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Short-Term Neuroplastic Effects of Brain-Controlled and Muscle-Controlled Electrical Stimulation

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Objectives: Functional electrical stimulation (FES) has been shown to facilitate the recovery of grasping function in individuals with incomplete spinal cord injury. Neurophysiological theory suggests that this benefit may be further enhanced by a more consistent pairing of the voluntary commands sent from the user's brain down their spinal cord with the electrical stimuli applied to the user's periphery. The objective of the study was to compare brain-machine interfaces (BMIs)-controlled and electromyogram (EMG)-controlled FES therapy to three more well-researched therapies, namely, push button-controlled FES therapy, voluntary grasping (VOL), and BMI-guided voluntary grasping.

Materials and Methods: Ten able-bodied participants underwent one hour of each of five grasping training modalities, including BMI-controlled FES (BMI-FES), EMG-controlled FES (EMG-FES), conventional push button-controlled FES, VOL, and BMI-guided voluntary grasping. Assessments, including motor-evoked potential, grip force, and maximum voluntary contraction, were conducted immediately before and after each training period.

Results: Motor-evoked potential-based outcome measures were more upregulated following BMI-FES and especially EMG-FES than they were following VOL or FES. No significant changes were found in the more functional outcome measures.

Conclusions: These results provide preliminary evidence suggesting the potential of BMI-FES and EMG-FES to induce greater neuroplastic changes than conventional therapies, although the precise mechanism behind these changes remains speculative. Further investigation will be required to elucidate the underlying mechanisms and to conclusively determine whether these effects can translate into better long-term functional outcomes and quality of life for individuals with spinal cord injury.

Keywords: Brain-machine interface, electromyography, functional electrical stimulation, neuroplasticity, spinal cord injury

Conflicts of Interest: The authors declared no conflicts of interest.

INTRODUCTION

In cases of spinal cord injury (SCI), the corticospinal tract is damaged, and descending signals from the brain cannot proceed beyond the site of injury, or in cases of incomplete SCI, do so at a greatly decreased signal strength. The effect of this is that muscles whose innervating motor neurons are below the site of injury cannot receive commands from the brain, and are either paralyzed or impaired. In high-level injuries (spinal levels C4 to C7), this leads to decreased hand function, the recovery of which has been cited by individuals with high-level SCI as their top therapeutic priority (1).

Functional electrical stimulation (FES) is a treatment that has been found to facilitate the recovery of grasping function when applied for long durations shortly after an incomplete SCI (2). It is vital for the success of this therapy that the stimulation is used only to facilitate movements that the recipient is volitionally attempting to perform. In current clinical trials, this is achieved by allowing the practitioner running the treatment sessions to trigger or change the stimulation with a push button, on the understanding that they are to provide stimulation only to facilitate movements that the recipient voluntarily attempts. If FES is applied without the recipient's voluntary involvement, its therapeutic effects are reduced by approximately half (3). The proposed reason for this is that FES is thought to work by inducing neuroplastic changes, specifically long-term potentiation (LTP), at synapses in the spinal cord between upper motor neurons and α motor neurons. This LTP is triggered when descending signals from the brain reach the synapse at approximately the same time as antidromic volleys from the stimulated peripheral nerves (4), in accordance with classic "Hebbian" principles of neuroplasticity (5). It should be noted, however, that this hypothesis has not been rigorously validated, and alternate hypotheses, such as the induction of cortical plasticity, do exist.

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Within the framework of this proposed mechanism, it can be seen that the manual activation and deactivation of electrical stimulation may cause discrepancies between the recipient's voluntary intention and the stimulation itself, thereby decreasing the effectiveness of neuroplasticity induction. An automated system that is able to detect user intention in an empirical fashion may be able to provide a more consistent pairing of the two signals, and therefore, more extensive neuroplasticity and greater functional improvements.

Two such systems that can be proposed are brain-machine interface-controlled FES (BMI-FES) and electromyogram-controlled FES (EMG-FES). A BMI-FES system would detect the user's intention to move based on recordings of brain activity from the primary motor cortex and activate stimulation accordingly. This system would be based on existing BMIs, in which event-related brain activity is interpreted for the purpose of controlling external devices such as prosthetics, computer cursors, or communication aids (6). An EMG-FES system would detect small amounts of residual muscle activity in the muscle of interest and also activate stimulation at that time. While both BMI-FES and EMG-FES systems have previously been developed, they were primarily intended for long-term use, essentially being thought of as orthoses (7–12).

To date, three studies have shown neuroplasticity in response to BMI-FES. Daly et al. (13) recruited a single stroke patient and showed increased range of motion in the index finger after several sessions of BMI-FES, with no control comparison offered. Takahashi et al. (14) also recruited a single stroke patient and showed transient increases in voluntary tibialis anterior EMG activity and ankle range of motion following a single session to a much greater extent than those induced by a conventional FES protocol. Lastly, Niazi et al. (15) recruited 16 able-bodied participants, divided into three groups, and showed greater upregulation of tibialis anterior motor-evoked potentials (MEPs) in the BMI-FES condition as compared with motor imagery or random electrical stimulation. While the first two studies provide limited evidence due to their nature as single-participant case studies, the third study suffers from control groups that do not represent standard treatments, and the significant confound that the BMI-FES treatment was more than twice as long in duration as the interventions that either of the control groups received. The question of whether the use of a BMI-based control scheme is truly beneficial to FES treatment therefore remains open.

