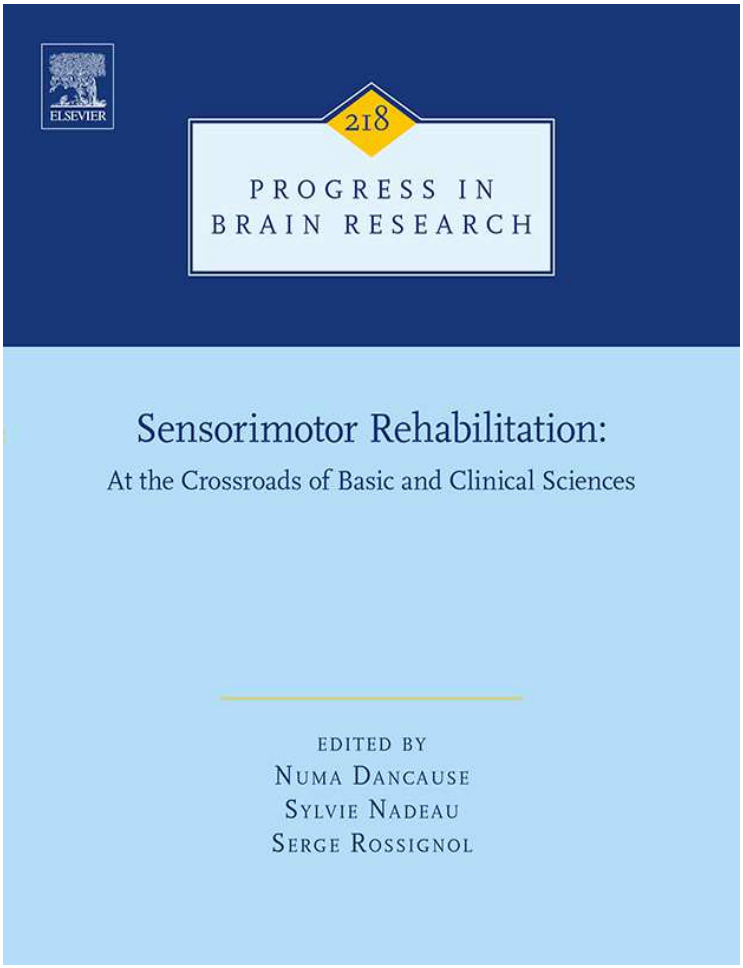

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CHAPTER

Restoring motor function with bidirectional neural interfaces

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Abstract

Closed-loop brain–computer interfaces have bidirectional connections that allow activity-dependent stimulation of the brain, spinal cord, or muscles. Such bidirectional brain–computer interfaces (BBCI) have three major applications that can be used to restore lost motor function. First, the brain could learn to incorporate a long-term artificial recurrent connection into normal behavior, exploiting the brain's ability to adapt to consistent sensorimotor conditions. The obvious clinical application for restoring motor function is to use an artificial recurrent connection to bridge a lost biological connection. Second, activity-dependent stimulation can generate synaptic plasticity on the cellular level. The corresponding clinical application is to strengthen weakened neural connections, such as occur in stroke. A third application involves delivery of activity-dependent deep brain stimulation at subcortical reward sites, which can operantly reinforce the activity that generates the stimulation. The BBCI paradigm has numerous specific applications, depending on the source of the signals and the stimulated targets.

Keywords

brain–computer interface, closed loop, bidirectional, plasticity, activity-dependent stimulation

1 INTRODUCTION

Closed-loop brain–computer interfaces offer a promising new modality for restoring motor function (Edwardson et al., 2012). By delivering activity-dependent stimulation continuously during free behavior, bidirectional brain–computer interfaces (BBCI) can create artificial recurrent connections that can bridge lost biological connections. Conventional brain–machine interfaces have already demonstrated that brain signals can be tapped to directly activate external devices (Carmena et al., 2003; Hochberg et al., 2012; Nicolelis, 2003; Santhanam et al., 2006; Velliste et al., 2008). But the consequences of long-term BBCI are just beginning to be

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explored. This chapter reviews some recent experiments involving direct connections between brains and computers implemented by bidirectional interfaces.

