BIDIRECTIONAL INTERACTIONS BETWEEN THE BRAIN AND IMPLANTABLE COMPUTERS

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Recent advances in brain-computer interfaces (BCI), also known as brain-machine interfaces, have demonstrated that brain signals can be tapped directly to allow subjects to control external devices, such as robotic arms or cursors on a computer screen (Carmena et al 2003, Donoghue 2002, Nicolelis 2003, Velliste et al 2008). These signals can be obtained from the scalp via electroencephalographic (EEG) recording, from the surface of the brain via electrocorticograms (ECoG) or from single or multiple neurons in the brain via intra-cortical microelectrodes. The invasiveness of each procedure is inversely proportional to the spatiotemporal specificity of the signals. The subject typically learns to optimize the signals for control of the external device through visual feedback of the ongoing consequences. Efforts are currently underway to provide other modalities of feedback about the controlled device through electrical stimulation of the brain (Bensmaia & Miller 2014).

In contrast, bidirectional brain-computer interfaces (BBCI) provide direct closed-loop activity-dependent stimulation without any external controlled device beyond the computer. The computer itself can be small enough to be carried around and operate continuously during free behavior. We have developed a head-fixed system called the "neurochip" which records activity of cortical neurons in freely behaving monkeys and delivers activity-dependent stimulation to the brain, spinal cord or muscles (Mavoori et al 2005, Zanos et al 2011). Similar closed-loop BBCIs have also been developed (Azin et al 2011), some of them operating via tethered cables (Moritz et al 2008, Rebesco et al 2010, Rolston et al 2010, Venkatraman et al 2009) or through telemetry (Delgado et al 1970, Rouse et al 2011) to provide connections to external computers. The advantage of continuous operation of the-BBCI during free behavior is that the brain can learn to

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incorporate the artificial recurrent connection into normal behavior. When the loop time is sufficiently short, BB CIs can also produce spike-timing dependent synaptic plasticity (SPTP) by spike-triggered stimulation.

We have demonstrated the ability of a BBCI to bridge a lost physiological connection and allow brain cells to control functional electrical stimulation (FES) of paralyzed muscles (Moritz et al 2008). The experimental setup is shown in Fig. 1A. The monkey first controlled the position of a cursor on the screen by generating normal torques about the wrist to place the cursor into the target. After the nerves to the muscles were blocked with an anesthetic the monkey quickly learned to control the cursor with activity of a motor cortical neuron. Interestingly, it did not matter whether the cell had any prior relation to the wrist; the activity of essentially all motor cortex cells can be volitionally controlled (Fetz & Baker 1973). Next, the cell activity was converted to electrical stimulation of the agonist muscle, which generated torques that again drove the curser (Fig. 1B). Thus the BBCI allowed the monkey to readily acquire new targets by cell-controlled FES. Bidirectional wrist torques could be produced by using two cells, one activating flexor muscles and the other extensors, or by using one cell and allowing increases and decreases of activity to stimulate a different muscle group. Since any motor cortex cell could be volitionally controlled, this paradigm expands the pool of potential control sources well beyond those neurons that might be originally related to the wrist. Indeed, neurons in many other cortical areas are also likely to be modulated by "top-down" volitional signals (Fetz 2007), making this a powerful paradigm for controlling FES. One might imagine that this strategy puts a considerable "cognitive load" on the brain to control these independent signals, but many experiments have now shown that the brain can quickly adapt to new contingencies. For example, humans required to activate six forearm muscles in unnatural combinations in order to acquire targets learned to do so in about 200 trials (Radhakrishnan et al 2008). Similarly, monkeys learned to control a population of motor cortical neurons in novel ways to drive a cursor into targets in two dimensions (Ganguly & Carmena 2009) or three (Jarosiewicz et al 2008). The remarkable ability of the brain to adapt to new contingencies provides a powerful mechanism to allow arbitrary neurons to control FES.

