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Progress towards restoring upper limb movement and sensation through intracortical brain-computer interfaces

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Abstract

Bidirectional brain-computer interfaces (BCIs) make use of neural recordings to restore movement while conveying somatosensory information back to the user through direct stimulation of the nervous system. Decades of research on motor control have enabled impressive demonstrations of brain-controlled arm and hand movements in people with paralysis. Furthermore, recent efforts to restore somatosensation have shown that intracortical microstimulation of somatosensory cortex can generate focal, graded, and digit-specific sensations after chronic spinal cord injury. Non-human primate work suggests that restored somatosensation can be used to improve BCI task performance. The combination of BCI-enabled motor control and sensation is an area of recent investigation for human clinical studies, and the interplay between these two domains represents an opportunity for scientific discovery. Here we review recent progress towards the development of bidirectional BCIs.

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Introduction

Brain-computer interfaces (BCIs) make it possible to communicate directly with the brain by circumventing the normal peripheral sensors and effectors used to interact with the world. By establishing this direct link, the aim is to restore the normal communication channels between the brain and the world that were lost with traumatic injury or disease. In this review, we will focus on BCIs designed to restore upper-extremity movement and sensation, highlight progress over the last 5 years in the field of human BCI, and summarize the basic science discoveries that have enabled the development of this technology.

From an engineering perspective, volitional movement can be considered a mechanism for enacting a desired action on the world. Reaching, grasping, and manipulation are the primary behaviors we perform with our arms and hands. Reaching transports the hand to a targeted object and these movements are achieved by muscles that generate force and produce torque about the joints of the limb. Once object contact occurs, interaction forces between the hand and object must now be accounted for in the motor plan. These interactive forces are sensed by a variety of mechanoreceptors distributed throughout the hand and arm and these sensations are critical for skilled object manipulation. A BCI must therefore extract signals representing the intended movement, and at the same time, inject signals back into the nervous system to describe the result of the actions produced by those extracted signals. Here we describe progress towards this goal of a 'bidirectional BCI', the components of which are illustrated in Figure 1.

BCIs fundamentally rely on the fact that information within the nervous system is conveyed by the patterns of electrical activity in neurons. While there are different technologies to extract these electrical signals, in this review, we will consider only implanted intracortical microelectrode arrays, which can record the action potentials of individual neurons. For a single neuron, e*ncoding* equations define the movement parameters correlated with changes in firing rate. *Decoding* algorithms transform the recorded neural activity into motor output. Motor control parameters are then sent to
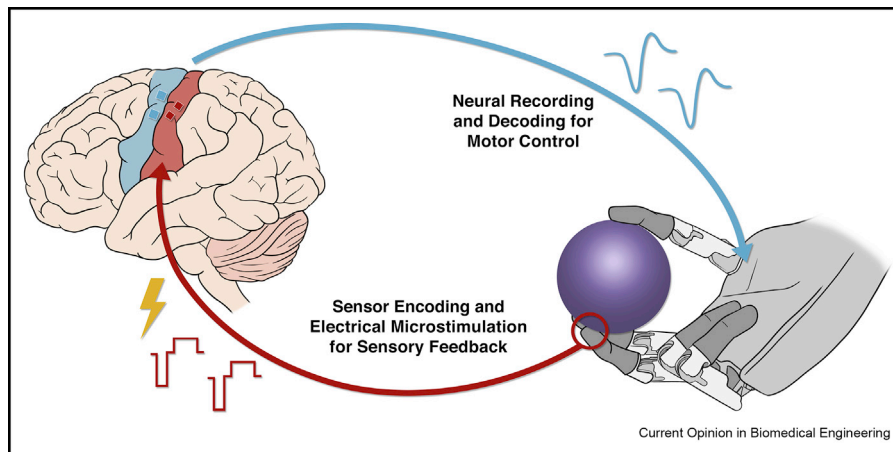
Bidirectional BCI. Intracortical microelectrode arrays are implanted in motor cortex (blue) to record action potentials, which are decoded into motor control commands for an end effector, such as a prosthetic hand. Sensor data from the end effector are then converted into stimulation pulses that are delivered through microelectrode arrays implanted in somatosensory cortex (red) to convey feedback about interactions between the prosthesis and the environment (Image Credit: Kenzie Green).

an effector, such as a robotic arm or a functional electrical stimulator (FES) used to activate the muscles of a paretic limb.

