PNAS COMMENTARY

The importance of volitional behavior in neuroplasticity

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It was postulated by Donald Hebb (1) and even earlier over a century ago by William James (2) that correlated activity between pre- and postsynaptic activity would lead to strengthening of the synaptic efficacy between the two neurons, and it is believed to form the basis for long-term memory formation. Long-term potentiation (LTP) induced by high-frequency stimulation of afferents to a neuron and by paired stimulation of pre- and postsynaptic neurons are Hebbian forms of plasticity that have been experimentally validated extensively beginning with the seminal work of Bliss and Lomo (3) in the hippocampus (4). Spike timing–dependent plasticity (STDP) has refined this idea by demonstrating that the precise timing between pre- and postsynaptic activity can result in either potentiation or depression of the synapse (5). Nevertheless, most studies that have induced LTP and STDP have focused on synaptic plasticity outside of the context of behavior. In PNAS, Moorjani et al. (6) have demonstrated a form of plasticity using electrical stimulation that depends critically on volitional behavior and have shown that changes in connectivity strength can be maintained and even enhanced following the induction phase for days or even longer as long as the appropriate volitional behavior occurs.

The key insight in the study by Moorjani et al. (6) is the use of movement-gated intracortical microstimulation (ICMS) in motor cortex (M1) of nonhuman primates that primed the system for further enhancement of connectivity with ongoing motor behavior even after electrical stimulation ended. The approach involved identifying paired sites in M1 that exhibited reciprocal connectivity as assessed by stimulus-triggered evoked potentials (EPs) at one site due to a single test stimulation at the other site. One site was designated as the test site (referred to as Ntest), and monkeys were trained to perform wrist movements (flexion or extension) based on the evoked electromyographical (EMG) output at the Ntest site using high-frequency suprathreshold stimulation (Fig. 1*A*). For example, monkeys were required to volitionally flex their wrist if the evoked EMG output of that site was flexion. At the same time, another site (referred to as Nstim) that received a functional connection from Ntest was stimulated with ICMS at 10 Hz during the preferred movement of Ntest (e.g., flexion) such that neurons near the Ntest site were presumably firing, while induced firing occurred simultaneously among neurons near the Nstim site. Thus, the induction phase involved coactivation of neurons at Ntest and Nstim sites consistent with Hebbian plasticity. A strengthening in functional connectivity between Ntest and Nstim based on an amplitude increase of the EP occurred during movement-gated stimulation, which would be expected (Fig. 1*B*). What was striking, however, was that further increased connectivity strength occurred after stimulation ended as long as the monkeys continued to perform wrist movements associated with the preferred movement of Ntest (e.g., flexion) (Fig. 1 *C* and *D*). Appropriate controls were performed to demonstrate that movement-gated stimulation without further behavior or behavior without movement-gated stimulation did not result in increases in functional connectivity from Ntest to Nstim. Interestingly, there was no evidence of increased functional connectivity in the reverse direction from Nstim to Ntest.

The role of behavior as a necessary component in inducing plasticity is not entirely novel. Using a different induction paradigm in the auditory cortex of nonhuman primates, a series of studies found that inferred connectivity between two neurons increased only when animals were engaging in an auditory discrimination task (7, 8). In those studies, the spiking of one neuron triggered an auditory stimulus that evoked a response in another neuron, resulting in correlated firing during the induction phase. This correlated firing as assessed with cross-correlation was maintained even after the induction phase ended but only when the animal was engaging in the task during induction. However, over minutes, this increase in inferred connectivity faded and returned to baseline. The study by Moorjani et al. (6), in contrast, demonstrated long-term maintenance and even enhancement of connectivity after the induction phase as long as the animal continued to engage in the appropriate voluntary movement.