While the neuroplastic effects of EMG-FES have been more frequently investigated, they are almost universally compared with non-FES conditions such as standard physiotherapy (16–20). As with BMI-FES, the effect of the control scheme on therapeutic outcomes is therefore currently uncertain.

It should be emphasized that the purpose of the BMI-FES and EMG-FES control strategies is not to explicitly synchronize each descending command with a single pulse of stimulation (as was done by Niazi et al. (15) and Mrachacz-Kersting et al. (21)). The purpose is merely to provide more consistent pairings between upper motor neurons and α motor neurons activity on a gross scale than are achievable through manual activation of FES. Imperfections in the control schemes will by necessity result in circumstances in which this pairing is not achieved.

Based on the limitations of the current literature, the present study sought to clarify the effects of the BMI- and EMG-based control of FES by applying both of these treatments, along with conventional FES, BMI-guided voluntary grasping, and fully voluntary grasping, in a sample of able-bodied participants. Because each participant needed to be exposed to all five treatment conditions, only short-term, transient effects of the treatments could be measured, primarily the MEP.

METHODS

All procedures were approved by the research ethics boards of the University of Toronto and the Toronto Rehabilitation Institute—University Health Network. All procedures were conducted in an electromagnetically shielded room (Raymond EMC, Ottawa, ON, Canada). Coordination between different devices was achieved using a computer with a data acquisition card (National Instruments, Austin, TX, USA) and custom-written LabView scripts.

Participants

In total, ten able-bodied participants completed all five sessions, six men and four women. Participants were 24–32 years of age (mean ± standard deviation: 28.4 ± 2.3). All participants self-identified as right-handed and performed all grasping practice with their left hands.

Interventions

Each session's intervention involved one hour of grasping and manipulating small wooden blocks in a self-directed manner. This task was chosen so as to mimic the motor tasks used in recent clinical trials of conventional FES therapy (22). The five different interventions dictated the manner in which grasping was performed and the devices used during the session, as represented in Figure 1 and outlined below. Sessions were separated by a minimum of three days in order to allow for washout of any effects of the interventions. Interventions were applied in a randomized order for each participant.

In the "voluntary" (VOL) condition, grasping was performed as normal, without assistance.

In the "FES only" condition, the participant was able to begin performing a grasp, but was asked to only complete it with the aid of FES. Self-adhesive electrodes (StimTrode ST5050, Axelgaard, Fallbrook, CA, USA), coated with a conductive gel (Spectra 360, Parker Laboratories, Fairfield, NJ, USA), and a stimulator (DJO Global, Surrey, United Kingdom) (23) were used to stimulate the following muscles: flexor carpi radialis, flexor digitorum superficialis, and flexor digitorum profundus (FCR/FDS/FDP), abductor pollicis brevis/flexor pollicis brevis (APB/FPB/OP), and extensor digitorum (for wrist/finger extension). Note that more specific muscles within the different muscle groups could not be isolated from each other because of their small size and close proximity. The observed effects of stimulation for the various muscle groups were wrist/finger flexion from FCR/FDS/FDP, thumb adduction from APB/FPB/OP, and wrist/finger extension from extensor digitorum. Stimulation pulses were charge-balanced biphasic and were applied at a frequency of 40 Hz. The pulse width increased from 0 to 250 μsec when stimulation was turned on and decreased back to 0 μsec when it was turned off. Stimulation amplitudes (i.e., currents) varied by session, participant, and muscle and were determined at the start of each session that used FES, in such a way as to provide functionally relevant contraction, to the extent that it was considered tolerable by the participants. The stimulation switched between three modes, beginning at rest (no stimulation). The press of a push button held by the experimenter then switched the stimulation into flexion mode, in which FCR/FDS/FDP and APB/FPB/OP were activated. A second press of the push button then switched the stimulation into extension mode, in which only extensor digitorum was activated. Extension mode switched automatically into rest mode after a duration of 3.5 sec. The experimenter attempted to provide stimulation

