Neurosciences and the Human Person: New Perspectives on Human Activities
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New Interfaces for the Brain

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Between Man and Machine

We interact with the world by receiving input from an exquisite group of sensors that provide the brain a filtered sample of the world and a set of artfully arranged muscles that provide the brain's only conduit for action. The brain's vast neural networks, joining billions of neurons, link percepts derived from sensors to thoughts, memories, and actions. Nearly infinitely-flexible connection patterns in the human brain permit remarkable behaviors, ranging from gymnastic leaps to piano arpeggios, to paintings, to speech. Vast sensorimotor interactions, flavored by emotion, drives, and reveries, are the essence of our humanity. How activity patterns emerge from the networks of our brain to create human activity remains one the greatest mysteries of science. Diseases or disorders that disconnect the brain from the world profoundly influence our being. Here, I will focus on the loss of the connections from the brain to the muscles and efforts to combine the knowledge from neuroscience, engineering and medicine to provide unique technology to reconnect the brain to the outside world for people with paralysis. I will then discuss the potential impact of this emerging neurotechnology on what it means to be human.

When we express a behavior, patterns of electrical impulses emitted from the cerebral cortex pass to the brainstem and spinal cord through a pencil-lead thick fiber bundle possessing about 1 million axons. It is this route by which commands from cortex reach the rest of the nervous system. This tenuous bundle of cortical fibers orchestrates voluntary movement patterns in the spinal cord, which in turn coordinates volitional muscle action. Strokes, traumatic brain injury, or degenerative diseases can damage the brain's ability to address the muscles, leading to paralysis. Damage to the corticospinal pathway anywhere along its path to the spinal cord, disconnects the brain from everything below the damage, producing voluntary actions of those body parts. In the worst case when the injury is high in the neuraxis tetraplegia results, making a person fully dependent on others because no useful body movements are possible. There is no cure for this devastating damage, which robs the person of a critical part of their humanity – the freedom to act on the world as they wish. However, these people with such disorders frequently retain their full complement of cognitive abilities, but they cannot express their thoughts. People with tetraplegia, as occurs after cervical spinal cord injury or brainstem stroke, or neurodegenerative diseases like amyotrophic lateral sclerosis (ALS; Lou Gerhig's disease), are completely reliant on others for even the most basic of human functions like eating or grooming. With locked-in syndrome, which is the most severe form of disconnection, people can be fully conscious but unable to speak or make nearly any useful movements, limiting communication to slow and tedious repetitions of a few spared actions, like eyeblinks. Even less debilitating paralysis from disease or injury, as might result from a smaller stroke, limits action of one part of the body, not uncommonly one arm. Loss of arm function can also severely restrict everyday self-care as well as skilled activities needed for employment or recreation. There is excitement and hope for stem cell therapy to repair damaged axons or replace lost neurons; this biological repair strategy appears to have an encouraging, but still complex and protracted path ahead before humans will benefit (Sahni and Kessler, 2010). Advances in neurotechnology and neuroscience in recent years are beginning to show that a physical repair of damaged pathways is a viable alternative path for neurorestoration.

Neurotechnology as a physical bridge from brain to the outside world

A revolution in neurotechnology is providing a new approach to restore lost functions (Donoghue, 2008). Neural interfaces are devices that couple with the brain to sense, adjust, or replace activity. That is, neural interfaces have the potential to either *write in* signals to the brain by stimulating neurons, or activity can be *read out* by sensing ongoing activity. One class of already successful *write in* neural interfaces is based on electrical stimulation that is used to influence brain circuits, an approach called neuromodulation. Deep brain stimulation (DBS) is one established success of a neuroan interface of this type. Patterns of localized electrical stimulation in the subthalamic nucleus (STN, a small collection of neurons in the center of the brain) are able to reestablish a balance of activity in Parkinson's disease (PD), restoring the ability to resume everyday functions (Weaver *et al.*, 2009). Stimulation in the STN reduces overactivity in the muscles, reducing tremor and rigidity. The exact mechanism by which disrupted circuits reestablish balance is not clearly understood but it is thought to modulate the interactions of circuits that have lost their appropriate interactions to control movement. While DBS restores the ability to move more ably, it does not slow the ongoing degeneration of dopaminergic neurons that cause PD. Implantation of DBS electrodes for neuromodulation is no longer rare: more than 80,000 people have already had these mm-size electrodes that are permanently inserted approximately 4 cm into the brain. Neuromodulation technology is also being tried for debilitating mood and behavioral disorders like severe depression or obsessive compulsive disorder, with encouraging initial results (Benabid and Torres, 2012). However, the ability to manipulate mood and affect by external interventions raises important ethical issues that require careful, ongoing evaluation as these technologies become more and more broadly applied (Kuhn *et al.*, 2009). Another form of *writing in* employs stimulation to replace lost senses. Patterned stimulation of the auditory nerve within the cochlea using cochlear implants has been enormously successful in restoring useful sound perception in more than 200,000 people with deafness, including many children. In addition, stimulation of the retina, by a small array of electrodes placed inside the eye of those with blindness from photoreceptor degeneration, is beginning to show promise as a way to provide at least crude visual perception (Humayun *et al.* 2012). These devices are replacement parts for lost inputs that can restore more useful interaction with the world for people with profound sensory loss.

