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Brain-controlled muscle stimulation for the restoration of motor function

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Abstract

Loss of the ability to move, as a consequence of spinal cord injury or neuromuscular disorder, has devastating consequences for the paralyzed individual, and great economic consequences for society. Functional Electrical Stimulation (FES) offers one means to restore some mobility to these individuals, improving not only their autonomy, but potentially their general health and well-being as well. FES uses electrical stimulation to cause the paralyzed muscles to contract. Existing clinical systems require the stimulation to be preprogrammed, with the patient typically using residual voluntary movement of another body part to trigger and control the patterned stimulation. The rapid development of neural interfacing in the past decade offers the promise of dramatically improved control for these patients, potentially allowing continuous control of FES through signals recorded from motor cortex, as the patient attempts to control the paralyzed body part. While application of these 'Brain Machine Interfaces' (BMIs) has undergone dramatic development for control of computer cursors and even robotic limbs, their use as an interface for FES has been much more limited. In this review, we consider both FES and BMI technologies and discuss the prospect for combining the two to provide important new options for paralyzed individuals.

Keywords

Functional Electrical Stimulation; Spinal cord injury; Paralysis; Brain Machine Interface; Motor Cortex

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Introduction

Paralysis resulting from spinal cord injury (SCI), cortical lesion or neuromuscular disease is devastating, dramatically reducing the range of activities of daily living (ADL) and quality of life of patients. In addition to the direct effects, a number of secondary complications emerge as a result of disuse, such as muscle atrophy, contractures and pressure sores (Baldi et al., 1998; Ragnarsson, 2008). Among those patients with tetraplegia, the great majority identify the return of hand function as their most critical need (Anderson, 2004; French et al., 2010). Those patients with loss only of lower limb function list a number of different priorities. If the motoneurons remain intact after injury, muscles can still be made to contract through the application of electric currents to the nerve or neuromuscular junction, a procedure referred to as functional electrical stimulation (FES) (Peckham and Knutson, 2005; Ragnarsson, 2008). In the past several decades, important progress has been made using FES to assist or restore motor function in patients, enabling them to improve their gait (Daly et al., 2011; Granat et al., 1993; Thrasher et al., 2005), grasp objects (Alon and McBride, 2003; Peckham et al., 2001; Peckham et al., 1980; Popovic et al., 2002), and to augment bowel and bladder function (Gaunt and Prochazka, 2006). FES systems can be of great benefit to paralyzed patients, by providing an increase in autonomy through improvements in their activities of daily living.

A variety of control sources have been used to command FES. Foot drop correction can be controlled by a simple switch activated by sensors near the heel of the foot, by sensing acceleration or by signals recorded from the peroneal nerve (Pappas et al., 2001; Popovic et al., 1993; Rueterbories et al., 2010; Skelly and Chizeck, 2001; Tong and Granat, 1999; Williamson and Andrews, 2000). Likewise, switches can be used to activate pre-programmed stimulation patterns for grasp, and to initiate sit-to-stand movements (Gallien et al., 1995; Graupe et al., 1998; Graupe and Kohn, 1998). More finely-graded control can be achieved by joint angle sensors or measurement of residual muscle activity. However, these control modes are limited in bandwidth, and are initially unnatural and unintuitive for patients. Furthermore, with increasingly high level SCI, the patients have at once greater need for replaced function and fewer available control options.

The advances made in the field of brain-machine interfaces over the past 10 years provide the possibility to extract a user's own movement intent directly from the brain. The majority of these applications have been intended as communication interfaces through the control of a computer cursor (Carmena et al., 2003; Hochberg et al., 2006; Kennedy and Bakay, 1998; McFarland et al., 2010; Serruya et al., 2002; Taylor et al., 2002), or as a means to control a robotic limb (Chapin et al., 1999; Collinger et al., 2013; Hochberg et al., 2012; Velliste et al., 2008). Less often, similar methods have been used to provide voluntary control of paralyzed muscles (Ethier et al., 2012; Moritz et al., 2008; Nishimura et al., 2013; Pohlmeier et al., 2007a). Where robotic limbs may provide great functional benefits for amputees, restoring to spinal cord injured patients control of their own muscles, may provide an even greater impact on their overall physiological and psychological well-being (Nightingale et al., 2007; Ragnarsson, 2008). Moreover, there is evidence that the activation of paralyzed muscles, closely timed to the patient's intent, may contribute to greater

therapeutic effects than are typically achieved by standard therapy (Daly and Wolpaw, 2008; Popovic et al., 2011; Rushton, 2003).

Our review is divided into several sections, addressing current clinical uses of FES, the general techniques used to decode movement intent from the brain, and applications of these decoding methods to the restoration of motor function through FES.