In order to introduce artificial sensory signals into the nervous system, we must control the activity of neurons that normally encode sensory information. This can be achieved by manipulating the electric field in the vicinity of populations of neurons. Electrical stimulation changes the extracellular voltage potential, which in turn causes individual neurons to depolarize and generate an action potential. While electrically-induced changes in neural activity would ideally reproduce the patterns of neural activity that occur during natural behavior, electrical stimulation can recruit tissue in ways that do not normally occur. As such, understanding the most important features of sensation to encode through stimulation and the fidelity with which this can be achieved using a BCI remains an open question. In this article, we review evidence that demonstrates that despite the limitations of electrical microstimulation, simple encoding schemes can be interpreted as conveying useful information about peripheral somatosensory events.

## Neural encoding of arm movement

It has been known since the 1980's that the firing rate of motor cortical neurons are correlated to the direction of arm movement [1]. The relation between direction and firing rate is well characterized by a cosine tuning function (Figure 2) with a peak, termed the *preferred direction*, in which the neuron fires at a maximal rate.

This type of tuning can be described mathematically with a tuning function:

$$f = b_0 + b_x d_x + b_y d_y \tag{1}$$

where f is a neuron's firing rate, b_0, b_x, and b_y are regression coefficients, and d_x and d_y are components of a unit vector pointing in the direction of movement. Since d is a unit vector, and by ignoring the offset term, b_0, for simplicity, Eq. (1) can be written as the dot product of two vectors:

Figure 2
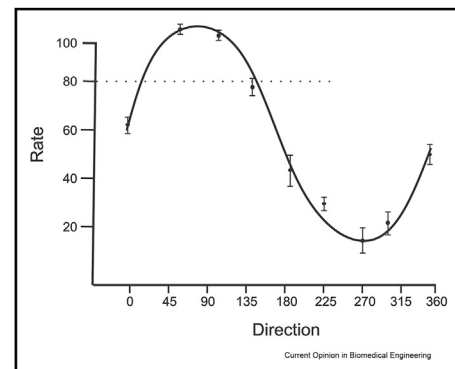
Cosine Tuning Function. Firing rate data are plotted as eight dots. Each indicates the mean firing rate (Y axis, across repeated trials) of a neuron recorded as a monkey moved its arm to targets in eight different directions (X-axis) from a center start position. The data are fit with a cosine function having a peak at 90° which for this example is the neuron's *preferred direction*. The dotted line at 80 impulses/sec crosses the tuning function twice, showing that each firing rate is mapped to two directions.

$$f = \boldsymbol{b} \bullet \boldsymbol{d}$$

where $\boldsymbol{b}$ points in the preferred direction with components b_x and b_y and a magnitude equal to the maximum firing rate. The dot product operation can be visualized as a projection of $\boldsymbol{d}$ on $\boldsymbol{b}$, and the magnitude of the result is the firing rate when moving in direction $\boldsymbol{d}$. This linear projection is a useful concept because experimental results show that the dimensionality of the vectors can be increased merely by adding terms for each encoded parameter to Eq. (1). The form of this encoding function remained valid across a series of experiments in which the dimensionality of the movement increased from two [1] to three [2], four [3], seven [4], and ten dimensions [5]. From a basic science perspective, these findings emphasize the multifactorial nature of neuronal encoding, whereby many aspects of movement contribute to firing rate variability.