Reading out for action restoration

Neurotechnology to read out or sense neural signals as a direct control source to restore movement for people with paralysis is in early stage development, but showing considerable promise. A brain computer interface (BCI) is a neural interface system designed to form a new bridge from the brain to the world, bypassing injured motor pathways that prevent volitional action. Stroke, spinal cord injury, or degenerative diseases often leave cerebral motor structures intact but block the route for commands to reach the body when they damage the corticospinal pathway. Thus, a principle goal of a BCI is to read out motor intentions from their origins in the brain and deliver a derived command to assistive technologies that can restore useful functions. BCIs employ sensors to detect neurally-based movement signals, which are subsequently translated into motor commands using computer algorithms that interpret or *decode* neural activity. These commands then control devices that can carry out lost functions, such as those that are ordinarily performed by the arm. Some types of BCIs attempt to capture any recordable brain signal that can be co-opted to become a new communication channel (see: Wolpaw and Wolpaw 2012). Evoked or brain state related potentials, such as the electroencephalogram (EEG), can be used as a 'switch' typically to indicate a yes-no like choice. EEG signals, which reflect a more global intention or brain state rather than exact movement commands are of interest because they can be obtained from the scalp. More high fidelity sensors must be placed in contact with the brain. However, even this minimal enhancement can be highly valuable for people who are locked-in, without any useful means to express their thoughts or needs. Others are developing technology that has a more ambitious goal – to reconnect the brain's motor areas to devices that can fully perform the lost action, either through a replacement device such as a robot or computer, or through a physically reconnection between the brain to the body that could reanimate the paralyzed muscles themselves.

The BrainGate Pilot Human Clinical Trial

Initial clinical trials of BCIs to restore movement control and independence for people with profound paralysis have already begun. Our research group is developing a 'first of its kind' BCI, called BrainGate (www.braingate2.org). This neural interface system is being designed to allow people with paralysis to use their own volitional movement signals to operate a range of assistive technologies. Our major emphasis is to emulate arm function for those that cannot use their arm, because of importance of the arm in so many everyday human activities. BrainGate consists of a tiny 4 x 4 mm sensor that is implanted in the arm region of the motor cortex, where commands to move are accessible and partially understood. Neural signals recorded from even a small patch of motor cortex can reflect both intended hand movement in space and a hand squeeze. These intentions can be decoded from patterns of neural activity into machine commands sufficient to operate a computer, control robotic assistants, or potentially even drive paralyzed muscles themselves. In proof of concept preclinical studies we demonstrated that BrainGate could be safely implanted in animals and provide useful control signals (Serruya *et al.*, 2002); other work in animal models has extended this initial observation and demonstrated a wide potential to achieve complex control based on a remarkably small sample of cortical activity (e.g., Taylor *et al.*, 2002; Carmena *et al.*, 2003; Hatsopoulos *et al.*, 2004; Achtman *et al.*, 2007; Velliste *et al.*, 2008; Vargas Irwin *et al.*, 2010). These basic science successes led to testing of the BrainGate neural interface system in people with paralysis[1] (Hochberg *et al.*, 2006; 2012; Simeral *et al.*, 2011).

Sensors, Signals and Sources

The fundamental problems to be solved for a BCI are: first, to localize and detect sources of movement control signals in the brain; second, de-

[1] Caution: investigational device. Limited by federal (USA) law to investigational use.

code or translate them into useful commands, and third, to identify or develop assistive technologies that can be usefully operated directly from the brain by people with paralysis. We know from years of neuroscience research that the primary motor area (known as M1), which is essential for volitional action in humans, resides within a strip of cerebral cortex coinciding with the precentral gyrus on the surface of each cerebral hemisphere. M1 is divided into separate lateral to medial regions that command face, arm and leg, and is a major source of volitional commands that run in fiber pathways to the spinal cord (for the body) and brainstem (for the head). Neurons in the M1 arm area work together as ensembles, creating activity patterns that relate to the motion of the hand in space, or movement of the fingers and wrist. We know enough about M1 activity patterns from recordings in animal studies to estimate an intended action, such as move the arm up, left, down or right, or open and close the hand; it is likely that much more information about the arm could be harvested from neural activity patterns. Other cortical areas have arm related signals as well (Kalaska *et al.*, 1997; Sathanam *et al.*, 2006) and these areas may also provide useful command signal sources in humans, especially if M1 itself were to be damaged.