FES Systems

Muscle activation by FES

FES can be beneficial for patients suffering from a wide range of motor deficits involving muscle paresis or paralysis, including spinal cord injury, stroke, multiple sclerosis, or cerebral palsy. In addition to the replacement of motor function that is its most obvious benefit, FES can have more general benefit as well. FES improves the contractile force of the remaining motor units to which the patient has voluntary access (Baldi et al., 1998; Powell et al., 1999), as would traditional muscular training. It also may improve the range of motion of the affected limb beyond that of passive physical therapy (Kraft et al., 1992; Pandyan et al., 1997), particularly for less severely affected patients (Powell et al., 1999; Sonde et al., 1998; von Lewinski et al., 2009). FES may also reduce spasticity and contractures, though this remains unclear (Alfieri, 2001; Malhotra et al., 2012). In addition, there are indirect effects that result from contracting paralyzed muscles: activation of the cardiopulmonary system, strengthening of bones, and relief of pressure sores. Finally, the neuronal activity generated by FES may lead to activity-dependent plastic changes in the nervous system. These effects can be difficult to evaluate in light of the changes in the periphery. However, FES has been shown to contribute to neurogenesis (Liu et al., 2013a), axonal growth (Al-Majed et al., 2004; Liu et al., 2013b), sensory neuron regeneration (Geremia et al., 2007), and to promote recovery of spinal reflexes (Knikou and Conway, 2005; Lynskey et al., 2008).

Popovic *et al.* listed three requirements that need to be fulfilled in order to include FES as a rehabilitation tool (Popovic et al., 2001). First, the muscles that are intended for FES need to be accessible for electrode placement. Surface electrodes have few contraindications aside from the pain they may cause if sensation is intact, but they cannot activate deeper muscles well. Percutaneous or implanted electrodes are more selective, but are more invasive and may not be indicated for some patients, particularly in the early stages after injury.

Second, there should not be a major degree of motoneuron or nerve root damage of the stimulated muscle. Intramuscular stimulation normally activates muscles indirectly, by first evoking action potentials in the nerve terminals. SCI patients often have some level of motoneuronal damage around the level of injury, which may restrict the use of FES for some muscles. Activation of denervated muscles is possible with much higher current, but is not very effective as a means to recruit muscles in a selective and functionally useful manner (Kern et al., 2002; Mayr et al., 2002).

Third, Popovic and colleagues noted that for FES to be useful, the voluntary function of the more proximal limb muscles must remain intact if the FES control of distal muscles relies on

voluntary control of proximal muscles. However, if FES can be controlled directly from the brain activity of paralyzed patients, it could provide beneficial effects even in the absence of more proximal muscle control. Brain-controlled FES could be particularly relevant for patients with higher-level spinal cord injury, who have fewer means of interacting with the external world.

In addition to the current need to use intact, residual muscle activation for control, FES remains limited by the means now available to activate muscles strongly and selectively. High-density grids of surface electrodes (Malešević et al., 2012) offer a means of achieving reasonable muscle selectivity but is not ideal for practical and cosmetic reasons. Implanting large numbers of intramuscular electrodes is effective, but requires extensive surgery. Multi-contact peripheral nerve stimulation is being investigated as a means to provide access to a large numbers of muscles with fewer implant sites (Badia et al., 2011; Brill et al., 2009; Normann et al., 2012; Rodriguez et al., 2000; Schiefer et al., 2010; Tyler et al., 2002). All of these methods induce greater than normal fatigue, because of their inability to reproduce normal motor unit recruitment order. Significant experimental work has also been done to investigate the use of stimulation within the spinal cord (Bamford and Mushahwar, 2011; Mushahwar et al., 2000; Tai et al., 2003; Zimmermann et al., 2011). Spinal stimulation has the potential advantage that motoneurons are recruited transsynaptically, in an order that approximates the normal small-to-large recruitment sequence. This may allow better force control and less fatigue. It may also be possible to activate useful whole-limb synergies with single contact stimulation. On the other hand, the ability to activate individual muscles selectively is quite limited with this approach.

Recently, optogenetic approaches have been tested as a means to provide more selective muscle activation. Opsins injected directly in the muscles can be transported retrogradely into the motoneuron axons through the neuromuscular junction (Towne et al., 2013). This technique has been used to activate single muscles in freely moving rats. In mice, orderly motor unit recruitment was achieved with optical stimulation (Llewellyn et al., 2010). By using opsins responding to different wavelengths (Prigge et al., 2012), it should be possible to activate multiple muscles independently. More studies will be required to evaluate the potential and safety of these techniques, but they could dramatically improve the effectiveness of FES. Such improvements would warrant even more, the potential improvements in control offered by a brain interface.

