sode of major depressive disorder during the follow-up period (Biol Psychiatry. 2002;51:446-456).

"These types of measures will be critically important for identifying those who are at greatest risk for depression," Armitage said. Despite the complex intersection of brain structure, various molecules, and environmental factors that influence depression, the tried-and-true public health model of early detection, early and effective treatment, and prevention of progression is needed to combat depression.

“We need to treat all the components and all of the issues, such as addressing stress," said John Greden, MD, chair of psychiatry and executive director of the University of Michigan's Depression Center. "We can't separate these things out." □

Harnessing Brain Signals Shows Promise for Helping Patients With Paralysis

M.J. Friedrich

In THE DIVING BELL AND THE BUTTERFLY, Jean-Dominique Bauby, former editor-in-chief of the French magazine, Elle, recounts waking one morning in 1995 to a body that was almost completely paralyzed (Alfred A. Knopf, New York, 1997). A massive stroke in his brain stem left the 43-year-old editor's agile and creative mind virtually imprisoned in an unresponsive body. Bauby eventually composed his account of being "locked in" his body by blinking his left eye, the only means of communication available to him.

As Bauby's literary achievement highlights, the desire to communicate is a fundamental human need, and a growing number of researchers in the field of brain-computer interface (BCI) development are working toward providing patients who have severe motor disabilities with the means to communicate and function independently. Also called neural prostheses and brain-machine interfaces, BCIs are designed to translate brain signals into commands that allow disabled patients to operate various tools, such as a computer. Eventually, researchers predict, BCIs might provide patients with more complex types of control, such as the ability to drive a wheelchair or operate a prosthetic limb.

Although the concept of a BCI has been around for most of the last century, the field has grown explosively in the last 5 years, said Jonathan R. Wolpaw, MD, neurophysiologist and neurologist at the Wadsworth Center, part of the New York State Department of Health in Albany. The reason for such explosive growth, said Wolpaw, is a convergence of such factors as advances in neurobiology and the availability of relatively inexpensive but sophisticated computer software and hardware. Researchers and physicians also have a better appreciation that even patients with the most severe motor disabilities can benefit from even simple devices for communication and control.

Some BCIs detect electrical activity in the brain indirectly and noninvasively through the scalp via electroencephalography (EEG). These devices pick up general brain signals, which patients learn to control to perform a command. Other BCIs use components implanted in the brain to directly record signals from individual neurons that the brain uses for movement and intent—a more direct line to the brain, say researchers who are studying this approach.

TRANSLATING THOUGHT TO DEED
After years of laboratory development, some BCIs are now making their way into clinics and even into patients' homes. Psychologists Andrea

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Kuebler, PhD, and Niels Birbaumer, PhD, of the University of Tuebingen, Germany, and colleagues have been training patients—primarily those with amyotrophic lateral sclerosis—to use BCI-driven communication and control devices in their homes.

The BCI used by the Tuebingen group uses EEG activity recorded from the scalp. In the 1980s, Birbaumer's group was the first to teach subjects to control brain waves called slow cortical potentials. Through training—a form of biofeedback—subjects learn to make these potentials more positive or negative, a skill that can be used to move a cursor on a computer screen and operate a computerized spelling device.

The researchers do not actually understand how individuals learn to regulate these brain waves, and not all patients succeed. "We don’t provide them with a strategy; we just advise them to try different thoughts to move the cursor and try to find out which thoughts work best," said Kuebler.

The training requires a major commitment from both the researcher and the patient. The BCI trainer must learn the idiosyncratic signs each patient uses to communicate, and assess the patient's cognitive functioning and psychological factors (such as depression) that can impair BCI control and performance. It is also important, said Kuebler, to clarify the limits of the technology to avoid unrealistic expectations on the part of patients.