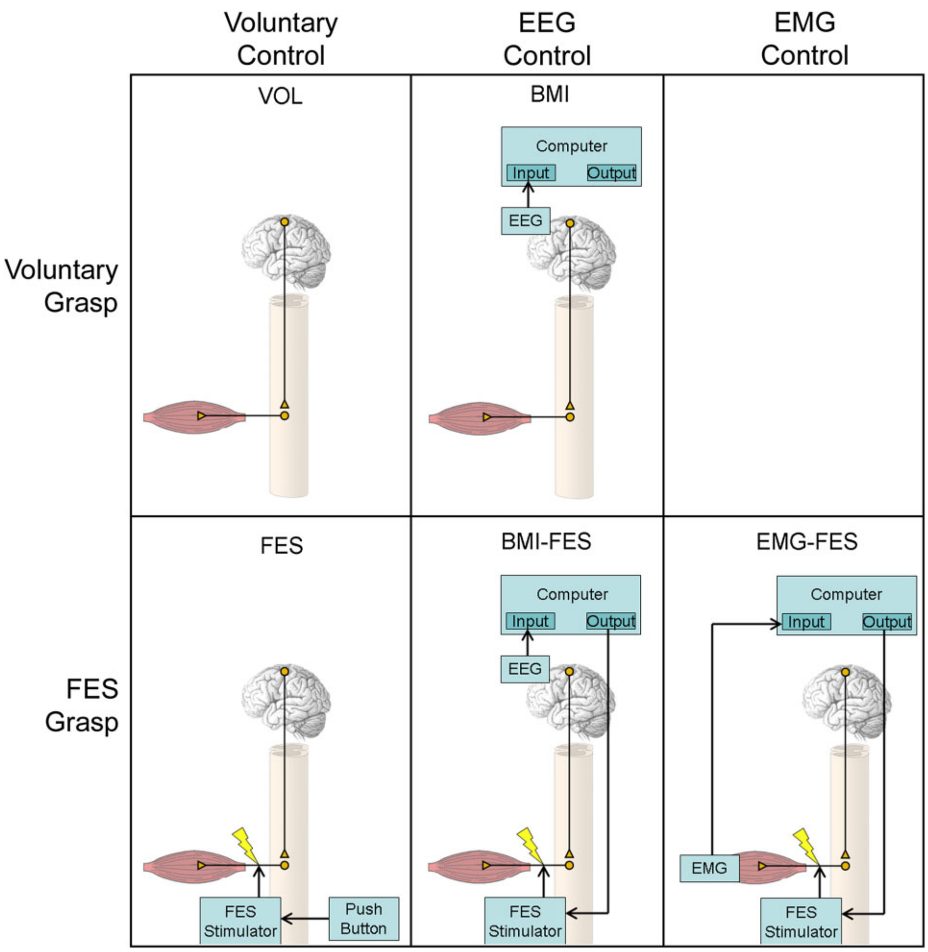

Figure 1. The five intervention groups used in this study. Vertical categories indicate the manner of grasp production, and horizontal categories indicate the strategy by which this grasping is controlled. Electromyogram (EMG) control with voluntary grasp was not investigated. Full descriptions are found in the Methods section. Each participant was tested with each of the five interventions, for one session each. BMI, brain-machine interface; EEG, electroencephalography; FES, functional electrical stimulation; VOL, voluntary.

in such a manner as to facilitate what they perceived as the participant's voluntary movements.

In the "BMI only" condition, the participant was able to initiate a grasp voluntarily, but only completed the full grasp when a noninvasive, electroencephalography (EEG)-based BMI predicted that they were attempting to perform a grasp. The EEG signal was bipolar, representing the potential difference between locations C2 and C6 on the 10–20 grid, and was amplified with a Grass IP511 AC amplifier (Astro-Med, Brossard, QC, Canada). This was intended to approximately represent the activity in hand-related areas of the right primary motor cortex. The BMI cued the user to grasp in response to a decrease in the bandpower of a specified frequency band across a manually set threshold. The bandpower used was individually determined for each participant based on an empirical calibration program. This program asked the user for two 10-sec EEG recordings—one while the user was at rest and the other while they were performing voluntary thumb adduction. The program then determined which BMI parameters (including frequency band) provided the most accurate classifications of various time windows within the recordings. The frequency bands thus employed were all 2 Hz in width and ranged from 10–12 Hz to 13–15 Hz.

In the BMI-FES condition, the participant was able to begin performing a grasp, but could only complete it with the aid of FES (as outlined above in the FES condition). The switch from rest mode to flexion mode FES was automatically activated when an EEG-based BMI predicted that they are attempting to perform a grasp, as described above for the BMI condition. The switch from flexion mode to extension mode was still controlled by a push button (because the stimulation introduced large artifacts into the EEG signal), and the switch from extension mode to rest mode was still automatically timed, as in the FES condition.

In the EMG-FES condition, the participant was able to begin performing a grasp, but could only complete it with the aid of FES, (as outlined above in the FES condition). The switch from rest mode to flexion mode FES was activated when bipolar EMG electrodes recording from APB/FPB/OP, amplified with a Bortec AMT-8 amplifier (Bortec Biomedical, Calgary, AB, Canada), detected this preliminary muscle activation. Activity was defined as detected when the difference between the maximum and minimum rectified EMG values within a 125 msec time window increased above a manually set threshold. The switch from flexion mode to extension mode was still controlled by a push button (because the stimulation introduced large artifacts into the EMG signal), and the switch from extension mode to rest mode was still automatically timed, as in the FES condition.