FES for lower limb function

FES has been used in various forms for over half a century. Foot drop, the failure to dorsiflex the ankle at the onset of swing, was the first and is probably the most widespread clinical FES application (Liberson et al., 1961). Properly timed stimulation of the peroneal nerve or the tibialis anterior muscle can provide a more effective gait and reduce the risk of injuries due to falls (see (Hansen et al., 2004; Lyons et al., 2002; Thrasher and Popovic, 2008) for reviews, and Figure 1A). There are several commercial systems available, including the WalkAide System (Innovative Neurotronics, Austin, TX), the Odstock O2CHS (Odstock Medical, Avon, MA) the ActiGait (ottobock), and the Bioness L300 (Bioness Inc., Valencia, CA).

FES for standing and transfer, despite the greater mechanical complexity, was first demonstrated in the 1960s, about the same time as for foot drop (Kantrowitz, 1960). In the 1980s, systems were introduced for paraplegic gait that used quadriceps stimulation for stance with initiation of the swing phase induced by activation of the withdrawal flexion reflex at the hip, knee and ankle through peroneal nerve stimulation (Bajd et al., 1983a; Kralj et al., 1980). Clinical systems available today, like the Parastep™ (Sigmedics, Inc., Fairborn, OH), use switches located on a walker, enabling user to activate sequences of muscle stimulation automatically.

Development work in laboratory animals to improve the effectiveness of FES has gone well beyond that currently available to human patients. Control of isometric ground reaction forces in a wide range of directions has been achieved in the rat, by stimulating as many as 11 different muscles (Jarc et al., 2013). Likewise, over-ground locomotion was produced in anesthetized cats using a hybrid CPG controller and extensive artificial sensory feedback to stimulate a large group of muscles (Mazurek et al., 2012). These results suggest that quite accurate control of the lower limb in patients may ultimately be possible.

FES for upper limb function

Despite the mechanical complexity of the hand, grasping an object, even a range of different objects, can be accomplished with quite stereotypic movements. This makes possible the use of the preprogrammed stimulus patterns in existing clinical FES systems. Three generations of implantable FES prostheses for grasp function have been developed at the Cleveland FES Center and tested in human SCI patients (Kilgore et al., 2009). The first (Smith et al., 1987) was implanted in a human volunteer in 1986 (Keith et al., 1989) and became known as the Freehand System® (NeuroControl Corp., Elyria, OH) (Peckham et al., 2001). The patient could select between two pre-programmed stimulation patterns providing either lateral pinch or palmar prehension (Kilgore et al., 1989), and used a shoulder mounted sensor to grade the grasp closure (Johnson and Peckham, 1990). Figure 1B illustrates the latest version of this device. Another hand grasp system, the NESS H200, is a hybrid orthosis-neuroprosthesis also controlled by residual EMG activity. It is now available with a wireless interface (IJzerman et al., 1996; Nathan, 1993).

These systems have had an important impact in the lives of hundreds of patients, by increasing their autonomy and improving quality of life (Peckham et al., 2001). However, their range of restored function falls far short of the dexterity of the hand of able-bodied individuals. Peckham and Kilgore have suggested that one of the main reasons is the limited control information currently available from patients (Peckham and Kilgore, 2013). This limitation is particularly evident in those patients with higher spinal cord injuries, who have at once greater need for replaced function, yet fewer muscles under voluntary control.

Decoding Motor Intent from the Brain

In the past decade, a new field of research has flourished, with the goal of using information decoded from cortical activity to allow patients with neuromuscular disorders to interact with the environment. Today, the techniques are often divided between non-invasive approaches based on EEG (Fig 2A), approaches based on implanted intracortical electrodes

(Fig 2B), and intermediate approaches using electrodes implanted either sub- or epidurally (Fig 2C).

There are a number of considerations related to the choice of recording interface. Multi-electrode Arrays (MEAs), by directly recording the activity of tens to hundreds of single neurons or small groups of neurons, provide the greatest spatial and temporal resolution and probably the highest information bandwidth among these technologies (Carmena et al., 2003; Collinger et al., 2013; Ethier et al., 2012; Gilja et al., 2012; Hatsopoulos et al., 2004; Santhanam et al., 2006; Velliste et al., 2008). These factors will be of critical importance when a high-dimensional control signal is required, as may be the case for a robotic prosthesis with many degrees of freedom, or the independent stimulation of a large number of muscles. On the other hand, MEAs require surgical implantation and, at least with current technology, a percutaneous connector that presents a path for infection. Local field potentials (LFPs) can also be acquired from MEAs, and may still provide substantial movement information (Flint et al., 2012b; Mehring et al., 2003; Scherberger et al., 2005; Wang et al., 2014; Zhuang et al., 2010).