The BCIs developed by various research teams can differ in a number of ways, such as how signals are detected or translated, and even in the type of signal that is detected. For example, the BCI developed by the Tuebingen group detects slow cortical potentials, while the BCI from Wolpaw’s group in Albany has focused on mu and beta rhythms produced by the sensorimotor cortex. Because of such differences, said Wolpaw, it is important to compare, combine, optimize, and apply the various approaches to find out what works best for patients.

To this end, Wolpaw and colleagues have designed a general-purpose BCI system called BCI2000 that can compare and combine different types of signals and adapt to different processing methods and different applications. His team is using the BCI2000 system in a collaboration with Kuebler’s group to evaluate the ability of severely disabled patients to control several different EEG signals. The system also has been made freely available to many other research groups throughout the world, who are now using it in a wide variety of studies, said Wolpaw. The expectation, he said, is that some methods will work better in some individuals, while others will be more useful to other patients.

**DIRECT CONNECTION**

At the same time that BCIs using brain signals recorded from the scalp have been undergoing rapid development, surgically implanted BCIs that “snuggle up” against neurons to record their electrical activity are also being developed. Although clinical studies of such devices have been minimal, efforts are now under way to test these devices in patients.

One group poised to bring this technology into clinical trials is led by John Donoghue, PhD, professor of neuroscience at Brown University, Providence, RI. Proof-of-concept experiments by his team and by another group at Arizona State University, Tempe, have demonstrated that monkeys given a neuromotor prosthesis could control machines directly and immediately using the electrical activity of brain cells in cortical areas that control voluntary movement (Nature. 2002;416:141-142; Science. 2002;296:1829-1832).

Based on this work, Donoghue and colleagues developed the BrainGate system, a neuromotor prosthetic device suitable for humans. The group received approval in April from the US Food and Drug Administration to proceed with a clinical trial of the device in a small group of quadriplegic patients. (The researchers founded a company, Cyberkinetics Inc in Foxborough, Mass, to commercialize the BrainGate system; Donoghue serves as chief executive officer.)

The system consists of a microelectrode array sensor—a platform smaller than a baby aspirin and about as thick as a contact lens—which is implanted on the brain’s surface, its 100 electrodes penetrating into the primary motor cortex. The implant is connected by wires to external components stored on a cart—signal processors and amplifiers (for decoding the neural signals) and computer hardware. The researchers aim to reduce the external components down to the size of a microchip in the next generation of the device.

The device is intended to provide patients with a way to achieve point-and-click actions on a computer, similar to a mouse and keystroke action. Through the computer, said Donoghue, patients could access the Internet and control everyday devices through inexpensive interfaces that operate lights and appliances, such as a television. The computer also could serve as a gateway for controlling robots or the patient’s own paralyzed muscles.

The researchers plan to use the insights from the clinical trial in designing the next generation of neuromotor prostheses, which they envision to be fully implantable, portabel, and wireless. "I expect this technology will follow a developmental path somewhat like heart pacemakers, which progressed from bulky external boxes with leads through the heart to the fully self-contained internal systems we have today," conjectured Donoghue.

**DEEPER THOUGHTS**

Other investigators are studying BCIs implanted in subcortical structures that are deeper within the human brain than the motor cortex. In a study to be published in the July 2004 issue of Neurosurgery, researchers at Duke University Medical Center, Durham, NC, demonstrated that neural signals recorded from the thalamus and subthalamic nucleus could be used to operate such external devices as a robotic arm.

While previous studies have shown that recordings from cortical areas in monkeys can be used for such a pur-
pose, it had been unclear whether subcortical structures could also yield enough information for control, said neurosurgeon and professor of neurobiology Dennis Turner, MD. In the new work, led by Turner and Duke neurobiologist Miguel Nicolelis, MD, the researchers recorded signals from 11 patients with tremor disorders and Parkinson disease who had electrodes inserted into the thalamus and subthalamic nucleus. This area, which is part of the motor circuit involved in motor planning, fires milliseconds before the motor cortex goes into action, said Turner.

