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Brain-Controlled Neuromuscular Stimulation to Drive Neural Plasticity and Functional Recovery

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Abstract

There is mounting evidence that appropriately timed neuromuscular stimulation can induce neural plasticity and generate functional recovery from motor disorders. This review addresses the idea that coordinating stimulation with a patient's voluntary effort might further enhance neurorehabilitation. Studies in cell cultures and behaving animals have delineated the rules underlying neural plasticity when single neurons are used as triggers. However, the rules governing more complex stimuli and larger networks are less well understood. We argue that functional recovery might be optimized if stimulation were modulated by a brain machine interface, to matched the details of the patient's voluntary intent. The potential of this novel approach highlights the need for a better understanding of the complex rules underlying this form of plasticity.

Introduction

Brain Machine Interfaces (BMIs) hold great promise for improving the lives of patients with motor disabilities caused by stroke or spinal cord injury (SCI). Over the last 15 years, BMI users, mostly non-human primates, have controlled computer cursors [1–3] or robotic devices [4] directly from their thoughts. For a small number of human patients with neurological disorders, a BMI has actually replaced lost motor function [5,6]. These neuroprostheses typically rely on 'decoders' that map neural activity into the desired control signals, for example, cursor or robot motion.

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A much larger number of patients with SCI or stroke have benefited from functional electrical stimulation (FES), electrical stimuli applied to muscles or nerves, used to restore both arm and leg function [7]. The most common application addresses foot drop by stimulating the common peroneal nerve to generate ankle dorsiflexion at the onset of swing (Figure 1A). Current FES neuroprostheses that restore grasp rely on preprogrammed stimulation patterns that the patient can initiate by residual proximal limb movements (Figure 1C).

Recently, in experiments with monkeys, BMIs have been used to supply the control signals for FES, thereby overcoming the need to rely on residual movement [8–11]. Our group demonstrated the potential of this approach by restoring grasp in monkeys temporarily paralyzed by peripheral nerve block. We used the combined activity of nearly 100 cortical neurons to predict forearm flexor EMGs, which served as control signals driving stimulation of five electrodes [10].

There is an intriguing potential additional benefit of BMI-controlled FES: Its use in patients recovering from SCI or stroke may lead to recovered function beyond that of standard therapy. In a small number of patients with a variety of motor disorders, the use of FES to assist movement has led to recovered function that persisted after FES was discontinued in both walking (Figure 1B) [12,13] and use of the hands (Figure 1D) [14–16]. The functional recovery resulted from neural plasticity, likely including long-term potentiation (LTP) and depression (LTD) of existing synapses, axonal sprouting, and synapto- and neurogenesis, among other mechanisms [17,18]. Numerous studies involving single-neuron trigger sources have demonstrated the importance of timing of pre- and post-synaptic activity in the generation of these plastic changes [19,20] (see Figure 2A and text box). However, the importance of precise timing is less clear when numerous, continuously modulated neural pathways are involved.

Text Box

The complex timing of stimulus-driven plasticity

In 1949, Donald Hebb suggested the postulate, now famously summarized as ‘neurons that fire together, wire together’ [64] that has formed the basis for many subsequent studies (see the reviews in [65,66]). Spike timing dependent plasticity (STDP) is an expression of a Hebbian mechanism, in which both the sign and magnitude of synaptic modification are determined by the precise timing of spikes (see Figure 2A; [19,20] and the review in [65]). Synapses tend to be strengthened as a result of a causal (i.e. greater than 0 and less than ~50ms) relation between pre- and post-synaptic activity. The opposite timing leads to decreased synaptic strength (postsynaptic activity leading presynaptic activity by <100ms; see Figure 2A). This law holds true under the relatively simple conditions that can be achieved in vitro, with constrained network properties, low stimulus rates, and a well-defined type of targeted receptor. However, it fails to describe more complex conditions, e.g., with triplets, quadruplets or trains of stimuli of higher frequencies [65,67]. These latter conditions are more similar to in vivo conditions, with more extended networks and higher firing rates. These conditions are often more accurately described by the Bienenstock-Cooper-Munro (BCM) model [68]. The BCM

model is not based on individual spike events, and therefore does not consider precise timing but only the pre- and postsynaptic firing rates. Notably, the BCM and STDP models may lead to contradictory predictions even in simple scenarios. For example, when low frequency presynaptic stimulation is followed by postsynaptic stimulation, STDP predicts that the synapse will strengthen, while the BCM model predicts it will weaken because of the low frequency. The complexity of the rules underlying plasticity (see, e.g., [65–67,69,70] for more details) illustrates the challenge for inducing predictable large-scale plastic changes to promote recovery.