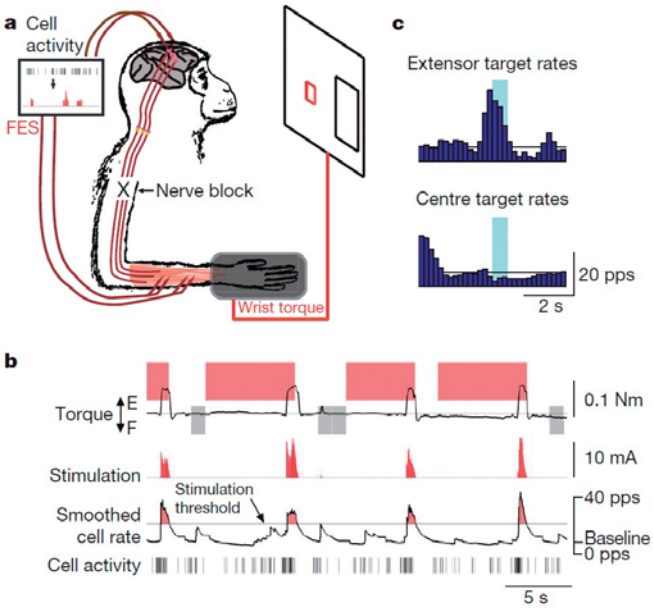

Figure 1. Brain-controlled functional electrical stimulation (FES) of muscle. a. Schematic shows cortical cell activity converted to FES during peripheral nerve block. b. Example of motor cortex cell activity controlling FES of paralyzed wrist extensors. Wrist torque targets for extension (red shading) and center hold (grey 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/sec, 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).

While possible in principle, the FES of muscles through nerves is problematic because electrical stimulation recruits the motor units of a muscle in unnatural order, with large and rapidly fatiguing units recruited first. Also, finely controlled synergistic activation of multiple muscles via FES is challenging. A possible solution is to stimulate in the spinal cord, which evokes synergistic combinations of muscles and recruits motor units in natural order (Moritz et al 2007). Cortically controlled stimulation of spinal cord via BBCIs is a promising strategy to circumvent damaged corticospinal connections (Jackson et al 2006b, Jackson & Zimmermann 2012). In a recent case study of a monkey that had learned

the target tracking task and was subsequently rendered paretic by a spinal cord injury, the monkey learned to control intraspinal stimulation by generating increases in cortical field potentials, allowing him to acquire targets again (Nishimura et al 2013b).

A second type of application for BBCIs is to induce synaptic plasticity. Spike-triggered stimulation of a cell's target neurons can strengthen the synaptic connections between them. A first demonstration involved an implanted BBCI that recorded cell activity at one motor cortex site and delivered spike-triggered stimuli at a neighboring site (Jackson et al 2006a). After operating for a day or more during free activity and sleep, the outputs evoked from the two sites changed, and suggested stronger connections from the recording to the stimulation site. These changes were obtained only when the delay between the spike and the stimulus was 50 ms or less, consistent with the effective window for STDP (Caporale & Dan 2008, Dan & Poo 2004, Markram et al 2011). The changes lasted for several days past the end of conditioning, indicating a remarkably robust effect. A similar phenomenon has also been demonstrated in rat cortex, where spike-triggered stimulation changed the inferred functional connectivity between sites (Rebesco et al 2010).

Cortical plasticity could also be produced by using a BBCI to deliver cortical stimuli triggered from EMG of forearm muscles (Lucas & Fetz 2013). The muscle served as a more easily recorded surrogate of cortical cells, whose activity was correlated with the muscle. This EMG-triggered stimulation was sufficient to produce similar cortical reorganization, although the effects did not last as long as with spike-triggered simulation, perhaps due to looser timing between the cortical and muscle activities.

More direct evidence of inducing STDP was obtained by changing the strength of synaptic connections between corticomotoneuronal (CM) cells and their target motoneurons (Nishimura et al 2013b). The spikes recorded from individual CM cells were used to trigger intraspinal stimuli at the site of the cells' target motoneurons during free behavior (Fig. 2). The strength of the CM cell's synaptic connection was measured by the size of the post-spike effects of the cell on its target muscles. These post-spike effects increased in size after a few hours of spike-triggered stimulation, and sometimes remained augmented for days after the end of conditioning. Again, the effective spike-stimulus delays that

strengthened the connections were consistent with the STDP window. Interestingly, spike-triggered stimuli delivered at zero delay decreased the strength of the connection. At zero delay the motoneurons were activated before the arrival of the corticospinal impulses. The STDP rule says that if the postsynaptic cell is consistently activated prior to the presynaptic input the connection strength will decrease, as confirmed in this experiment. This study provides the first direct demonstration that STDP can be produced in single cells using normal firing rates of cells recorded during free behavior.