The clearest line dividing these approaches is perhaps that of the need for surgery, however one might also divide between the use of field recordings and single neurons, the latter probably providing somewhat greater bandwidth for control. Critically, current intracortical recording technologies have the serious limitation that potentials from single neurons can rarely be recorded for longer than 2–3 years after implantation (Barrese et al., 2013; Judy, 2012; Prasad et al., 2012). There is good reason to believe that field potential recordings will be longer lasting, and despite their lower bandwidth, may offer a better alternative. In any case, the invasiveness of brain-recording technologies needs to be evaluated as a balance between risks and benefits (Millán and Carmena, 2010).

Scalp EEG as a brain interface

Scalp EEG recordings have the obvious advantage that they require no surgical procedures and pose little risk (Nicolas-Alonso and Gomez-Gil, 2012). In addition to this obvious benefit to patients, this also allows development work to be done with motor-intact subjects as well as patients. One common application of EEG signals is the detection of the P300, or ‘odd-ball’ response that is evoked when a person attends to the presentation of an infrequently occurring visual stimulus. A variety of systems using P300 have been developed as communication interfaces, typically to select letters or symbols from a grid (Lenhardt et al., 2008; Townsend et al., 2010). This method is fundamentally limited by the 300ms latency of the effect, and the fact that the salient stimuli must be presented relatively infrequently. Unlike more invasive approaches, systems using this technology are actually in use by a small number of patients in their own homes (Sellers et al., 2010b). As of 2008, a 51-year-old ventilator dependent man with advanced ALS had used the system as a computer interface for 2.5 years, and achieved stable performance of just under 20 bits/min. Using word prediction and other optimization schemes, these systems can support word processing at rates of around 2–4 words/min (Daly and Wolpaw, 2008).

Application of EEG signals to continuous cursor control has also been undertaken. EEG-based approaches typically require that the subjects learn to modulate the power in mu

and/or beta rhythms recorded over sensorimotor cortex, using motor imagery of hand or foot movements on one or both sides of the body (Bradberry et al., 2010; Daly and Wolpaw, 2008; McFarland et al., 2010; Yuan and He, 2014). One of the first neuroprosthetic devices to be tested in humans allowed intact subjects to move a computer cursor up and down based on EEG recordings (Wolpaw et al., 1991). Since that time, control has progressed to two (Wolpaw and McFarland, 2004), and even three dimensions (McFarland et al., 2010). Estimates of the amount of time required for naïve subjects to learn the necessary motor imagery vary widely, from several sessions weekly over 2–3 months (Kübler et al., 1999; McFarland, 2013) for single axis control, to a study that achieved shorter training times, ranging from 60 min for adequate one-dimensional control to ‘many hours’ for two- or three-dimensional control (Sellers et al., 2010a).

Continuous control of robotic limbs has not been accomplished with non-invasive brain recording techniques, but several studies have used classifiers or narrow-band power thresholds to control transitions between states, such as hand opening and closing, joint rotation, or discrete direction of motion (Bryan et al., 2011; Mueller-Putz et al., 2010; Muller-Putz and Pfurtscheller, 2008; Ubeda et al., 2012). The motor imagery used in these studies is typically chosen not for its similarity to the controlled movements, but for the separability of control states, and relative immunity to movement artifact and other noise sources. One has to assume that the use of imagined foot movement to control hand movement (Guger et al., 2003; McFarland et al., 2010) would impose as much or more cognitive burden on the patient than would the use of sensed residual proximal limb movement.

Field recording using electrode grids implanted on the surface of the brain

Electrocorticography (ECoG) offers another method to record field signals, by placing grids of electrodes under the skull, either on the dural surface, or directly on the pial surface of the cortex (Figure 2C). The surgery is somewhat less invasive than that of intracortical electrode arrays, but the major difference may be between those approaches that require the dura to be opened, and those that do not.

Being closer to the neurons than EEG electrodes, ECoG electrodes provide a larger, more robust signal that is less prone to movement artifact. ECoG or epidural recordings are used to detect epileptic foci in human patients (Berger et al., 1989; Goldring and Gregorie, 1984), and BMI research employing them in humans is secondary to the clinical needs. As a consequence, the location and type of electrodes, as well as the time and resources allowed for BMI testing is often suboptimal for a thorough evaluation of their capabilities. Time available for experiments is limited to a few hours any given day, and rarely continues longer than 1–2 weeks with any given patient. Nonetheless, it has been possible to predict both reach trajectory (Nakanishi et al., 2013; Schalk et al., 2008; Wang et al., 2013) and grip force (Flint et al., 2014) using this approach.