Limitations of representational models and emerging views of motor control

In addition to an inherently noisy relation between firing rate and movement parameters [6,7], other factors contribute to the challenges with defining neural tuning models. First, it has become clear that motor cortical neurons encode multiple parameters simultaneously and the tuning to these parameters is labile. Tuning can change in a context-dependent manner and even within a single reach, where discrete changes in a neuron's preferred direction seems to depend on behavioral state [8,9]. Furthermore, movement parameters may not be independent or have non-linear relationships, necessitating the use of decoders capable of handling these interactions [10−15]. The relation between movement direction and firing rate is a governing principle in these decoders. In addition to directional information, other studies suggest that motor cortex activity reflects the dynamics of muscle activity [16], which is likely important for BCIs that drive actuators capable of exerting dynamic forces on the environment [17−19].

It is important to note that BCIs make use of movement intention that can be inferred from the, albeit noisy, neural recordings. Recent descriptions of multiple epochs with different tuning properties during reaching [8,20] support the idea that the motor system undergoes a number of state transitions during single movements. This has led to the proposal that the system is obeying a set of intrinsic dynamics where one state leads to another [21−23]. One advantage of recent approaches is the use of dimensionality-reduction to find structure from the pattern of correlation in a population of firing rates recorded simultaneously from neural units [24,25]. This approach does not rely on an initial assumption of which parameters are represented in neural discharge. However, in order to be useful, factors identified with dimensionality reduction must ultimately be related to physical parameters. BCIs for restoring upper limb function have yet to incorporate models of neural dynamics into their control schemes, although it has begun to be investigated in BCIs for cursor control [26,27]. This idea of incorporating neural dynamics into BCI control, represents an area for future research as this may help mitigate challenges with task and context-dependent tuning. It remains an open question whether motor control principles derived from reaching movements will translate to hand movements, which involve smaller body segments and fine coordination of muscle activity patterns to manipulate objects.

Decoding neural activity to estimate arm and hand movement

Despite the known limitations, representational encoding models remain the basis for most BCIs for restoring arm and hand function. Whereas neural encoding is used to describe how a set of movement parameters relates to firing rates, reversing the process, to estimate movement parameters from the patterns of neural activity, is termed "decoding." A question may arise as to why the tuning function of an individual neuron cannot be used directly to estimate movement direction. Using the tuning function in Fig. 2 (dotted line) as an example, a firing rate of 80 impulses/sec might be measured. One could simply find the corresponding direction by noting the intersection on the tuning function for that specific Y value. However, the curve crosses 80 twice, once at 23° and again at 156°. This redundancy increases as the number of dimensions increases. The ability to decode with this method is also limited by the noisy relationship between firing rate and direction.

For BCIs that are based on representational encoding models, population-based approaches can lessen the impact of individual neuron variability on performance. Population-based extraction algorithms typically operate by inverting the encoding equations of the sampled units. Originally, this inversion was carried out mechanistically by summing the preferred direction vectors from a population (each with a length proportional to its corresponding neuron's observed firing rate) to form a single vector [1]. This *population vector* pointed reliably in the movement direction. Although it could be shown that this estimate of direction was optimal if neurons were cosine-tuned and if the sample population had a uniform distribution of preferred directions, in practice, these criteria were rarely met. The population vector algorithm has been largely replaced by the Optimal Linear Estimator (OLE) decoder [28]. This procedure uses the Moore−Penrose pseudo-inverse to form a matrix of cosine tuning equations calculated for each neuron in the population, followed by inversion [3,4,29]. This assigns optimal weights to each unit's population-vector contribution. Since the introduction of these early decoders, a number of alternative extraction algorithms have been devised. Some of these are based on

the idea of Bayesian inference, in which the most likely set of movement parameters are chosen given the sampled combination of simultaneous firing rates. The Kalman filter [30,31] uses this principle, along with the prior history of firing rates, to decode movement parameters, which can increase the smoothness of control. Other decoders are non-parametric such as the particle filter [32] or are designed to handle non-linear encoding of movement [14,15]. All of these decoders rely on population recordings of firing rates from multiple neurons in order to capture movement representations that may be weakly represented by single neurons.