Assessments

All assessments were conducted immediately prior to and immediately following the one-hour intervention. Therefore, these assessments were not conducted during the recording of neurophysiological signals and did not interfere with recordings. All assessments except the BMI control test involved recording EMG activity from the APB/FPB/OP muscles in a bipolar configuration, as described in the outline of the EMG-FES intervention above.

MEP

MEP was elicited with a Medtronic MagPro R30 + M transcranial magnetic stimulator with a MagVenture MCF-B65 figure eight coil (Medtronic, Minneapolis, MN, USA). MEPs were evoked and recorded at a range of transcranial magnetic stimulation (TMS) intensities, each separated by 10% of the maximum stimulator output, with ten magnetic stimulations being applied at each intensity. The order in which the intensities were presented was kept constant, but followed a pre-generated pseudo-random pattern, so as to prevent hysteresis effects that can skew the response curve (24). The recorded EMG traces were later analyzed offline in accordance with the methods of Devanne et al. (25) and Knash et al. (26), in order to determine the following values: the maximum MEP amplitude, the TMS intensity that produced a half-maximal response (intended to detect a leftward shift in the response curve, indicating increased sensitivity), the approximated MEP amplitude at the TMS intensity that produced a half-maximal MEP prior to intervention, the MEP amplitude at the lowest TMS intensity to produce a mean response of at least 1 mV prior to intervention, and the MEP amplitude at the TMS intensity that most closely approximates 120% of the resting motor threshold.

Grip Force and Maximum Voluntary Contraction

Grip force was assessed by asking the participant to grip a hand dynamometer (Patterson Medical, Mississauga, ON, Canada) as strongly as they could, for 3 sec. The grip force for each repeat was taken to be the maximum force achieved. While the participant was gripping the dynamometer, EMG activity was being recorded from the APB/FPB/OP muscles. Maximum voluntary contraction (MVC) was determined by recording the mean rectified EMG signal for each repeat. Participants were asked to complete three repeats for each hand in each round of assessments. The means of these three repeats were derived for each hand, and the ratio between the left (treated) and right (untreated) sides was taken as the outcome measure of these assessments. This analysis process was the same for both MVC and grip force.

Matched Forces

This assessment was based on the method presented in Taylor and Martin (27). Its purpose was to measure changes in the input–output relationship of the spinal synapses on both sides of the body. Participants were asked to perform weak, ballistic, bilateral contractions of their APB/FPB/OP muscle, by adducting their thumb across their palm. Contractions were to be done every 5 sec in accordance with a color-coded cue signal. Visual feedback was presented to the participants in the form of a virtual dial. This dial represented the mean rectified APB/FPB/OP EMG activity in their untested side, with an upward position indicating 10% of the pre-intervention MVC. Participants were not informed that this feedback was only coming from their untested side. The purpose of this was to require participants to generate the same amount of descending voluntary drive from both sides of the body, both before and after the intervention. Any changes in the resulting EMG could therefore be taken as indicative of subcortical mechanisms, such as plasticity at the spinal synapse. Because the participants were asked not to correct their movements after the initial contraction, but rather to return immediately to a resting position, the involvement of sensory feedback was expected to be minimal. Following a brief practice, they were asked to complete 20 repetitions of the movement. From each EMG trace, the maximum rectified value was taken, and the mean ratio between the maximum values of the two sides was taken as the outcome measure.

BMI Control Test

In both treatment conditions in which the BMI was employed (BMI and BMI-FES), an additional test was conducted both before and after the intervention to test the user's level of volitional control over the BMI. In this test, the user was given textual cues that alternated between "Relaxed" and "Active" for two minutes. During the "Active" periods, subjects were asked to perform motor imagery pertaining to a grasping movement, while in the "Resting" periods, they were asked to remain relaxed. The program simultaneously analyzed the incoming EEG patterns, classifying them as "Resting" or "Active." Because equal time was devoted to both the "Relaxed" and "Active" cues, a classification accuracy of 50% would represent chance (no apparent volitional control of the BMI).

Statistics

Data from each outcome measure were first analyzed using a repeated-measures analysis of variance (ANOVA). A given outcome measure was considered to respond to the interventions in the repeated-measures ANOVA if the time *x* condition interaction term varied significantly ($p \leq 0.05$). The key reason why the interaction term was taken as the primary statistical measure is that it best addressed the question of whether or not the different treatments being applied differentially affected the pre- post-change in the outcome measures.

Following this, post hoc tests were applied. This consisted of an additional repeated-measures ANOVA for each pairing of treatment conditions, with the input data set narrowed down to only those results that came from one of the two treatment conditions in question. Again, the interaction term was taken as the primary statistical measure. Statistics were completed using the Statistics toolbox in MATLAB (MathWorks (Natick, MA, USA)).

RESULTS

The outcomes of all outcome measures except the BMI control test are summarized in Figures 2–4.