In general, there are three major applications for BBCIs. First, the brain could learn to incorporate a long-term artificial recurrent connection into normal behavior, thanks to the brain's remarkable ability to adapt to consistent sensorimotor conditions. In clinical treatment of motor impairment due to lost biological connections, an artificial recurrent connection could reconnect the separated sites. A second type of application is to use activity-dependent stimulation to generate synaptic plasticity on the cellular level. This has clinical applications in strengthening weakened neural connections, such as occur in stroke or spinal cord injury. A third type of application involves delivery of activity-dependent stimulation at subcortical sites to operantly condition the activity that generates the reinforcement or to implement activity-dependent deep brain stimulation (DBS). This chapter summarizes initial efforts to investigate these three applications in nonhuman primates with a BBCI called neurochip (Zanos et al., 2011), as well as related experiments.

2 BRIDGING LOST CONNECTIONS

The ability to bridge a lost connection with a BBCI was demonstrated in studies in which monkeys controlled functional electrical stimulation (FES) of paralyzed muscles with cortical neurons (Moritz et al., 2008; Pohlmeyer et al., 2009). In one study, the monkeys first generated normal wrist torques to drive a cursor to a target (Fig. 1). After the nerves were blocked with anesthetic and the muscles became paralyzed, the cursor was driven by neural activity and the monkey quickly learned to control the cursor position with appropriate changes in cortical cell activity. Then, the neural activity was converted to proportional stimulation of the paralyzed muscles, allowing the monkeys to perform the task with electrically evoked wrist torques to acquire the targets. Significantly, the recorded neurons did not initially need to be related to wrist movement, as long as the monkey learned to volitionally control the neural activity through an operant conditioning stage. Thus, this paradigm expands the potential sources of command signals to any cells that can be volitionally controlled. This includes virtually any cell in motor cortical areas, as well as cells in traditional association and sensory areas that receive top-down signals (Fetz, 2007). An alternate strategy involves decoding the activity of multiple motor cortical neurons and recoding the spatiotemporal patterns of stimulation of multiple muscles (Pohlmeyer et al., 2009). The latter strategy involves searching for the appropriate cortical neurons, whose relation to movement is considered fixed. A rationale for this approach is that it could require less of a cognitive load than implementing direct connections. However, there is ample evidence that given relatively little time the brain can rapidly learn to adapt to new contingencies of motor control of populations of cortical neurons (Ganguly and Carmena, 2009) or forearm muscles (Radhakrishnan et al., 2008).

FES of muscles via peripheral nerves has limitations in that motor units are generally recruited unnaturally, in order of large fatiguing units to small nonfatiguing