Calibration procedures

BCIs are designed to restore movement for people with paralysis, which creates a challenge in terms of defining the neural encoding model; that is, how does movement change the firing rates of neurons? The relationship between neural activity and motor commands needs to be defined in the absence of overt movement by the subject. BCI calibration procedures rely on action observation or motor imagery to elicit repeatable patterns of neural activity that represent movement intention. In these paradigms, the subject attempts to replicate movement of an end-effector (e.g. robot, computer display, or an actual hand) driven to move along a prescribed trajectory in a series of movements. Non-human primate studies have shown that neural activity recorded during observed or attempted movement is similar to that measured during overt movement [33] and can be used for BCI control [3,34]. Human BCI studies have used observation-based calibration to enable control of robotic arms [4,35] and movement of a participant's paralyzed limb through FES [36,37]. Recent human work has shown that motor imagery may be used to obtain control of a computer cursor after a short closed-loop calibration without the need for an explicit observation phase [38].

One challenge with this approach is that neural encoding is task-dependent [9,39,40]. One such example is the finding that motor cortex activity, when reaching to

an object, is different than when the same movement is performed in an empty workspace [40]. Reaching to and grasping different objects is associated with object-specific kinematics that modulate intention [41] and brain activation [42]. Non-human primate studies have found kinematically-linked object dependent neural activity in motor, parietal, and premotor cortices [39,43]. Our research group has shown that calibration with virtual objects (Figure. 3) improved motor control with a prosthetic limb, suggesting that accounting for variation in task context can improve BCI control [5]. Calibration procedures that encompass a wide range of behavioral contexts will be essential for enabling BCI performance in everyday settings. For bidirectional BCIs there is an opportunity to study whether restored somatosensation impacts neural activity and dynamics, which could aid in the design of calibration paradigms that enable BCI decoding schemes that optimally integrate somatosensory information.

Of course, there is a limitation to the number of movement conditions and contexts that can be sampled during a calibration session. Recent approaches have used computational techniques such as neural networks to take advantage of large and robust datasets to derive BCI decoding algorithms that can account for changes in context or other sources of variability [44,45]. Additionally, isolation of single-unit waveforms is unstable [46,47], requiring re-isolation of the waveforms and recalibration of the BCI system. This is an ongoing area of research using adaptive algorithms and machine-learning approaches [44,48−50].

Demonstrations of BCI-controlled arm and hand movements

The discovery of velocity encoding in motor cortex, along with advances in neural recording technology and calibration techniques, enabled early demonstrations of robotic arm control in non-human primates [3,51,52]. Using this foundation, human BCI studies have also used velocity-based models for robotic arm control [4,5,35]. In an early demonstration, participants had

Figure 3

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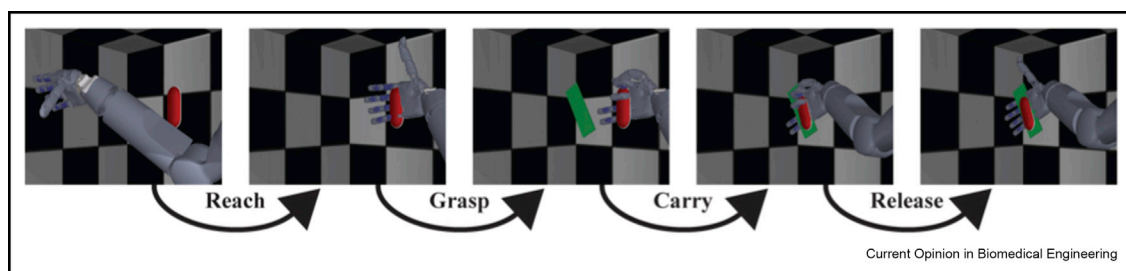
Screenshots of a virtual reality-based calibration paradigm where the participant attempts to move the arm and hand through a series of reaching, grasping, and transport activities to move a virtual object in the workspace.