A significant amount of work has also been done with animal models. In these, as well as the work with human patients, it has been possible to classify brain activity into discrete states (Pistohl et al., 2012; Williams et al., 2013), make offline reconstructions of limb movement (Chao et al., 2010; Pistohl et al., 2008), grasp force (Chen et al., 2014), or

perform continuous control of cursor movement (Chen et al., 2013; Rouse and Moran, 2009). There is some evidence from studies using rather similar tasks, that subjects are able to learn to use control based on ECoG signals more quickly than EEG (Schalk et al., 2008; Wolpaw and McFarland, 2004). On the other hand, comparisons made to several primate studies using intracortical microelectrode arrays are difficult to judge, because of the greater complexity typical of the tasks in the primate studies (Carmena et al., 2003; Serruya et al., 2002; Taylor et al., 2002). At least one of the ECoG studies achieved offline reconstruction of 3D arm movement trajectories that were correlated to the actual movements nearly as well as those based on intracortical recordings. Although not tested online, the offline performance of the fixed decoders in that study was stable as long as 3–4 months (Chao et al., 2010).

Intracortical recording of neuronal action potentials

Intracortical electrodes can be used to record action potentials from single neurons, but in brain interface applications, they are increasingly being used to record the combined actual potentials from multiple neurons near the electrode tip (Chestek et al., 2011; Fraser et al., 2009; Stark and Abeles, 2007). Although a small number of human patients have now received intracortical implants of this type (Collinger et al., 2013; Hochberg et al., 2012; Kennedy and Bakay, 1998), unlike EEG interfaces, the method remains entirely experimental.

Using a combination of single and multi-units recorded from the arm area of the dorsal premotor cortex to classify the intended targets, two monkeys achieved an information transfer rate of 6 bits/sec (Santhanam et al., 2006), 10–20 times greater than the highest P300 rates cited above. However, most BMIs based on intracortical recordings use a ‘decoder’ that transforms neural discharge into continuously varying outputs rather than discrete classes. The earliest examples were of 1D control by rats (Wessberg et al., 2000) and a single human patient with ALS (Kennedy and Bakay, 1998) and 2D (Serruya et al., 2002) and 3D (Taylor et al., 2002) cursor control by monkey subjects. Since that time, advances in decoding strategies have led to dramatically improved cursor control, in some cases, nearly rivaling that of the human arm (Gilja et al., 2012). The current state of the art allows a paralyzed human patient to control 7 degrees of freedom of an anthropomorphic limb (Collinger et al., 2013). In those experiments, continuous 3D hand movements were achieved with a few hours of training, with full control accomplished in less than 4 months. It is important to note that changes to the control algorithms were implemented during the same time, that were intended to direct the patient’s behavioral adaptation.

The decoder is typically computed from neuronal signals recorded during actual limb movement, or the observation of movement. The essential approach is to compute a mapping (either linear or nonlinear) between the recorded neural activity and the actual or observed movement (Yu et al., 2007). This approach has its origin in early experimental work to establish the relation between movement and the activity of single neurons or groups of neurons in motor cortex. Although the earliest evidence was of the direct relation between M1 discharge and force (Evarts, 1968; Humphrey, 1972), later work revealed a simple relation to the direction of hand movement as well (Georgopoulos et al., 1982).

Currently, the great majority of brain interfaces under experimental development owe their fundamental design to the observations of Georgopoulos, in that they seek to extract from the brain, purely kinematic information about the direction of limb movement.

Brain-controlled FES strategies for replacement of function

Existing clinical FES systems rely on preprogrammed patterns of stimulation to control movement, in large part because there is currently no good way for patients to provide the wide bandwidth control signal that would be necessary to control movements continuously. However, work is being done to develop both feedforward (FF) and local feedback (FB) controllers to allow continuous control of muscle stimulation (Crago et al., 1996; Frankel et al., 2011; Jagodnik and van den Bogert, 2010; Mazurek et al., 2012; Pedrocchi et al., 2006; Sinkjaer et al., 2003; Watanabe and Fukushima, 2011). One approach, tested in simulation, used artificial neural networks trained from an inverse dynamics model of a simple six-muscle limb, using a minimum energy solution (Figure 3) (Blana et al., 2009; Praagman et al., 2006). Although the performance of the FB controller alone was nearly as good as FF +FB, the combined controller used significantly less muscle activation. Given the concerns about muscle fatigue, this is a critical consideration. The use of feedback derived from natural muscle receptors rather than mechanical transducers is a very appealing possibility that has recently been demonstrated in an awake cat model of locomotion (Bruns et al., 2013). Use of the FF controller alone did not provide adequate performance, even under these ideal simulated conditions. In practice, developing adequate models from patients, whose muscles are weakened, and produce time varying force, will be much more difficult.