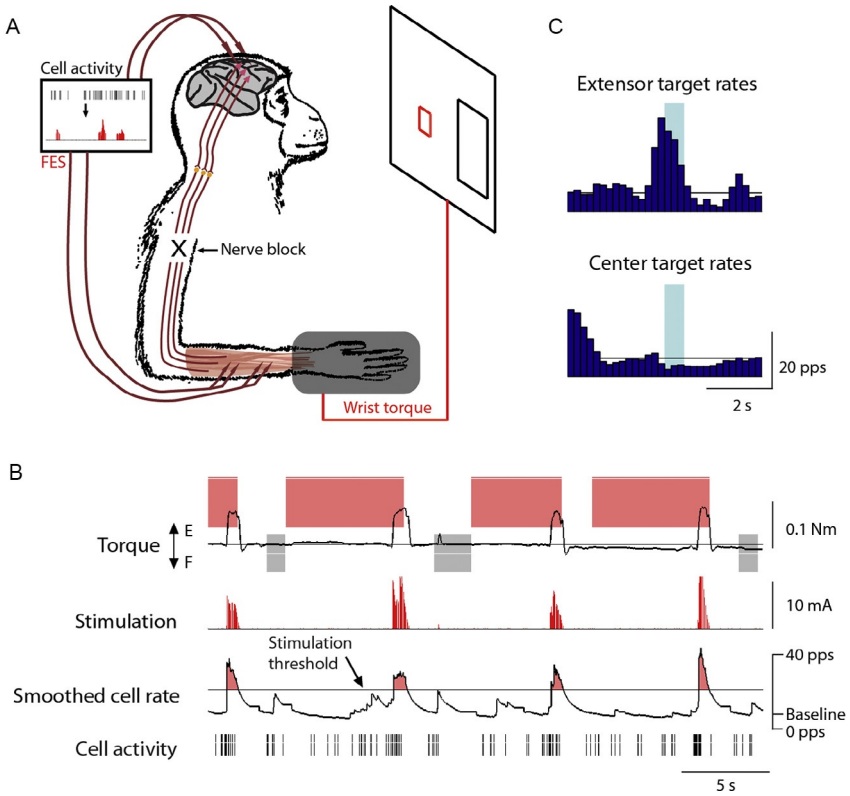

FIGURE 1

Brain-controlled functional electrical stimulation (FES) of muscle. (A) Schematic shows cortical cell activity converted to FES during peripheral nerve block. (B) Example of motor cortex cell activity controlling FES of paralyzed wrist extensors. Wrist torque targets for extension (red shading; dark gray color in the print version) and center hold (gray shading) were randomly presented. Monkeys learned to modulate smoothed cell rate to control proportional muscle stimulation. In this case, FES was delivered to muscles EDC and ED4-5 at 50/s, with current proportional to cell rate above a stimulation threshold. Pps indicates pulses per second. (C) Histograms of cell rates while acquiring the extensor and center targets, illustrating cell activity used to control FES. Shading indicates target hold period and horizontal line denotes baseline cell rate.

From Moritz et al. (2008).

units. Direct FES also presents a challenge in achieving fine control of synergistic activation of multiple muscles. A promising alternative is to stimulate in the spinal cord, where electrical stimulation typically recruits multiple synergistic muscles and activates motor units in their natural recruitment order (Moritz et al., 2007; Mushahwar et al., 2004; Zimmermann and Jackson, 2014; Zimmermann et al., 2011).