The patients (who were undergoing surgery to ease their tremors, a procedure that involves implanting electrodes in the brain to deliver small electrical currents) remain awake during the surgery; for this study, they were asked to play a simple video game for about 5 minutes. A standard part of the therapeutic procedure involves recording from the electrodes to make sure they are placed appropriately in the subcortical area, said Turner. This allowed the researchers to record the signals generated by the task, which provided enough information to predict hand motion, he said.

“There are a number of reasons to consider the thalamus as an alternative site to the cortex,” said Turner. For one thing, 25 to 30 years of recording in the subcortical area in humans have demonstrated that it is a safe procedure. Also, because the thalamus has a higher density of neurons than are found in the cortex, it increases the likelihood that electrodes will connect with a greater number of neurons. The deeper implant also is anchored more firmly in the brain, making the electrodes more stable, he noted.

**COMPLEX CONTROL**

Conventional wisdom among BCI researchers has held that while scalp-recorded EEG signals are useful for relatively simple functions, such as computer word processing, the complex control necessary for operating prosthetic limbs would require brain signals recorded from implanted devices. However, data from Wolpaw’s laboratory suggest that signals recorded from the surface of the scalp might indeed be used in more complex ways, perhaps obviating the need for implants.

“We have shown that these signals can be used to provide multidimensional movement control,” he said.

In Wolpaw’s view, the ultimate goal of a BCI would simply be to communicate a goal, such as picking up a book, to a neuroprosthetic arm, and a downstream interface would translate that command into the muscle activity needed to reach out and pick up the object. “This kind of distributed control could closely approximate what we actually do when we execute a motor task,” he said.

However, others are skeptical that such simple commands would be sufficient to replicate our everyday movements in paralyzed patients. “The ability to perform the complex coordinated voluntary movements of our fingers, hands, and arms as fast as it is done by the intact nervous system is likely to require many additional signal channels,” said Donoghue. “Furthermore, direct signals may provide a signal that is as natural to use as the hand itself, while indirect signals require learning and may be disrupted when other cognitive or motor actions [like speech] occur.”

It remains to be seen whether controlling prosthetic devices is best achieved by detecting direct brain signals directly using implants or by detecting signals indirectly via the less invasive method of sensors attached to the scalp. It seems likely, however, that usefulness of different types of neural prostheses will vary according to the nature of an individual’s impairment, so a long-term goal will be to tailor such devices to each patient’s needs. Meanwhile, researchers will continue to explore harnessing patients’ own brain signals as a means to communicate and function independently.

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**Low Health Literacy Called a Major Problem**

**Brian Vastag**

Two major reports conclude that nearly half the adults in the United States have trouble interpreting medical information, thus jeopardizing their health and inflating costs while complicating the work of health professionals, conclude two major reports.

Consent forms, prescription drug directions, and oral instructions to patients are often communicated in language more complex than the average comprehension level of US adults, conclude both studies, one from the Agency for Healthcare Research and Quality (AHRQ) and the second from the Institute of Medicine (IOM).

As a result, patients often take medicines on erratic schedules, miss follow-up appointments, and otherwise fail to grasp physicians’ expectations. Dramatic examples shared at a press conference include that of a college-educated woman who did not unwrap a suppository before use, and a mother who poured antibiotic syrup into her daughter’s painful ear. One study found that the majority of adults tested could not pick a teaspoon out of a utensil lineup.

**HEALTH CARE CURRENCY**

“The main currency in health care is communication and information,” said Carolyn Clancy, MD, AHRQ director at a press conference unveiling the

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The Thought-Translation Device (TTD): Neurobehavioral Mechanisms and Clinical Outcome

Niels Birbaumer, Thilo Hinterberger, Andrea Kübler, and Nicola Neumann

Abstract—The thought-translation device (TTD) consists of a training device and spelling program for the completely paralyzed using slow-cortical brain potentials (SCP). During the training phase, the self-regulation of SCPs is learned through visual-auditory feedback and positive reinforcement of SCPs; during the spelling phase, patients select letters or words with their SCPs. A psychophysiological system for detection of cognitive functioning in completely paralyzed patients is an integral part of the TTD. The neurophysiological and anatomical basis of SCP-regulation was investigated by recording of BOLD-response in functional magnetic resonance imaging. Results showed involvement of basal ganglia and premotor cortex for required SCP positivity. The clinical outcome of 11 paralyzed patients using the TTD and quality of life of severely paralyzed patients is described. First attempts to improve learning of brain regulation with transcranial magnetic stimulation were successful.