Because neurons are tiny and their signals are weak, recordings are obtained from an array of hair-thin electrodes that must be placed very near individual cells. These microelectrodes detect trains of millisecond-long impulses known as spikes (or action potentials); the spiking of many neurons (typically up to a few dozen) provides an evolving pattern in time, with each neuron emitting a pulse sequence much like a series of 0s and 1s. Device placement requires an invasive procedure by a neurosurgeon where the brain is exposed and the array placed. For the BrainGate trial the 4 x 4 mm array has 100 electrodes, each 1.5 mm long, arranged in a 10 x 10 matrix (Rousche and Normann, 1998). We adapted this sensor so that it could be permanently implanted in the human M1 arm cortex. The initial sensor for humans has a cable running from the array in the brain, out across the skull to a small plug mounted on the head that emerges through the skin. This percutaneous plug is all that is visible once surgery is completed. The plug serves as the connection to the MI implanted array for the few hours of each recording and testing session in the pilot study. Currently, neural signals are processed and decoded by a nearby rack of electronics that converts the pattern of neural signals into commands. When our participant imagines moving their arm, the resultant volitional neural activity leads to the movement of a cursor on a computer screen or other assistive technologies, such as a robot arm.

Useful actions after years of paralysis

The pilot clinical trial is testing the safety and potential utility of the BrainGate neural interface system. So far, seven people with tetraplegia have had an array implanted and have been part of our trial. All were enrolled more than one year since they had their stroke, spinal cord injury or onset of ALS (Lou Gerhig's disease; motor neuron degeneration); they had all been consented through an approved, institutionally and FDA guided process under an Investigational Device Exemption (IDE).

Our participants have shown that despite their long-standing paralysis, the motor cortex remains fully able to generate movement commands, as if the arm were actually engaged in reaching and grasping when they imagine these actions. This has been a surprising finding in that this part of the brain, thought to be key for volitional movement, had lacked a meaningful output for years. Nevertheless, yet it seemed to act as if it were commanding actual movement. Using their own decoded M1 signals participants have operated a computer to emulate mouse pointing and clicking actions (by imagining moving their hand and then squeezing to click). Neural patterns based only on thoughts of (imagined) arm and hand actions allow them to navigate software and type messages. People with severe paralysis from stroke have also been able to use robotic arms to perform reach and grasp actions. One participant unable to move or speak, recently was able to serve herself her own morning coffee for the first time in nearly 15 years (Hochberg *et al.*, 2012). These self directed, BCI-based actions are slower and less accurate than able-bodied people, but they are major advances for those completely reliant on others. It is important to note that in the study, participants only use the system for a few hours a week when they engage in a session; the technology is not yet available for everyday use. Control is not always useful. Changes in the signal can degrade performance. These are issues that only can be resolved by working with the system to advance its reliability and stability, which is now a major effort in a large number of laboratories interested in furthering BCIs for people with paralysis.

Promise of BCIs

These first human clinical tests are small steps towards restoring independence and dignity to people deprived of the ability to voluntarily perform everyday actions, freeing them from reliance on others often for even the most basic human activities. The current BCI systems remain to be made better, faster and more reliable, with implanted wireless sensors that replace the head plug and a tethering cable now required. Others are testing sensors that may make command signals more reliable, stable, or longlasting.

Promising advances in neurotechnology are underway but will still take a number of years of engineering and science, at great expense and effort, before they are generally available. While the current systems are being evaluated in severely disabled people, technology like BrainGate could help millions worldwide who have more limited paralysis, particularly from stroke which affects hundreds of thousands of people each year. A successful BCI could provide a means for them to once again move their paralyzed arm or stand and walk. Connecting brain to muscles using technology is not as remote as it might seem. Neural signals could be routed to electrical stimulators implanted in the arm that can activate muscles. Functional electrical stimulation systems have already been deployed in people with spinal cord injury, although commanded by switches rather than the brain (Peckham and Knutson, 2005). A BCI to FES system would effectively create a physical bridge to replace the missing neural link between brain and muscles and allowing volitional control over one's own body.

Beyond clinical applications, sensors used to detect neural movement activity patterns are also providing a unique glimpse into the human brain in everyday operation and a cellular level picture of the effects of disease and damage. The recordings of a very small ensemble of neurons reveal a rich and complex processing in which neurons reflect much more than a movement command, raising more questions about the processes that lead from perception and thought to action in the human brain. In the very long term this physical nervous system has a major goal to restore dignity and control by making the person indistinguishable from any other, fully capable of pursuing goals available to any fully functioning person.

Neuroethics

Restoring people to a level where they can realize all of their potential is hardly an issue that most would consider to be controversial. However, advances in understanding how the brain plans, organizes and transforms thoughts to become actions could lead to applications that might extend human capabilities. These applications present ethical challenges: if we could augment human performance by direct brain control, who would have access, who would pay, would it be appropriate, how would it be controlled? What would it mean to be human if the brain was fused to a machine? Some of these same challenges are present for neurally active pharmacological agents or even augmenting external prosthetic limbs which may serve as a model for BCIs. At present we are a long way from meaningful readout of a brain that is good enough to infer innermost mental activity. Such a feat may never be met because the full richness of human cognitive behavior seems to emerge at a level that might be immeasurable. In addition the need for surgical procedures, which is highly regulated and monitored, presents a substantial barrier to entry for mundane or recreational applications of invasive BCIs. However, the responsible conduct of scientists, engineers, clinicians and a wide range of societal organizations in this emerging field requires that there be an ongoing debate of the use of neural interface technology and its implications for what it means to be human.

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