Pre- post-changes in the maximum MEP amplitude were found to vary across conditions ($p = 0.0320$) and to be greater in the BMI-FES condition than in the FES condition ($p = 0.0212$), greater in the EMG-FES condition than in the FES condition ($p = 0.0194$), and greater in the EMG-FES condition than in the BMI condition ($p = 0.0499$).

Pre- post-changes in the estimated MEP amplitude in response to a stimuli that produced a half-maximal response pre-intervention were found to vary across conditions ($p = 0.0436$) and to be significantly greater in the BMI-FES condition than in the VOL condition (p

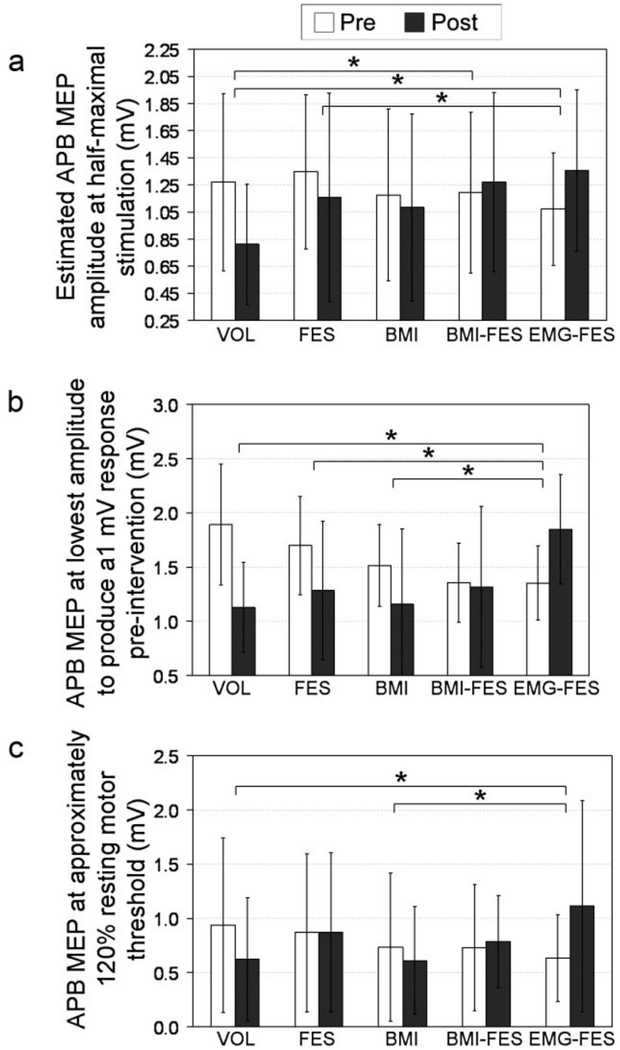

Figure 2. Summary of the motor-evoked potential (MEP) results in which the MEP amplitude was investigated at a given stimulation intensity, in each of the five treatment conditions: a. estimated MEP amplitude in response to a stimuli that produced a half-maximal response pre-intervention; b. MEP amplitude at the lowest TMS intensity to produce a mean response of at least 1 mV prior to intervention; and c. the MEP amplitude at the TMS intensity that most closely approximates 120% of the resting motor threshold. * indicates a significant difference between treatment conditions ($p \leq 0.05$). APB, abductor pollicis brevis; BMI, brain-machine interface; BMI-FES, brain-machine interface-controlled functional electrical stimulation; EMG-FES, electromyogram-controlled functional electrical stimulation; FES, functional electrical stimulation; VOL, voluntary.

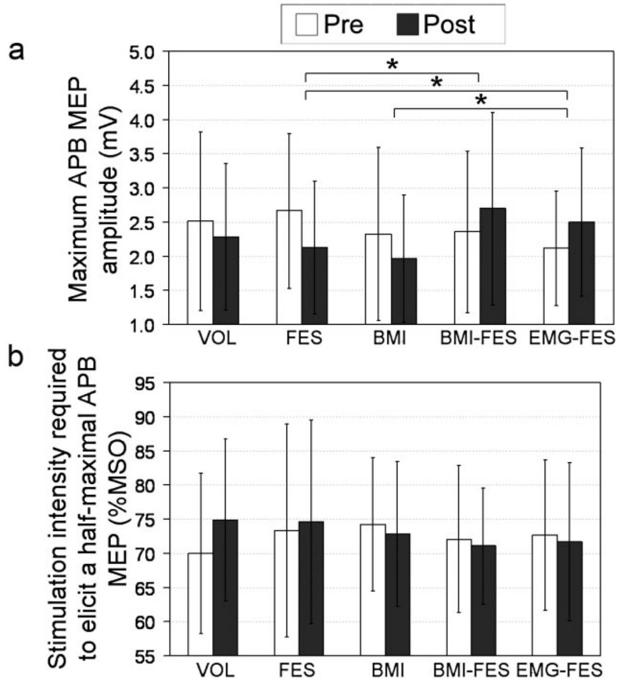

Figure 3. Summary of the additional motor-evoked potential (MEP) results: a. maximum MEP amplitude; and b. stimulation intensity that elicited a half-maximal contraction. * indicates a significant difference between treatment conditions ($p \leq 0.05$). APB, abductor pollicis brevis; BMI, brain-machine interface; BMI-FES, brain-machine interface-controlled functional electrical stimulation; EMG-FES, electromyogram-controlled functional electrical stimulation; FES, functional electrical stimulation; MSO, maximum stimulator output; VOL, voluntary.