A kinematic reference trajectory, as in these examples, would be well suited to a cortical interface. However, the use of purely kinematic control signals does not allow the user to adjust the impedance of the limb, its stiffness and damping, a mechanism of considerable importance during normal limb movement (Burdet et al., 2001; Hogan, 1984; Mah, 2001; Perreault et al., 2004). Furthermore, when we reach and grasp objects, we control much more than the position of our hand and fingers in space (i.e., movement kinematics). We can exert precise amounts of force on grasped objects, or generate large forces to manipulate heavy tools. Inverse models for FES control have been developed from isometric endpoint force to muscle activity that in principle could be used to control interaction forces (Scheerer et al., 2014).

Muscle activity and forces are well represented in primary motor cortex (Boline and Ashe, 2005; Capaday et al., 2013; Cheney and Fetz, 1980; Evarts, 1968; Hepp-Reymond et al., 1978; Holdefer and Miller, 2002; Humphrey et al., 1970; Kalaska et al., 1989; Smith et al., 1975), and can be predicted from M1 with the same methods used to predict movement kinematics (Carmena et al., 2003; Fagg et al., 2009; Humphrey et al., 1970). In practice, combining high-level control of motion as well as interaction forces will add considerable challenge, including the need to decode an appropriate control signal from the brain. One possible approach would be to use a decoder that switches control states as has been done in other contexts (Ethier et al., 2011; Wu et al., 2004; Yu et al., 2007).

An alternate approach would be to predict patterns of muscle activity, and use them with minimal modification, to control stimulation of the corresponding muscles. This approach would essentially replace the inverse dynamics and feedback controllers from the FES control system with dynamics information directly from the motor cortex. This should allow the patient full control of movement dynamics, interaction forces, and the resultant movement in an approximately normal manner. Although it has yet to be tested directly, it is a reasonable assumption that users would adapt more quickly to a BMI that controls dynamics like those normally represented by the signals within M1, than one having unnatural dynamics (Bensmaia and Miller, 2014). Several groups have demonstrated the feasibility of using intracortical activity to predict EMG for proximal arm and hand (Carmenta et al., 2003; Dong et al., 2008; Oby et al., 2010; Pohlmeier et al., 2007b) as well as leg (Hang et al., 2010) muscles. Remarkably, the accuracy of these predictions can be as good as or better than that of movement kinematics (see, for example, Fig 4). The limited information rate of EEG is not sufficient to predict EMG, but both intracortical LFP (Flint et al., 2012a) and electrocorticograms recorded from the surface of cortex (Shin et al., 2012) have been used successfully. Furthermore, we have shown for both reaching (Cherian et al., 2011) and wrist movements (Oby et al., 2013), that the mapping from M1 discharge to muscle activity remains more stable across altered posture and external dynamics, than does the corresponding mapping to movement kinematics. If prediction of muscle activity can provide control signals that are easy to learn, are robust across postural conditions, and provide direct control of limb dynamics, it is an approach that should be considered seriously along side the much more common kinematic interface.

Brain-Controlled Muscle Stimulation for the Replacement of Function

Restoration of grasping

Patients with high-level SCI, ranked restoration of grasp function above all other considerations combined (Anderson, 2004; French et al., 2010). These patients were willing to undergo surgical procedures to achieve this benefit, and to endure two to three months of reduced independence in the process. The opportunity for exercise was also important to the majority of respondents, including those with lower level injury. FES offers a means to these ends. While exercise might well be achieved with existing FES control sources, a higher-dimensional control signal than is currently available will be necessary for more dexterous grasping.

Some effort has been made to use EEG as a control signal for grasp FES, typically requiring the patient to learn to modulate beta power to control state transitions (Lauer et al., 1999; Pfurtscheller et al., 2003). However, it is very unlikely that EEG could provide continuous control for more dexterous movements. In 2007, our group pioneered the use of EMG predictions made from many spike signals recorded from a multi-electrode array chronically implanted in M1, to control the activation of wrist flexor muscles during nerve block at the elbow (Pohlmeier et al., 2007a). We used a Wiener cascade decoder (Westwick et al., 2006) trained using neural and EMG signals measured prior to the onset of paralysis. We mapped the real-time EMG predictions directly to stimulation pulse width whenever the predicted signal exceeded a noise threshold. We recently extended these results, moving from simple

isometric force to a functional grasp task designed to mimic the box and blocks test of manual dexterity (Ethier et al., 2012). We controlled stimulation of as many as five electrodes in wrist and finger flexor muscles paralyzed by nerve block. The system allowed monkeys to pick up and move weighted rubber balls, which was otherwise impossible during the nerve block. We tested one monkey's ability to compensate voluntarily for FES-induced muscle fatigue during a second task that required accurate force regulation. Neural activity revealed that the monkey simply 'tried harder', increasing M1 activation to generate greater EMG predictions and stronger stimuli as muscles fatigued. We anticipate this flexibility to adjust the strength and pattern of stimulation to be a major advantage of brain signals used for FES control.