Neurological injury triggers widespread changes across the CNS and increases its plasticity, opening a window for therapeutic intervention soon after injury [21,22]. Unfortunately, all plasticity is not necessarily beneficial; it can also lead to maladaptive reorganization [22–26]. Potentially, the most effective way to guide adaptive plasticity would be by using a BMI to assist the patient's attempted movements through control of a powered orthosis, or by artificially activating their own muscles through FES. The conjunction of cortical activity generated voluntarily, and movement-related afferent feedback may lead to adaptive plastic changes and improved functional recovery [11,26–31].

Induction of Synaptic Plasticity with Electrical Stimulation

In vivo, Spike-Triggered Stimulation to Induce Plastic Changes

Intracortical microstimulation (ICMS) triggered by naturally occurring action potentials has been used to induce neural plasticity in behaving animals, likely evoking mechanisms like those observed in vitro (Textbox 1). Following one or more days of spike-triggered stimulation in primary motor cortex (M1) of monkeys, test ICMS trains at the 'trigger' site began to activate some of the same muscles as the conditioned site, provided the trigger/target delay was less than 50 ms [32](Figure 2B). In a similar fashion, M1-triggered spinal stimulation was used to modify the strength of corticospinal projections [33]. The changes were seen in the post-spike facilitation of EMG, implicating an effect of the corticospinal terminals directly on motoneurons.

Our group evaluated the effects of spike-triggered stimulation on functional connectivity computed for small networks of neurons, and discovered that the stimulation altered not only the connectivity between trigger and target neurons, but also among neighboring cells [34]. These latter effects may have been due to preexisting network connections (e.g., horizontal fiber connections in M1 [25,35]) that distributed the stimulus effects to second-order neurons.

Spike-triggered stimulation has also been used to induce functional changes, including decreased detection thresholds for particular electrodes [36] and even recovery of reach and grasp function after motor cortical infarct in rats [37]. In that study, spike-triggered stimulation of somatosensory cortex (S1) 7.5 ms after spikes in premotor cortex significantly improved grasp function compared to rats receiving randomly triggered stimulation [37]. Results like these suggest an exciting potential application to neurorehabilitation.

Paired Stimulation to Induce Neural Plasticity

The paired associative stimulation (PAS) paradigm is a method used to induce neural plasticity non-invasively in humans. It has been applied both to healthy individuals [38] and patients suffering from stroke or other disorders (see [39] for a recent review). In a typical PAS experiment, neural plasticity is induced by the combination of transcranial magnetic stimulation (TMS) and peripheral nerve stimulation. As in STDP (Figure 2A; Textbox 1), the inter-stimulus interval can define both the sign and magnitude, and even the location of the effects.

If the inter-stimulus interval is such that the ascending afferent activity generated in motor cortex by the peripheral stimulation (blue pathway in Figure 3) coincides approximately with the post-synaptic cortical activity generated by TMS, the corresponding sensory inputs to the motor cortex will be potentiated [38,39]. In fact, a 25 ms inter-stimulus interval caused increases in the motor-evoked potentials generated in hand muscles by TMS [38], while a 10 ms interval (which reversed the timing between pre- and post-synaptic activity) caused decreases [40]. The effects are thought to be due to the induction of LTP and LTD, respectively. Similarly, TMS timed to generate presynaptic activity slightly preceding the antidromic activation of motoneurons (red pathway in Figure 3) caused the strength of corticospinal inputs to those motoneurons to be increased (black synapses on red cell in Figure 3). The changes were revealed by increased cervicomedullary motor-evoked potentials in the biceps [41]. Interstimulus intervals of either 22 or –13 ms led to the opposite effect. Finally, increases in the H-reflex following PAS have revealed changes in the spinal cord as well, potentially occurring in the synapses between Ia afferents and motoneurons, in the motoneurons themselves, or in presynaptic inhibition [42].

