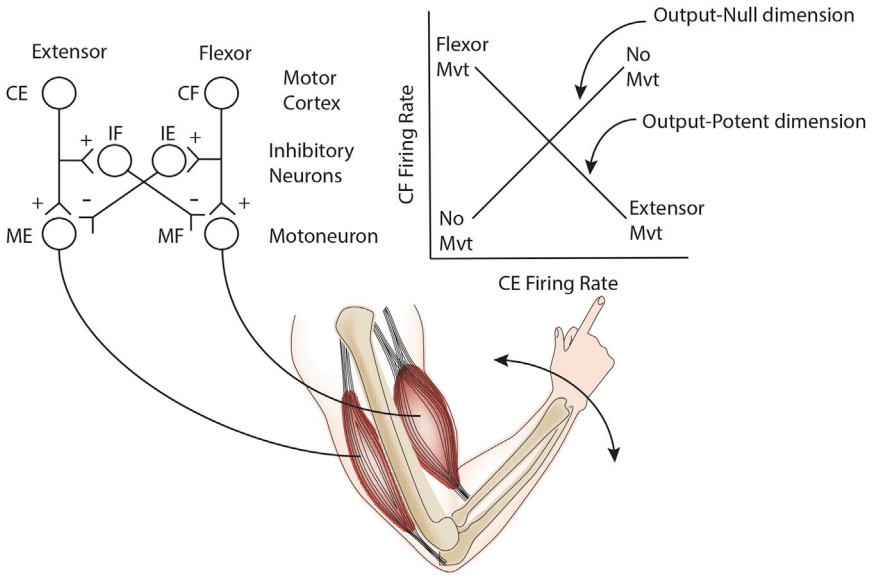

Figure 1. A Simplified Circuit to Generate Output-Potent and Output-Null Responses
A reciprocal pattern of activity in motor cortex leads to elbow flexion or extension (output-potent), whereas combined increases or decreases in their activity lead to no movement (output null). Diagram of arm adapted from Scott (2004) with permission.

a linear map between M1 activity and hand speed as the monkey performs a reaching task. This mapping provides an estimate of the output-potent solution space and, correspondingly, also identifies the output-null solution space. Next, they interleave trials in which the cursor representing hand motion randomly jumps laterally away from the direction of hand motion. In these situations, the monkey quickly makes a motor correction to counter the cursor jump and reaches the spatial goal. Perturbation-related activity arrived 70 to 120 ms after the cursor shift, but motor corrections occurred much later, 170 to 210 ms post-shift. Importantly, they found that the initial neural response was limited to output-null dimensions and thus would not lead to motor output: output-potent activity occurred later at 120 to 150 ms post-shift.

As pointed out in the paper by Stavisky et al. (2017), the mapping between M1 activity and hand speed is a crude approximation of the output-potent space for M1. They did a clever trick in experiment 2 to address this problem by creating a brain machine interface (BMI) that directly controlled cursor motion based on M1 activity. There is no ambiguity what the output-potent solution space with the BMI as it is explicitly defined by the mathematical transformation between M1 activity and cursor motion. With training, the monkey learned to quickly control motion of the cursor to spatial targets using the BMI. Critically, on random trials, cursor position was shifted laterally from the direction to the target. As in experiment 1, they found that neural activity immediately following the cursor jump was initially in the output-null space and thus did not lead to cursor motion. Approximately 40 ms later, activity began to emerge in output-potent dimensions appropriate for controlling the cursor with the BMI. Besides demonstrating how patterns of activity change during feedback processing, this study highlights how tools and technologies developed for helping individuals with severe motor impairments are now helping us understand more basic questions on brain processing and motor function.

The presence of output null activity in M1 provides an explanation for several common observations between M1 activity and motor output. As mentioned above, in reaction time tasks, M1 activity leads muscle activity by ~100 ms, much longer than the 10 ms transmission time between M1 and muscles (Cheney and Fetz, 1980). In this context, the initial activity in M1 following the presentation of the visual target or cue signal is likely also in output-null space and thus does not lead to muscle activity. As well, the initial M1 response often displays a large transient burst that is not observed—or at least is less than observed—in limb muscle activity (Sergio et al., 2005). Again, this transient burst in M1 may simply reflect output-null activity and thus does not generate any motor output. Finally, monkeys that are using BMI to control devices, such as a computer cursor, often stop moving their limb (Carmena et al., 2003). This cessation of limb movement could occur by simply shifting the activity pattern in M1 such that it is performing the task entirely in output-null dimensions for the limb—a useful strategy to minimize motor effort generating unnecessary arm movements! Thus, motor cortical activity may play an important role in voluntary control, but its activity can be dissociated from motor output.

While the target article provides compelling evidence that visual information is initially specified in output-null space, the reason for dissociating neural activity from output-potent space is less clear. As Stavisky et al. (2017) suggest, output-potent space is a very small portion of all possible neural patterns. Thus, it could be simply by random chance that the initial visual feedback is output-null. However, one would assume that if speed was paramount, the initial response could be altered to be output-potent.

One reason why visual feedback may initially be in output-null space is that it reflects sensory features of the stimuli and not the necessary motor response to attain a behavioral goal. There is a growing literature that long latency motor responses following a mechanical disturbance consider many factors, such as limb mechanics, goal-redundancy, task urgency, or even avoidance of obstacles in the environment (Scott, 2016). Previous work has demonstrated that the initial response in M1 to a mechanical disturbance begins as early as 20 ms but is not influenced by the mechanical properties of the limb or behavioral context (Pruszynski et al., 2011; Omrani et al., 2016). The same is true for the study by Tanji and Evarts (1976), where the perturbation instructed the monkey to generate a new motor action. Only at ~50 ms post-perturbation does neural activity start to reflect the motor requirements of the task. Thus, the initial default response is

likely maintained in output-null space so that it won't result in a muscle activity before M1 activity considers these behavioral contexts. The time required to compute the appropriate motor response (~30 ms) may reflect computational processes performed within M1 and/or processing in other brain regions that must be transmitted to M1 before executing the motor response.

Coexistence of output-null and output-potent activity in M1 can obfuscate analyses to correlate M1 activity directly to motor output. Even if M1 is involved in the selection, timing, and magnitude of muscle activity to generate a motor action, such output-null activity will alter overall M1 activity even though this activity has no impact on motor output. This suggests a need to first identify the output-potent space when exploring the link between M1 activity and motor output.

Output-null dimensions provide a potentially powerful approach for isolating certain types of information (i.e., sensory signals or preparatory activity) from downstream output signals. This likely reflects a general feature of cortical (and perhaps sub-cortical) processing that allows circuits time to complete essential processing before passing the results to downstream targets. Further, it may be that certain diseases or pathologies, such as impulsivity or focal dystonia, reflect a loss in this ability to dissociate input signals or ongoing computations from influencing downstream targets.

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