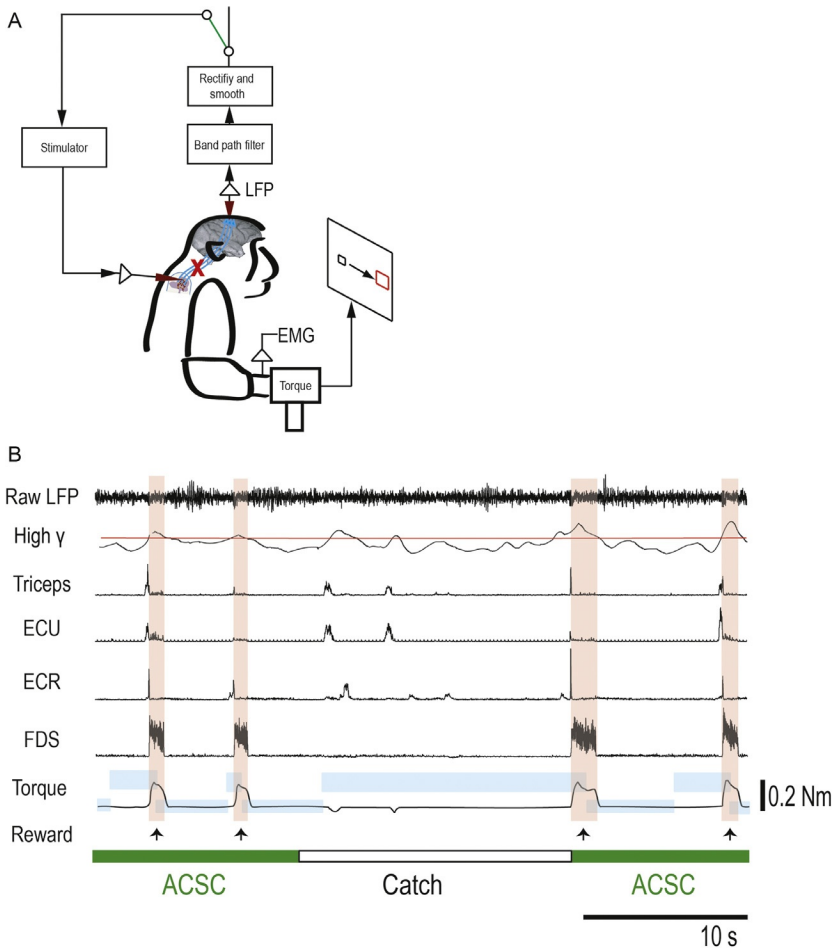

FIGURE 2

Brain-controlled intraspinal stimulation below a spinal lesion. (A) Schematic shows local field potential (LFP) in motor cortex gating trains of electrical stimulation (300 Hz) to a spinal site below the lesion (at X). The switch in the recurrent loop was opened for catch trials. (B) Four successful trials with the artificial corticospinal connection (ACSC, green; dark gray color in the print version) and one catch trial (white). During the catch trial, the monkey made several unsuccessful attempts to produce wrist torque, as seen in the EMG and gamma bursts. The blue rectangles (light gray color in the print version) indicate duration and force range of target. The pink vertical bars (gray color in the print version) indicate duration of electrical stimulation in the spinal site. The horizontal line in second trace represents the threshold for spinal stimulation. From top, raw LFP in motor cortex, rectified and smoothed high-gamma LFP (90–160 Hz), EMG from four muscles, and wrist torque. Arrows indicate times of successful task completion and reward.

From Nishimura et al. (2013b).

A case study of a monkey that had become paretic due to spinal cord injury (Nishimura et al., 2013b) demonstrated that the monkey learned to acquire targets by gating intraspinal stimulation through volitional increases in the gamma power of cortical field potentials (Fig. 2). This study also showed that the activity of the paretic muscle could be boosted by triggering spinal stimulation from EMG of the muscle via a positive feedback loop.

Berger and colleagues have proposed that lost neural circuitry could be replaced with VLSI models of the missing neural networks (Berger and Glanzmann, 2005; Berger et al., 2012). In this scenario, the VLSI circuitry receives spatiotemporal spiking patterns of multiple input neurons and delivers spatiotemporal patterns of stimuli to the downstream neurons. The application of this "cognitive prosthesis" in rat hippocampus has been reported to restore performance in a delayed nonmatch to sample task (Berger et al., 2012). A very similar paradigm applied in prefrontal cortex has been reported to restore memory functions (Hampson et al., 2012).

A BBCI prosthesis has also been applied in rats with motor cortex lesions that impaired reaching and grasping behavior (Guggenmos et al., 2013). The device detected action potentials in premotor cortex and delivered stimuli in sensory cortex. After 1 week, the spike-triggered stimulation produced improvements in reaching and grasping behaviors, and after 2 weeks of reaching performance approached prelesion rates. Noncontingent stimulation also improved performance, but not as much as activity-dependent stimulation, confirming the greater efficacy of closed-loop operation.

3 STRENGTHENING WEAK SYNAPTIC CONNECTIONS

The second application of BBCIs is inducing Hebbian plasticity through spike-triggered stimulation delivered at a synaptically connected site. This was first demonstrated when action potentials recorded at one motor cortex site (called Nrec) triggered stimuli at an adjacent site (called Nstim) (Jackson et al., 2006). The motor outputs from both sites were identified by the torques about the wrist evoked by trains of intracortical microstimulation, with the monkey seated passively with his wrist in a torque transducer (Fig. 3). In some cases, the EMG responses evoked in forearm muscles were documented as well. After identifying these outputs, the cell spikes were converted to stimuli delivered at fixed delays, as the monkey moved freely about the cage or slept. After about 24 h of such conditioning with short delays, the outputs evoked by microstimulation from the recorded site, Nrec, had changed to include the output previously obtained only from Nstim. These changes were obtained only when the delay between spikes and stimuli during conditioning were less than about 50 ms, consistent with the effective window for spike-timing-dependent plasticity (STDP). No conditioning occurred with longer delays, or for effects evoked from control sites, indicating that stimulation alone was insufficient to produce these changes. Interestingly, the changed outputs lasted for many days after the end of conditioning, despite the intervening return to normal activity.