Guiding Plasticity for Neurorehabilitation

Associating Stimulation and Voluntary Effort

Paired stimulation techniques such as PAS have been shown to induce cortical and spinal plasticity, with some evidence of functional recovery after SCI [43] and stroke [39] as well. There is some evidence that FES, using preprogrammed stimulus trains timed to coincide with voluntary effort and designed to effect movement, may accelerate recovery in both SCI and stroke [12–16,28,44]. Likewise, there is evidence that even continuous stimulation combined with voluntary effort can lead to improved motor function in both a rat model of SCI [31] and human SCI patients [29]. In these cases, recovery was dependent on stimulation, and progressed with continued treatment. In the rodent study, recovery was accompanied by remodeling of cortical projections to brainstem and spinal sites [31,45]. In more recent experiments, the same group monitored the gait cycle to modulate stimulation in real-time [46], in an attempt to match the resulting movements more closely to the voluntary effort.

The correspondence between voluntary effort and peripheral stimulation indeed appears to be an important factor [47]. This observation raises an important question: To what extent would functional recovery be improved by matching stimulus dynamics ever more closely to the patient's voluntary motor commands? Answering this question is critical, as the closest

match would likely be achieved only by using invasive, intracortical recordings. Unfortunately, there is little experimental evidence bearing directly on this question. Several studies have found improved finger movements in stroke patients, when EEG was used to trigger either a preprogrammed FES waveform [48,49] or orthosis movement [30] to assist function. Neither study addressed timing, and only the latter included a control group.

In healthy individuals, single peripheral stimuli paired with the onset of imagined leg movement detected by EEG induced LTP in the corticospinal pathway [50,51]. These effects were dependent on stimulus timing, but with less precision than that required by PAS (Fig. 1C). Another study in healthy individuals compared the size of MEPs following a series of grasping movements that were assisted by a fixed FES train triggered by EMG, EEG, or manually by the therapist [52]. In this study, manual triggering was least, and EMG most effective. In the following sections we review several approaches to detect motor intent, and their therapeutic potential.

EMG-Triggered Stimulation

For patients with adequate residual motor activity, EMG recordings may provide a good estimate of motor intent. Residual EMG used to trigger epidural spinal stimulation boosted the strength of muscle contraction achieved by a monkey with an incomplete SCI [11]. Stroke patients receiving preprogrammed FES patterns triggered from EMG outperformed patients who received FES only for strength training, or standard physical therapy [53–55]. Similar studies with SCI patients also report increased muscle force [56].

Despite its potential, EMG-triggered FES has at least three important limitations. First, it will be ineffective for patients who cannot voluntarily contract their muscles, or who display abnormal muscle activity patterns. Second, the use of pre-programmed stimulation patterns, necessitated in part by stimulus artifacts in EMG, may not match motor intent well. Finally, the delay between cortical and EMG activity may limit the ability to achieve optimal stimulus timing.

EEG-Triggered Stimulation

Detecting motor intent directly from the brain is an attractive alternative [26], particularly for patients with more complete loss of voluntary movement. However, detection of movement onset from EEG can be highly variable, ranging at least 100–300 ms [57,58]. Reliability can be improved with longer sampling times, but at the expense of even greater latency [59]. It is worth asking whether the apparent decreased sensitivity to timing [50,51] in these experiments compared to STDP or PAS (Figure 2) is simply due to the imprecision of movement detection by EEG. Perhaps greater detection precision would lead to even more pronounced effects, more sharply tuned in time. EEG has been used for continuous cursor control in two, and even three dimensions [3]. However, these subjects use learned arbitrary motor imagery, typically of different body parts, to control movement along different axes. As such, it would not likely represent an ideal control signal to match FES to natural motor intent.

Intracortical Control

Intracortical recordings as a means to control stimulation for restoration of function and functional recovery have been explored in monkeys by coupling LFP recordings to intraspinal stimulation, allowing limited control of voluntary movement after SCI [11]. Cortical recordings from spinal cord injured rats have also been used in real-time, to replace lever pressing [60] or control pelvic support force supplied through a robot [61]. Our group has used M1 discharge to make predictions of EMG [9,10,62]. This raises the possibility of using FES trains that are precisely modulated in time to match the motor intent for individual muscles. We speculate that this specific ‘association’ of motor intent with both peripheral afferent activity, and antidromic motoneuron activity (see neural pathways in Figure 3), might provide a much more effective stimulus for adaptive plasticity and functional recovery than the single pulses, or unmodulated FES trains used in most previous experiments. Further animal studies using invasive recordings will be required to explore the potential of this approach.