Rather than using predictions of muscle activity derived from large groups of neurons, Moritz et al. operantly conditioned monkeys to modulate one or two single neurons, the activity of which caused activation of individual wrist muscles using FES (Moritz et al., 2008). The monkeys learned to control isometric wrist force even when the recorded neuron was initially unrelated to wrist force during normal movement. Control based on such a small number of neurons is unlikely to be practical, but operant conditioning methods combined with larger numbers of recorded neurons may have real promise. More recently, the same group used LFP to control spinal stimulation and wrist flexion force in a monkey that was paralyzed by a spinal cord hemisection (Nishimura et al., 2013). Control in this case was much like that of the EEG studies reviewed above, with a fixed stimulus train delivered whenever high-gamma band LFP crossed a threshold. As such, these studies represent important proofs of concept, but did not provide a clear functional improvement over existing non-invasive neural recording techniques

The activity of the forearm muscles can be highly correlated during grasping. Consequently, many simple grasp tasks can be accomplished with a low-dimensional control signal, despite the mechanical complexity of the hand (Santello et al., 1998). However, to make use of the full flexibility of the hand in manipulating objects, a much higher-dimensional control signal will be needed (Todorov and Ghahramani, 2004). It is reasonable to expect that intracortical recordings have the greatest potential to meet that requirement. However, a systematic evaluation of the information rate achievable with these methods, and the number of degrees of freedom controllable through FES has not yet been performed. Studies addressing their full potential will be very important, and will provide the basis to evaluate the relative risks and benefits associated with the more invasive approach.

Restoration of lower limb function

Those patients with paraplegia desired primarily the return of sexual function, although this group had a much more even mix of secondary motor priorities, including bladder and bowel function, trunk stability, and walking (French et al., 2010). There has not been as much research on EEG-based BMIs for the lower limb as there has been for grasp. Studies have classified brain activity into two or more movement states that have been used to control fixed patterns of stimulation (Duvina et al., 2012; King et al., 2013; Pfurtscheller et al., 2006). Similarly, EEG has been considered as a means to correct foot drop. While seated, both able-bodied subjects and a single stroke patient could modulate between

“idling” or “dorsiflexion” states, although with delays ranging from 1 to 3 seconds (Do et al., 2011; Do et al., 2012). Applied to walking, it is not clear that this approach would have a functional advantage over the much simpler use of peripheral sensors or control switches mounted on a walker (Bajd et al., 1983b; Isakov and Mizrahi, 1993; Kobetic et al., 1997). If this type of interface were to be used to control a system such as the Parastep, it would have to be operated within a safe and controlled environment, as delays and errors would prevent users from reacting quickly enough to prevent falls when facing unexpected obstacles. This could potentially include a rehabilitation program under expert supervision.

Rodents, including rats, are widely used in studies of spinal cord injury and regeneration (David and Aguayo, 1981; Oudega and Hagg, 1999). They have also been used, though to a lesser extent, in BMI-related research, which offers the opportunity to make use of well-established spinal cord injury models (Borton et al., 2014). Recordings from the hindlimb cortical area of intact rats have been used to predict the phasing or force of the rat’s limb movements (Knudsen et al., 2012; Zhou et al., 2010). Similar recordings from spinal cord injured rats have been used in real-time, to replace lever pressing (Manohar et al., 2012) or control pelvic support force supplied through a robot (Song and Giszter, 2011). An interesting alternate approach used forelimb EMG recorded from muscles above the injury to trigger spinal epidural stimulation to facilitate stepping of the hind limbs (Gad et al., 2012). The information rate of this control is quite slow compared to that of intact monkey reaching experiments. There are numerous factors that may account for this difference, including the relatively small number of recorded neurons, the effect of the injury, and the more prominent role of the spinal cord during gait. All are likely to have contributed, though it should be noted that accurate reconstructions of leg kinematics during locomotion have been achieved using intracortical recordings from monkeys (Fitzsimmons et al., 2009; Foster et al., 2011).

Remaining challenges for brain-controlled FES

The direct decoding of muscle activity from M1 has many potential advantages for the control of FES, particularly, in patients with high-level injury and little residual voluntary function. However, it also poses a number of unique challenges. Chief among them is the question of how such a decoder could be implemented in paralyzed human patients. Increasingly, as BMI technology moves closer to the clinic, different groups have explored the use of ‘observation based’ decoders. While a paralyzed individual cannot generate actual movement, they can attempt to move, or imagine making a particular movement. Decoders have been computed based on the discharge recorded while a BMI user observes the movement of a cursor (Hochberg et al., 2006; Wahnoun et al., 2006). These decoders are typically subjected to subsequent adaptation based on errors in their initial use. Neither approach is immediately applicable to an EMG decoder, for which there is no explicit trajectory to observe, nor error to measure.