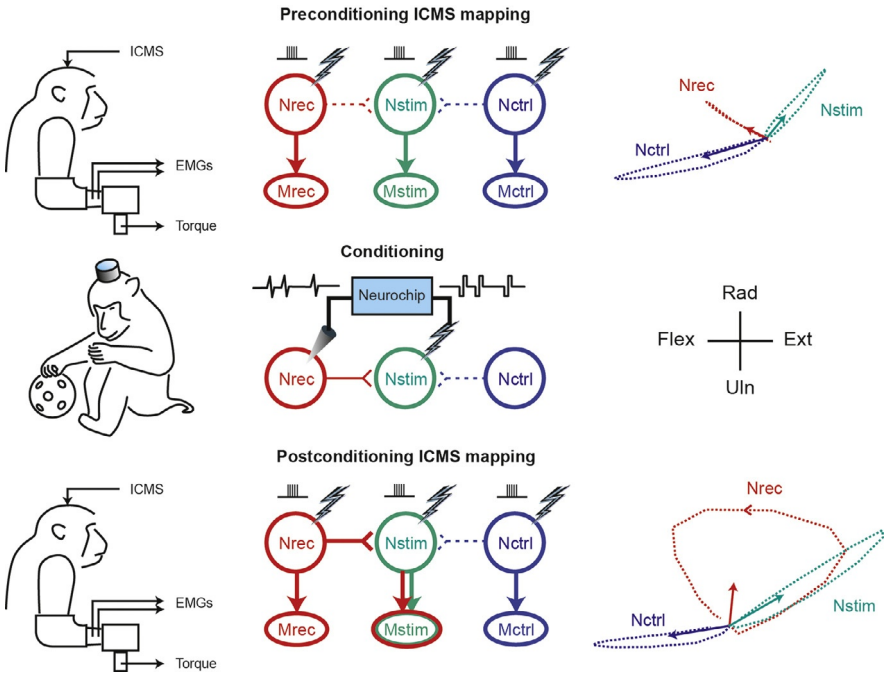

FIGURE 3

Schematic of cortical conditioning experiments. Intracortical microstimulation (ICMS) mapping was performed before the conditioning (top row) with the monkey seated (left). Trains of ICMS delivered at three cortical sites evoked responses in corresponding muscles (middle) and characteristic isometric torque trajectories about the wrist in the 2D flexion-extension and radial-ulnar plane (right). During conditioning (middle row), spikes recorded at Nrec-triggered stimuli delivered at Nstim while the monkey moved freely in the cage. After conditioning (bottom row), ICMS evoked new output in the Mstim muscle and evoked torques that included the Nstim direction. Stimuli at Nstim triggered from EMG in Mrec produced similar remapping effects (Lucas and Fetz, 2013).

Adapted from Jackson et al. (2006).

A similar conditioning effect was produced when stimuli were triggered from a muscle instead of a cortical neuron (Lucas and Fetz, 2013). This study identified a muscle Mrec that was activated by stimulating a cortical site Nrec. Single stimuli triggered from EMG in Mrec and delivered at cortical site Nstim produced changes in the subsequent outputs evoked from Nrec in a way very similar to the preceding study. However, the effects did not last as long after the end of conditioning, perhaps due to less precise temporal relationships between cortical cell and EMG activity. Significantly, these results indicate that motor cortical sites can be reorganized using signals obtained with minimally invasive techniques—from muscles rather than from intracortical neurons.

A study by Miller and colleagues (Rebesco et al., 2010) found that spike-triggered stimulation in sensorimomotor cortex of behaving rats produced changes in a measure of inferred functional connectivity between the connected sites. These changes were obtained for spike-stimulus delays of 50 ms, but not delays of 500 ms, suggesting that STDP was involved. In a related study, similar effects were obtained with paired stimulus trains delivered at two cortical sites (Rebesco and Miller, 2011). The site that was stimulated first developed greater inferred connectivity with the site that was stimulated second. Moreover, the threshold for perceiving electrical stimulation at the first site was reduced in similar manner, providing evidence that the strengthened connectivity was associated with behavioral consequences.