= 0.0476). They also were found to be greater in the EMG-FES condition than in the VOL condition ($p = 0.0020$). Lastly, they were found to be greater in the EMG-FES condition as compared with the FES condition ($p = 0.0341$).

Pre- and post-changes in the MEP amplitude at the lowest TMS intensity to produce a mean response of at least 1 mV pre-intervention were found to vary across conditions ($p = 0.0097$) and to be greater in the EMG-FES condition as compared with the VOL ($p = 0.0042$), FES ($p = 0.0054$), and BMI ($p = 0.0285$) conditions. Note that these results have a slightly lower sample size than most other measures ($N = 8$ for VOL and BMI; $N = 9$ for FES, BMI-FES, and EMG-FES), as some participants had a maximum MEP of less than 1 mV in some conditions.

Pre- post-changes in the MEP amplitude at the MEP amplitude at the TMS intensity that most closely approximates 120% of the resting motor threshold were found to vary across conditions ($p = 0.0207$) and found to be greater in the EMG-FES condition as compared with both the VOL condition ($p = 0.0088$) and the BMI condition ($p = 0.0312$).

Initial ANOVAs failed to show significant variance in the pre-post-changes of the TMS intensity that elicited a half-maximal contraction ($p = 0.3301$), left–right ratio of APB/FPB/OP MVC ($p = 0.1330$), left–right ratio of grip force ($p = 0.9690$), or left–right ratio of muscle activity during the matched forces task ($p = 0.4215$). Despite this, pre- and post-changes in the left–right ratio of muscle activity during the matched forces task were found in post hoc tests to be greater in the VOL condition than in the FES condition ($p = 0.0226$).

The mean accuracy obtained during the BMI control test was 49.4 ± 1.9% (range: 43.5–58.1%), with 50% representing chance, suggesting a level of control that was approximately equal to random chance.

DISCUSSION

Summary of Results

Taken as a whole, the MEP-based results suggest that BMI-FES and particularly EMG-FES provide greater MEP upregulation than conventional FES or voluntary grasping. This did not hold true in the more functional outcome measures. Inconsistency in the MEP-based results arises from high variability in the outcome measures and the relatively small sample size.

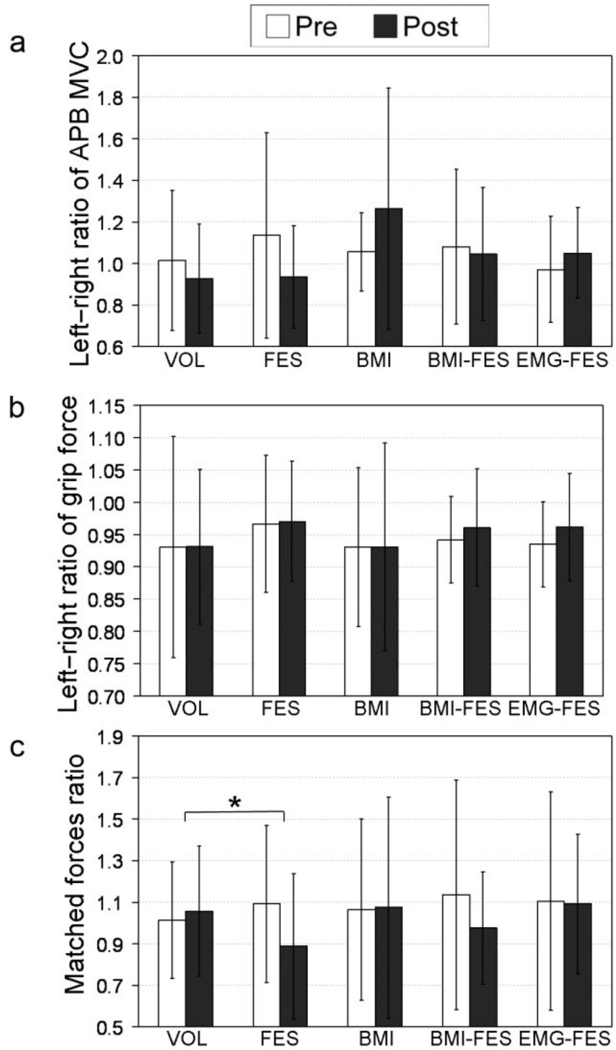

Figure 4. Summary of results for the non-motor-evoked potential (MEP)-based assessments in each of the five treatment conditions: a. ratio between left and right APB/FPB/OP MVCs; b. the ratio between left and right grip forces; and c. ratio between left and right muscle activity during the matched forces task. * indicates a significant difference between treatment conditions ($p \leq 0.05$). APB/FPB/OS, abductor pollicis brevis/flexor pollicis brevis; BMI, brain-machine interface; BMI-FES, brain-machine interface-controlled functional electrical stimulation; EMG-FES, electromyogram-controlled functional electrical stimulation; FES, functional electrical stimulation; MVC, maximum voluntary contraction; VOL, voluntary.