sequential control of 3D translational velocity and hand state (open or closed), allowing them to touch or grasp targets positioned in the workspace of the robot [35]. Our research group extended the endpoint velocity encoding model to include 7 dimensions: 3D translation velocity, 3D orientation velocity, and 1D grasp velocity [4]. This enabled a person with tetraplegia to perform reaching and grasping movements using an anthropomorphic robotic arm with a high level of performance that led to clinically significant gains in tests of upper limb function. In subsequent work, hand control was expanded to include four dimensions of hand shaping, and the same participant was able to perform posture matching and functional tasks using 10 simultaneously and continuously decoded degrees of freedom [5].

Recent exciting developments have been made in combining motor decoding with FES to reanimate participants' paralyzed limbs [36,37,53,54]. Reanimation is clearly preferred by people with spinal cord injury over prosthetic operation [55,56], however many challenges remain in order to restore complete movement to the arm and hand. The mechanics of the musculoskeletal system are complex and calculating the correct set of muscles to activate at the proper levels is difficult, especially when encountering external loading of the limb and in situations such as object interaction. Artificial electrical stimulation of muscles does not recruit muscle fibers in physiological ways, leading to muscle fatigue, especially in people with SCI. Therefore, BCI-FES studies, to date, have focused primarily on restoring hand function or single joint movements of the arm, which can be enabling for people with residual function of the proximal limb. Depending on the nature of a person's injury, they may receive some sensory feedback through residual afferent pathways, though in many cases sensory feedback will need to be restored through the BCI.

Progress towards restoring sensation

While the need for high-performance motor control is obvious, it may be less clear that somatosensation — the sense of touch and proprioception (limb movement) — is an important component of motor control. This concept is emphasized by observing the deficits that people with damage to these systems have when attempting to move. Although vision can be a powerful sensory modality that can often compensate for damage to the somatosensory system, even simple tasks like standing upright [57] or grasping small objects [58] are very difficult without proprioceptive and tactile sensations, respectively. In fact, there has been some suggestion that BCI performance will ultimately be limited if somatosensory feedback is not included in these systems [59–61]. In recognition of this limitation, several groups have begun to investigate this issue in both animal and human studies.

Since the experiments of Wilder Penfield, it has been clear that electrical stimulation to the brain's surface can be used to evoke percepts that a patient can recognize as originating from locations on their own body [62]. In a classic experiment, Romo showed that animals could be trained to tell the difference between temporal patterns of intracortical microstimulation delivered to tactile regions of somatosensory cortex that mimicked their ability to discriminate mechanical vibrations applied to their finger [63]. These early experiments established electrical stimulation of somatosensory cortex as a potential means for restoring sensation.

In 2012, our group began an effort to expand our existing motor BCIs and create a bidirectional system that could generate tactile percepts in a person with spinal cord injury through intracortical microstimulation of the somatosensory cortex. Regulatory approval of this new technique in people was made possible by pre-clinical data from non-human primates that demonstrated that stimulation amplitudes up to 100 µA (20 µC/phase) did not induce damage to the somatosensory cortex that was more than could be expected from the presence of the electrodes themselves [64] and that dexterous motor task performance was unimpaired by the presence of the devices or microstimulation through them [65]. In this first human implant, two microelectrode arrays were placed in the hand area of the somatosensory cortex, specifically in Brodmann's area 1, which contains a population of cells with exclusively cutaneous receptive fields and that may be important for processing texture [66]. Microstimulation through these electrodes evoked sensations that were perceived by the participant as originating from his contralateral hand [67]. The evoked percepts were arranged somatotopically such that the medial electrodes generated sensations from the little finger and the most lateral electrodes evoked sensations from the index finger.