Nonetheless, we have begun to explore the approach illustrated in figure 5. Here, an optimal set of EMGs is obtained, based on a cost function that includes knowledge of musculoskeletal mechanics, a measured force error, and minimization of overall muscle activity. This optimal pattern could be compared to the current prediction and used to update

weights in the neural to EMG decoder. Initial weights might be set randomly, or computed, as for an observation decoder, using knowledge of the EMG patterns typical of several simple motor behaviors.

The approach is challenging on a number of fronts, including the posture-dependence of the mapping from EMG to force, and the fact that the inverse mapping from force to EMG is underdetermined. It will certainly be necessary to learn a set of decoder weights across a range of postures and musculoskeletal mappings. However, given our evidence that the M1 to EMG mapping remains largely fixed as posture changes (Cherian et al., 2011; Morrow et al., 2007; Oby et al., 2013), there is reason to believe that a single decoder could be effective across a wide range of contexts.

Conclusions

FES has been used for several decades to palliate the debilitating consequences of brain or spinal cord injuries that result in the loss of voluntary motor control. Despite the success of this approach, the full potential of FES may yet be unrealized. The advances in brain recording technologies and in the development of brain-machine interfaces enable a new source of control for FES, which could prove to be literally life changing, particularly if paralleled by further improvements in muscle stimulation technology.

The control signals required to restore complex voluntary motor function through FES will require a high information bandwidth, making invasive techniques a more promising approach. However, further improvements in brain recording technologies, including long-term reliability, will be required to open the door to eventual clinical applications. Wireless and fully implantable recording technology will be required to make the technique more practical and cosmetically acceptable. Along with the potential advantages, decoder development for FES presents a number of challenges not present for kinematic decoders. FES technology itself is also improving, with the development of high-channel count devices for selective muscle recruitment from nerve stimulation, as well as new approaches to spinal cord stimulation. Optogenetic stimulation, despite its novelty, has real potential to improve our ability to activate paralyzed muscles more reliably. With continued improvement, there is a promising future for brain-controlled FES, providing paralyzed patients the means to regain control over their own body, and significantly increase their autonomy and quality of life.

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Highlights

Functional Electrical Stimulation (FES) restores motor function following paralysis

FES control signals are currently limited to patients' residual movements

Brain Machine Interfaces (BMIs) may offer more natural, dexterous control of FES

Figure 1.

Example of FES systems developed for human clinical use. A) The Bioness L300 uses a pressure sensor located in the insole of the shoe to sense heel-strike and lift-off. it communicates wirelessly with a cuff at the knee, positioned to deliver appropriate neuromuscular stimulation, causing ankle dorsiflexion. Figure courtesy Bioness, Inc. B) The Networked Neural Prosthesis System (NNPS) is based on a network of implanted modules distributed throughout the body, each dedicated to a specific sensing or stimulus function. Modules are linked to a centralized power source via a network cable through which they communicate. The NNPS can be used for upper or lower limb function. Figure courtesy of the Cleveland Functional Electrical Stimulation (FES) Center.

Figure 2.

Interfaces for recording neural signals from the cerebral cortex. A) 128 channel active EEG electrode system with electrodes held in pre-defined positions; g.tec medical engineering GmbH, Austria. B) inset: 100-electrode, 'Cereport' array allows intracortical single cell and LFP recording (Blackrock Microsystems, Salt Lake City, UT). Two arrays implanted in M1 and S1 in a monkey. C) ECoG electrodes used for monitoring and localization of epileptic foci during operative procedure. Adapted from (Roland et al., 2013).

Figure 3.

Combined feedforward (FF) and feedback (FB) FES controller. The FF controller allows for reduced levels of stimulation, but is not sufficiently accurate without FB control. The reference trajectory might be obtained from neural recordings using the same methods that are used to allow control movement of a cursor or robotic limb. From (Blana et al., 2009).

Figure 4.

Grasp-related raw data collected during normal conditions. A) Firing rates of 104 neuronal signals recorded during two grasps. B) Actual and predicted EMG during the same period as (A), including the finger muscles, extensor digitorum communis (EDC) and flexor digitorum superficialis (FDS), and wrist muscles, flexor carpi radialis (FCR) and extensor carpi radialis (ECR). Predicted EMG was computed using decoders trained from data collected earlier in the session. Vertical dashed lines mark the time of ball contact. Adapted from Figure 2 of (Ethier et al., 2012).

Figure 5.

Block diagram of an adaptive EMG decoder that can learn without an explicit motor error. EMG optimization and decoder adaptation would likely be feasible only during a series of simple, perhaps isometric motor behaviors. Generalization of the resulting decoder from these to more complex behaviors would be critical.