The mechanisms by which behavior acts to enable and even prime plasticity following induction are not known. Animals in the study by Moorjani et al. (6) performed a wrist task that was voluntary, goal directed, and rewarded, so a number of psychological processes may be at play, including attention, arousal, motivation, and even intentionality, which are associated with neuromodulation. A number of neuromodulator systems, such as dopamine, acetylcholine, neurepinephrin, and serotonin, have been shown to enhance plasticity, M1 motor maps, and motor learning through direct or indirect neuromodulator projections to M1 (4, 9–14). In particular, local cholinergic input to M1 has been shown to play a role in motor skill learning and to alter M1 output maps associated with learning (13). However, despite the fact that neuromodulation may play a critical role in Hebbian plasticity, it does not explain why continued behavior after the stimulation

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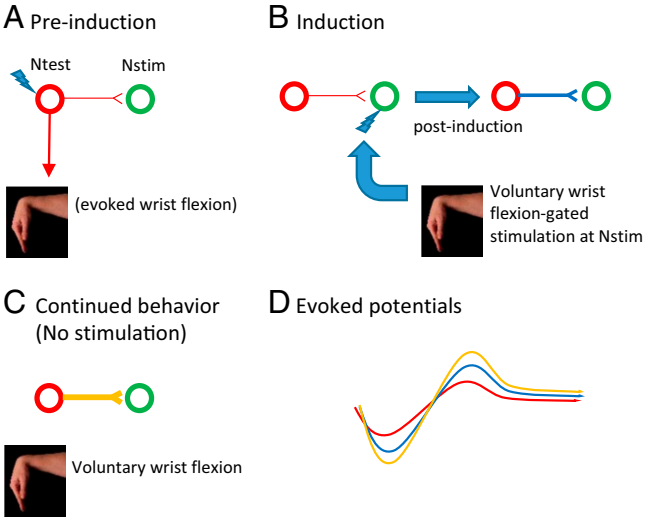

Fig. 1. Movement-gated stimulation paradigm. (*A*) Prior to induction, electrical stimulation is used to establish functional connectivity between Ntest and Nstim sites and to determine motor output of the Ntest site. (*B*) A 10-Hz stimulation at the Nstim site occurs only during voluntary wrist movements similar to those evoked by stimulating the Ntest site in *A*. (*C*) Continued voluntary wrist movements without stimulation. (*D*) Increasing EPs from preinduction (red) to postinduction (blue) to continued voluntary behavior with no stimulation (yellow).

induction phase has ended leads to further enhancement in functional connectivity in M1 as is demonstrated in the study by Moorjani et al. (6).

Synaptic tagging and long-term neuronal increases in excitability are posited by the authors as two possible mechanisms by which further enhancement in connectivity strength could occur following induction. Synaptic tagging describes the phenomenon whereby molecular changes at particular synapses that have undergone potentiation act as "tags" that capture plasticity-related proteins that can be synthesized before or after the induction period, and protein capture leads to persistent consolidation of the synaptic modification (15). Thus, in the context of the study by Moorjani et al. (6), synaptic tags may be established during the induction phase via movement-gated stimulation, which then capture plasticity-related proteins that are synthesized during ongoing behavior after stimulation ends assuming these proteins are indeed synthesized by the appropriate behavior. While this could explain the increases in connectivity strength following induction on the same daily session, it is hard to use the same argument for further increases in connectivity strength on subsequent daily sessions because the synaptic tags decay over the course of minutes to hours, at least in the hippocampus (15, 16).

Two further puzzling observations from the study by Moorjani et al. (6) need future experiments to resolve. The first is that increases in connectivity strength were directed from Ntest to Nstim sites and not vice versa, despite the fact that initially the two sites were reciprocally connected and the induction phase involved correlated firing at the Nstim and Ntest. There is no clear evidence for STDP where the Ntest spikes preceded the evoked Nstim spikes, and yet, connectivity increases were one way and not bidirectional. The second observation is that increases in functional connectivity from the Ntest site were not restricted to the Nstim site but extended to a number of other sites, indicating a more global change in network structure emanating from the Ntest site. Moreover, the magnitude changes in functional connectivity from Ntest were not correlated with the motor outputs of these other sites or with the distance of these other sites from Ntest even extending to the contralateral hemisphere.

Regardless of complete explanations of all these findings, one of the inferences that can be made from this study is that multiple sites in M1 that share the same motor output as Ntest and form functional connections with the Nstim site prior to movement-gated stimulation would also be the origin of increased directed connectivity strength following induction, implying large-scale modifications in connectivity across M1. There are clear neurorehabilitative implications of this study, whereby localized stimulation using invasive or even noninvasive methods triggered by particular movements could be used to enable global plasticity following brain injuries, such as stroke.

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