While cortical surface stimulation produces almost exclusively paresthetic sensations of 'buzzing' and 'tingling', intracortical microstimulation also evokes the sensations of pressure, touch and warmth, with many electrodes evoking more than one percept quality. These sensations are largely within the domain of tactile perception and a sense of motion did not occur as might be expected if stimulating proprioceptive regions of the cortex. Stimulation never produces painful sensations, and in some instances the participant describes the sensations as feeling very similar to natural mechanical stimuli. Stimulus detection thresholds are typically less than 40 µA, and the percept intensity can be modulated by changing the stimulus amplitude with a just-noticeable difference of approximately 15 µA. Recently, another group has also shown that microstimulation in human somatosensory cortex can evoke perceptible sensations in a person with a spinal cord injury [68]. The sensations were more broadly

distributed over the arm, with few sensations referred to the hand. Interestingly however, some of the evoked sensations were described by the participant as feeling like movement.

Apart from the consciously detectable component of sensation, which is behaviorally important and could improve embodiment of a prosthesis [69,70], an important factor is determining whether restored sensations could actually improve performance on motor tasks. There is some evidence that including tactile somatosensory feedback in a bidirectional BCI can improve performance in a task where the instruction was to grasp an object within a specified force range [71]. Additionally, a number of groups have demonstrated that intracortical stimulation in both tactile and proprioceptive regions of somatosensory cortex can provide behaviorally relevant information to animals performing behavioral or BCI tasks [72−74]. However, a clear demonstration that restoring somatosensory percepts through intracortical microstimulation can significantly improve motor performance on tasks that have not been specifically designed to highlight the impact of restored somatosensation (i.e. blindfolded subjects) is still needed.

In addition to this limitation of demonstrating meaningful functional motor improvements, there remain a number of significant challenges to creating bidirectional BCIs. First, electrical stimulation generates electric fields that contaminate recorded extracellular action potentials. While it is possible to mitigate the impact through a variety of methods [74−80], these methods tend to reduce the amount of available data, cannot operate in real-time, or don't generalize well to arbitrary multichannel stimulation conditions. The available parameter space for stimulation is also enormous and includes current amplitude, train frequency, train duration, and the number and location of simultaneously active electrodes. In some cases, these parameters interact in non-linear ways and the effects can only be assessed through subject report or careful psychophysical experimentation, both of which are time consuming. Advanced modelling and reverse translation experiments to animal models may help uncover general principles of stimulation that could significantly reduce the effective space. At least one other problem that must be addressed results from the significant cortical surface area dedicated to processing sensory input from the human hand. Available microelectrode arrays cover just a small fraction of this area, with an individual device able to evoke sensations from restricted regions of perhaps a few fingers. In order to achieve the goal of evoking sensations from the entire palmar aspect of the hand, new electrode technologies, as well as imaging techniques to guide intraoperative placement decisions, may be required. Optogenetic techniques are being extended to non-human primate models [81] and have the potential to eliminate stimulation artifacts and increase spatial coverage, however the selectivity and ability to evoke natural and useful sensations must still be evaluated.

Conclusions

In the past decade, basic science knowledge of motor control has been translated to clinical demonstration and investigations of BCI-controlled movement after chronic paralysis. Even more recently, clinical BCI trials have begun to use electrical stimulation of somatosensory cortex to restore cutaneous sensation. In the near term, a priority area for research investigation is to determine whether restored somatosensation can improve motor control and embodiment. BCI sensorimotor restoration can be improved through further investigation and engineering development. For example, there is increasing interest in understanding of the role of the motor cortex in controlling the kinetic, or force-related, components of dexterous movements. The obvious role of somatosensation for controlling these components and the context-dependent nature of motor cortex encoding, suggests that there is a rich interaction taking place in the networks operating during these behaviors. With an increased understanding of these cortical operations, new calibration paradigms and decoding algorithms can be designed to account for this latent activity, enabling robust and generalizable BCI control. The recent progress toward restoring movement and sensation through a bidirectional BCI brings the field closer to the goal of restoring independence to people with upper limb paralysis.

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Conflict of interest statement

Nothing declared.

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  ** of outstanding interest

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