Another example of Hebbian conditioning through a BBCI involved the corticospinal system (Nishimura et al., 2013a). This study used corticomotoneuronal (CM) cells, which have monosynaptic connections to motoneurons, as evidenced by postspike effects in spike-triggered averages of EMG (Cheney et al., 1985; Fetz and Cheney, 1980). In this study, the spikes of the same CM cell were recorded for several days and used to trigger intraspinal stimuli that activated the cell's target muscles (Fig. 4). For appropriate spike-stimulus delays (between 10 and 40 ms), such conditioning during many hours of free behavior increased the size of the postspike effects, indicating that the CM synapses had been strengthened. This study documented changes in synaptic connections directly for single neurons, induced by normal firing patterns during free behavior. Interestingly, when stimuli were delivered at zero delay, which activated the motoneurons prior to the arrival of the corticospinal impulses, the strength of the synaptic connection decreased. This result is consistent with the bidirectional STDP rule, which predicts that synaptic strength decreases when the postsynaptic cell is activated prior to the presynaptic input (Caporale and Dan, 2008; Dan and Poo, 2004). In this study, the effects of conditioning could last for several days after the end of conditioning, but typically decreased over time.

This Hebbian paradigm for creating synaptic plasticity has potential clinical applications if the recording and stimulation can be performed with less invasive electrodes—e.g., recording electrocorticographic (ECoG) potentials at the cortical surface and delivering stimuli at the cortical or spinal surface. It also remains to be shown that clinically useful changes can be obtained and sustained for long periods postconditioning. The efficacy and duration of the synaptic changes might be enhanced simply with more prolonged conditioning. The concomitant application of neuromodulators could also strengthen and prolong the conditioned effects.

4 ACTIVITY-DEPENDENT INTRACRANIAL DBS

A third application of BBCIs is the delivery of stimuli at intracranial sites. For example, in the monkey DBS at reinforcement sites can implement operant conditioning of neural activity during free behavior (Eaton and Fetz, 2012). Stimuli delivered in nucleus accumbens were confirmed to be rewarding because they sustained