Surprisingly, conventional FES treatments were shown to downregulate the corticospinal tract in all MEP-based measures except that tested at 120% of motor threshold, a finding that contradicts a wealth of existing literature showing MEP upregulation after FES (3,26,28–30). The most likely reason for this is that participants were fatigued for the post-intervention measurements, but not for the pre-intervention measurements. Indeed, a distinct trend was noticed for both APB/FPB/OP MVCs and grip forces to be decreased in both arms following the intervention, regardless of treatment condition ($p \leq 0.0001$, based on paired-samples *t*-tests comparing pre- post-intervention values across all treatment groups). Because both arms were fatigued in approximately equal measure, it can be suggested that this fatigue was less likely due to the actual grasping practice and more likely due to excessive temperatures in the unventilated electromagnetically shielded room in which the experiments were conducted. With this confound in mind, the pre- post-ratio of MEP amplitudes indicating no neuroplasticity may in fact be lower than 1. In this scenario, conventional FES might still cause upregulation of the corticospinal tract, but BMI-FES and EMG-FES would cause even greater upregulation.

More functionally relevant measures, such as the left–right ratios of APB/FPB/OP MVC and grip force, were not visibly changed by any of the interventions, suggesting that while neuroplasticity may be induced, it may not be sufficient to create functional improvements in a single session in able-bodied individuals. This does not, however, rule out the possibility of such effects being observable in situations in which the treatments are applied more long term and/or situations involving individuals with SCI.

Barriers to Long-Term Clinical Application

While these initial results with able-bodied participants are promising, they do not guarantee that these treatments would work the same way in a clinical application. One barrier to this translation is the differences in neurophysiology between able-bodied individuals and those with SCI. The injury, even if incomplete, will likely decrease the amount of voluntary descending signal that reaches the synapse between upper motor neurons and α motor neurons. This may weaken the pairing between descending signals and antidromic signals from the FES, which may in turn weaken the effectiveness of FES-based therapies. This is especially of concern to BMI-FES, as a discrepancy may exist between the voluntary activity recorded at the primary motor cortex and that which reaches the spinal synapse. Evidence exists to both support and refute this concern. The concern is refuted by, as one example, studies in which FES is shown to facilitate functional recovery after SCI (2) (suggesting that even the diminished descending signal that reaches the spinal cord is still sufficient to induce some neuroplasticity). The concern is supported by studies in which a wide range of neuroplasticity-based treatments which show MEP upregulation in able-bodied participants fail to show upregulation in participants with neurological conditions (including chronic stroke, incomplete SCI, traumatic brain injury, multiple sclerosis, and familial spastic paraparesis) (30). This issue therefore remains open.

Another barrier to translation is the fact that the treatment, as applied in this study, is short term and produces transient effects, whereas clinical benefit would need to arise from repeated treatment having long-lasting effects. However, the suggestion that one does indicate the other is supported by the theoretical nature of the MEP, by the finding that MEP amplitude and grip strength are correlated in stroke patients (31) and by the repeated findings that treatments that transiently upregulate MEP, such as FES (29) and paired associative stimulation (32), can also cause long-term functional benefits (2,33).

A final barrier to clinical application may be simple pragmatic concerns. Physiotherapists or other practitioners may find the setup and monitoring of a BMI-FES or EMG-FES system burdensome, as compared with a conventional FES system, hampering adoption. Furthermore, the automated control schemes may not be suitable for all users. For example, an individual with extensive traumatic brain injury comorbid with their SCI may have difficulties operating a BMI-FES system. Likewise, an individual with severe rigid spasticity or a more extensive injury may not have the residual muscular control necessary to operate an EMG-FES system. Thus, even if BMI-FES and EMG-FES are able to provide better functional outcomes than conventional FES, some individuals may still find it necessary to use conventional FES instead.

Limitations of Switch-Based FES Paradigms

All three FES paradigms applied in this study can be described as "switch based"—that is, the stimulation switches between different modes in response to a trigger command, from resting to flexion, to extension, and returning to rest. By contrast, one can conceive of non-switch-based systems, which respond to command signals in a graded fashion (e.g., an EMG-FES system in which a greater level of contraction results in a greater level of stimulation). The "switch-based" approach was chosen for two reasons. The first is that previous studies that have shown functional benefits from FES have employed switch-based control, such as Popovic et al. (2). Because our primary purpose was to compare across the three FES conditions (thus elucidating the effect of the control strategy), using switch-based control allowed us to directly compare the novel treatments (BMI-FES and EMG-FES) to the current "gold standard" (FES). The second reason is that current from the FES travels along the user's skin, reaching the EEG or EMG electrodes and severely contaminating the signals. Although many approaches to removing stimulation artifacts are proposed in the literature (7–9,11,12) and successful BMI-FES and EMG-FES systems have been developed with a more graded, continuous control, such approaches were not found to be successful in the current implementation. A switch-based strategy was therefore a necessity in the current systems.