Conclusion

Interventions that promote activity-dependent plasticity by associating motor intent with artificially generated movement and afferent activity using electrical stimulation constitute a promising avenue for promoting recovery after neurological injury. However, we still have an incomplete understanding of the principles underlying stimulus-driven neural plasticity, and how to apply it optimally to promote adaptive forms of plasticity while suppressing maladaptive changes. We know that timing is critical for paradigms used to induce plasticity based on the discharge of single neurons, both in vitro, and in vivo. However, the precise timing required for these approaches may be less relevant for the adaptive plasticity that underlies functional recovery in the context of large networks of neurons and continuously modulated activity. Simply increasing overall synaptic strength is unlikely to be optimal, as it would be expected to increase reflex gains as well as the strength of descending inputs, potentially increasing symptoms of spasticity. Rather, we speculate that by more closely reproducing the normal patterns of pre- and post-synaptic activity in corticospinal and reflex circuits, an optimal combination of synaptic potentiation and depression might be achieved.

However, there is as of yet no experimental evidence bearing directly on this possibility, nor on the time course after injury for which such an intervention might be most effective. It is not obvious that a stroke patient or an SCI patient with residual function would elect to receive an intracortical implant for the purposes of rehabilitation, particularly in the early stages of recovery. Compelling experimental evidence of superior therapeutic benefit compared to the current best clinical practice would be essential to tip the balance in favor of this substantially more invasive approach. The choice is made more difficult by the recognition that the mechanisms leading to recovery are complex and dependent on many factors, including the type and severity of the neurological injury and the time after the lesion. However, it should be recognized that deep brain stimulation for Parkinson’s disease, a considerably more invasive procedure, is now a well accepted procedure, despite remaining controversy surrounding its mechanisms of action [63]. We assert that the results

from studies that aim at driving plastic changes to improve recovery after SCI or stroke are sufficiently encouraging to warrant further research.

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- Brain-controlled Functional Electrical Stimulation (FES) can restore motor function
- Appropriately timed neuromuscular electrical stimulation drives plastic changes
- Site, sign, and magnitude of changes depend on coordination with central activity
- Hence, brain-controlled FES may cause long-lasting recovery following stroke or SCI

Figure 1.

Examples of the gain of function following long-term FES tested in the absence of stimulation. **A:** foot drop stimulator (L300, Bioness Inc., Valencia, CA, US) **B:** Long-term use (average: 5–6 months) improved several electrophysiological and biomechanical measures in patients with both nonprogressive (stroke and SCI) and progressive (multiple sclerosis) disorders. Improvement was greater in the former group (right panel). MVC = maximum voluntary contraction; Speed = walking speed; Bckgnd = voluntary contraction level at which the MEPs were measured; M_{max} = maximum value of the M-wave. Adapted from [13]. **C:** Surface stimulation used to provide improved grasp function. Adapted from [14]. **D:** Hand function improved significantly in acute stroke patients following FES-assisted grasping (average: 13 weeks). When compared to controls, patients who underwent FES therapy exhibited greater improvement in object manipulation, palmar grip torque and pinch grip force ($P < 0.05$). Adapted from [16].

Figure 2.

Time dependence of various types of mechanisms for the induction of neural plasticity. **A:** Change in excitatory postsynaptic current (EPSC) as function of the inter-stimulus interval, illustrating STDP in an in vitro study involving two cells. Adapted from [20]. **B:** Dependence of the conditioning effect (shift in joint torque, reflecting a change in the motor output of the small population of M1 neurons activated by the stimulation) as function of the spike-stimulus interval, in an in vivo experiment in monkeys. The dashed line represents the 95th centile for controls, and shows that no significant changes are elicited if the spike-stimulus interval is > 50 ms. Adapted from [32]. **C:** Change in the magnitude of the MEP depending on the phase of the movement related cortical potential (MRCP) at which an afferent stimulus was delivered, in a study in healthy humans. Each panel compares the pre- and post-intervention MEP after conditioning at different phases of the MRCP (see inset). Adapted from [50]. CNV = contingent negative variation, the first deflection of the MRCP following a cue to initiate movement imagination.

Figure 3.

After an ischemic stroke or SCI, motor deficits are caused by the death of a subpopulation of cortical neurons (hashed triangles) or the interruption of the descending pathways. Brain-controlled FES (purple line) may be used to strengthen the brain connections to the paretic muscles by inducing neural plasticity. FES-induced action potentials travelling antidromically to the motoneurons (red cell) may be made to coincide systematically with descending (black pathway) or sensory (blue) spinal cord inputs, thus altering their connectivity to motoneurons. FES-induced afferent activity (blue pathways) can also be made to coincide with the central activity related to voluntary effort (green and black cells) and induce plasticity in supraspinal networks.