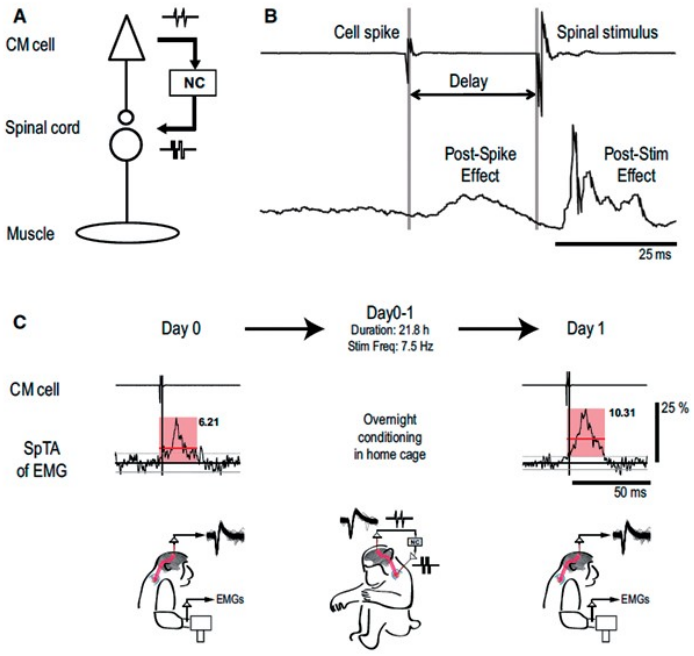

Figure 2. Corticospinal connections strengthened by a BBCI. (A) Schematic showing action potentials of CM cell triggering intraspinal stimuli via neurochip (NC). (B) Cortical recording (top) and SpTA of EMG (bottom) for CM spikes followed after delay of 25 ms by spinal stimulus. SpTA shows postspike facilitation and poststimulus response in same target muscle. (C) SpTAs of EMG acquired before (day 0) and after (day 1) a 22 hr period of conditioning, showing analysis interval (pink square), baseline ± 2 SD of SpTA (horizontal gray lines), and mean percent increase [MPI] above baseline of feature (horizontal red lines and black numbers). Conditioning increased MPI by 66% ($p = 0.0003$). Drawings represent monkey performing task on days 0 and 1 and behaving freely during conditioning. From (Nishimura et al 2013a).

A third application of BBCIs is to deliver activity-dependent reinforcement by contingent stimuli delivered to intracranial reward sites (Eaton & Fetz 2012). For example stimulating certain sites in nucleus accumbens can be shown to sustain performance on an operant task (like the target tracking in Fig. 1). Delivering stimuli in such a site triggered by increases in muscular EMG showed that the monkey generated more EMG triggers during "time-in" periods when the stimuli were available than during alternating "time-out" periods when the stimulator was turned off. Similar results were obtained when the stimuli were triggered from activity of motor cortex neurons (Libey et al 2013). By operating during free behavior, the BBCI can provide ample time for the monkey to discover the appropriate behavior that delivers reinforcement. An early demonstration of closed-loop operant conditioning was the study of Delgado in which amygdala spindling was used to deliver contingent stimulation in a brain-stem site, using telemetry to close the loop between the brain and requisite instrumentation (Delgado et al 1970). After 2 hours of activity-dependent stimulation the amygdala spindling was reduced specifically at the recording site (not the contralateral side), indicating that the stimulation was aversive, and the control was specific.

In summary, there are innumerable applications of BBCIs, depending on the type of signal recorded, where the stimulus delivered and the transform between recorded activity and stimulation. Each pair of sites has its own functional relationships, which can be investigated by closed-loop activity-dependent stimulation. Promising clinical applications of BBCIs are to bridge lost biological connections allowing the brain to regain function, and to strengthen weakened connections that have been damaged by injury. So there are innumerable promising basic research and therapeutic applications for BBCIs remaining to be explored (Potter et al 2014).

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