Unfortunately, switch-based control strategies, as implemented herein, are highly artificial and not ideal from the perspective of neuroplasticity induction, as they cause discrepancies between the user's volition and the stimulation. Despite this limitation, the results of the present study suggest that at least some level of positive neuroplasticity can be produced by switch-based BMI-FES and EMG-FES systems, leaving open the suggestion that more natural systems may be able to produce even greater effects.

Effect of Lack of Volitional BMI Control

Niazi et al. (15) found that the extent to which BMI-FES increased users' maximum MEP was correlated with the ratio of true-positive to false-positive predictions generated by their BMI. However, in our study, the use of the BMI to control FES was found to upregulate MEP amplitudes, despite the apparent lack of volitional control over the BMI. One explanation for this, based on neurophysiological theory, is that the connection between volitional control areas of the brain (mostly within the prefrontal cortex (34,35)) is not involved in the critical pathway (the corticospinal tract beginning in the primary motor cortex). The source of the cortical activity, whether it be in the prefrontal volitional areas or the somatosensory cortex or in subcortical areas such as the cerebellum or the basal ganglia, does not matter for the purposes of LTP induction, only that primary motor cortex activity detected by the BMI eventually reaches the spinal synapse. This result provides further evidence to support the clinical use of BMI-FES, as many noninvasive BMIs can require a training period of several months before considerable volitional control is obtained (36,37).

Effects of User Engagement

One factor not accounted for in the study design is participant engagement in the grasping training. The use of neurologically based control strategies may cause them to be more attentive to the grasping practice. This attentiveness could cause increased descending drive from the primary motor cortex, which could in turn enhance spinal plasticity. Attention has shown to be an essential part of other plasticity-inducing stimulation protocols, such as paired associative stimulation (38) and repetitive TMS (39). The suggestion that similar effects could be seen in FES protocols, while not specifically established in the literature, would be consistent with the finding that passive electrical stimulation did not induce as much neuroplasticity as electrical stimulation activated concurrently with voluntary activity (3). The attention-based explanation of the present findings therefore suggests that the BMI-FES and EMG-FES conditions have their enhanced neuroplastic effects because of increased descending drive, rather than a more consistent pairing of descending drive with antidromic firing.

In truth, the two hypotheses are not mutually exclusive, and both converge on the eventual explanation of neuroplasticity through synaptic LTP. While no participants self-reported a sense that their attention or engagement was different across condition, no direct empirical measure was employed, and these cannot be ruled out as confounding factors.

The practical ramification of this debate is that if attention and engagement are primarily responsible for the neuroplastic effects, then similar results should be achievable through simpler, lower cost modifications to FES training. A change in protocol as simple as reminding the participant to focus on the task at hand or conducting training sessions only when the participant is alert and unfatigued could hypothetically have the same effects. Elucidating whether or not this could be the case would, however, require an additional study, or at very least, additional treatment conditions added on to the present study.

CONCLUSION

The MEP-based results provide preliminary evidence to suggest that BMI-FES and EMG-FES are capable of inducing greater neuroplasticity than conventional FES or voluntary grasping in able-bodied individuals, although this is not accompanied by changes in grasping function following a single one-hour training session. The precise mechanism of these changes, however, remains speculative. Further investigation is recommended, in order to more thoroughly determine to what extent these effects are genuine, the mechanism behind these effects, and whether these novel control schemes can enhance FES-based treatments for individuals with incomplete SCI, and thereby enhance the recipients' grasping function and quality of life.

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Authorship Statement

Mr. McGie, Dr. Zariffa, and Dr. Popovic were all involved in document editing. Mr. McGie and Dr. Zariffa were both involved in study design and data collection. Mr. McGie was involved in the study concept, data analysis, and initial document writing. Dr. Popovic was involved in supervision and funding support. Dr. Nagai assisted statistical analysis. All authors approved the final manuscript.

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COMMENT

This is an interesting study demonstrating the value of EEG-BMI and/or EMG on modulating finger-grasp tasks in normal volunteers. The results provide some evidence that combining cortical detection of intended movements with functional electrical stimulation (FES) in upper extremity rehabilitation can improve not only the speed but performance of the task itself—attributed by the authors as neuroplasticity of cortical-spinal origin. Similarly, use of EMG signals detected in the limb being stimulated also appears to enhance grasping functions; and probably reflects a more "distal" control signal that can be enhanced through FES technology.

The clinical implication has value for rehabilitation strategies and neuromodulation devices involved with impaired upper extremity function. The authors make a good argument for considering development of an EEG-BMI or EMG guided FES rehabilitation device for improved hand and arm function in spinal cord injured individuals.

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Comments not included in the Early View version of this paper.