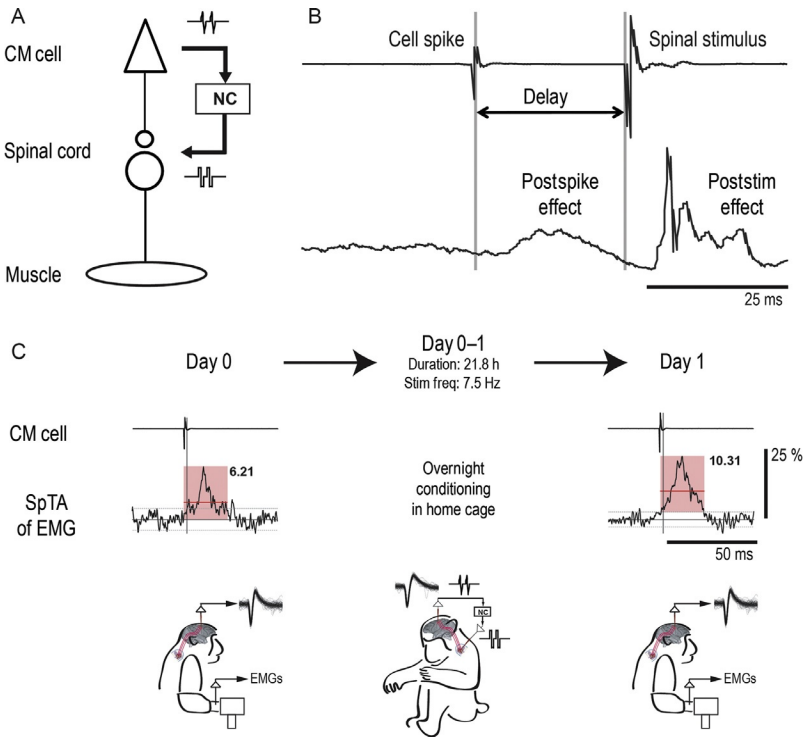

FIGURE 4

Corticospinal connections strengthened by a BBCI. (A) Schematic showing action potentials of CM cell triggering intraspinal stimuli via neurochip (NC). (B) Cortical recording (top) and spike-triggered average (SpTA) of EMG (bottom) for CM spikes followed after delay of 25 ms by spinal stimulus. SpTA shows postspike facilitation and poststimulus response in same target muscle. (C) SpTAs of EMG acquired before (day 0) and after (day 1) a 22-h period of conditioning, showing analysis interval (pink square; gray color in the print version), baseline ±2 SD of SpTA (horizontal gray lines), and mean percent increase (MPI) above baseline of feature (horizontal red lines (dark gray color in the print version) and black numbers). Conditioning increased MPI by 66%. Drawings represent monkey performing task on days 0 and 1 and behaving freely during conditioning.

From Nishimura et al. (2013a).

performance of a conventional step-tracking task. When such stimuli were contingent on muscle activity, the monkey consistently activated the triggering muscle during the periods that reinforcement was available. This paradigm could also be used to reward increases in neural activity (Libey et al., 2013). The monkeys demonstrated more robust volitionally controlled increases of neural activity when seated in the confines of a behavioral booth than when moving freely about their home cage.

This difference may be related to the fact that the cage environment presented more opportunities for competing behaviors. As one consequence, the neurons had higher levels of baseline activity during free behavior, so the volitional increases were relative greater in the restricted environment of the training booth. Operant conditioning of neural activity in rats by contingent stimulation of intracranial reward sites has also been demonstrated for neurons in brainstem (Olds and Olds, 1961) and prefrontal cortex (Widge and Moritz, 2014). The latter has been discussed as the first step in implementing an affective BBCI to treat psychiatric conditions (Widge et al., 2014).

The potential clinical applications of activity-dependent DBS for motor recovery would be continuous reinforcement of desired activity, such as movements of paretic limbs. For locked-in patients, who often have severely reduced ability to communicate with brain–machine interfaces (Hinterberger et al., 2005), the intracranial reinforcement of neural activity could motivate subjects to learn to volitionally control these signals and use them for communication or control of external devices. The clinical applications for intracranial reinforcement are currently limited due to the invasive nature of the implanted electrodes. The possibility of less invasive stimulation of intracranial sites, for example with focused ultrasound, remains to be explored. A more practical alternative for treating motor disorders like spasticity is to provide normal reinforcement through successful game play (Donoso Brown et al., 2014) or monetary rewards.

5 CONCLUDING COMMENTS

In general, the BBCI paradigm can be applied to many scenarios, depending on the types of signals recorded, the sites stimulated and the transform between recorded activity and stimulation. Signals could be derived from a variety of sources, including, from most to least invasively recorded: neural action potentials (Guggenmos et al., 2013; Jackson et al., 2006; Nishimura et al., 2013a; Rebesco et al., 2010), field potentials (Nishimura et al., 2013b), ECoG activity (Wander et al., 2013), EEG (McFarland et al., 2010), EMG (Lucas and Fetz, 2013), and even accelerometers. The stimuli could be delivered anywhere in the brain, spinal cord, or muscles. And the transform could involve direct stimulation proportional to the intensity of the recorded signal or some computed function of one or more signals. The paradigm can be applied for many different brain sites, each having its own functional context. So far, motor systems have been most extensively explored, but sensory and association areas and noncortical sites remain to be investigated. In addition, there is ample opportunity to apply the paradigm to clinical treatments, both in bridging lost connections and in strengthening weakened synaptic connections in a targeted manner (Edwardson et al., 2012). More sophisticated closed-loop scenarios become possible with increases in the number of recurrent channels and the computational capability of the computer chips (Berger and Glanzmann, 2005).

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