Index Terms—Amyotrophic lateral sclerosis (ALS), locked-in-syndrome, physiological brain regulation, slow cortical potentials.

This report provides an update of results obtained with the thought-translation device (TTD) since its first report in IEEE TRANSACTIONS ON REHABILITATION ENGINEERING in 2000 [1]. Methodological details and details of results can be found in Kübler et al. [2], [3], Wolpaw et al. [4], Kübler and Birbaumer [5], Kochtcheou et al. [6], and Hinterberger et al. [7].

I. TECHNOLOGY AND FUNCTIONING

In its present form, the core of the TTD consists of a single computer program that runs under all MS-Windows versions. This software contains the functions of electroencephalogram (EEG)-acquisition, storage, signal processing, classification, and various applications for brain–computer-communication such as spelling. It was written in C++ for Windows and uses the BCI-2000 common standard developed in cooperation with the Wadsworth Center group (see Wolpaw et al. [32]). The BCI-2000 software can be obtained free of charge from G. Schalk at http://www.bciresource.org. The file format is fully compatible with the standard. The patient receives visual feedback on a separate monitor and/or auditory feedback. The TTD-software can be connected to several EEG amplifier systems. At the patient’s home, an eight-channel EEG-amplifier (PsyLabs, EEG8) with a time constant of 16 s is connected to an A/D-converter (Computerboards, PCIM-DAS 1602/16) serving as the interface to the TTD. As this A/D-converter is also available for notebooks, a portable version of the TTD can also run on notebooks. An interface to an MRI-compatible 16/32-channel EEG-amplifier (EMR16/32, Schwarzer, Munich) allows the TTD to be used in functional magnetic resonance imaging (fMRI)-studies investigating the basic mechanisms of EEG self-regulation.

The TTD also encompasses a psychophysiological system for detection of cognitive functioning in locked-in-syndrome, vegetative state, apallic syndrome, and coma [8]. This system for detection of cognitive functioning consists of a series of hierarchically ordered experiments using auditory event-related brain potentials (ERPs). The hierarchy of experimental paradigms begins with a simple auditory oddball using frequent and rare tones; it ends with complex sentences using semantic and syntactic errors for detection of the N400 and P600 waves reflecting higher processing capacities. Application of brain–computer interface (BCI) systems and the TTD in completely paralyzed patients is useful only if a minimum of cognitive and neuropsychological functioning is ensured. Only patients with intact ERP differentiation participate in TTD training.

The TTD and BCI-2000 permit recording and online-feedback and reinforcement of slow cortical potentials (SCPs), ERPs, mu rhythm, and other EEG signals in frequency bands up to 40 Hz. Feedback of brain activity in patients with closed eyes or impaired vision can be given auditorily or with bright light through closed eyes. The system for detection of cognitive functioning is available in Hebrew and French, and partly in English, Italian, and German. The spelling system consists of a letter selection system [9] combined with rapid word and sentence completion based on psycholinguistic principles. Letters are presented visually or auditorily by the computer and can be selected with one of the previously mentioned EEG activities. The TTD requires a learning phase of instrumental (operant) learning of physiological self-regulation of brain activity in which 1–8-s epochs with a particular potential (mainly SCP or mu) are fed back and the achieved brain changes are positively reinforced by a smiling face and a harmonic tone sequence. For patients unable to select letters and with no remaining visual function a digital "yes"—"no" version allows the patient to respond to external questions with a brain response, e.g., a negative or positive SCP polarization in a continuous fashion.

II. NEUROBEHAVIORAL MECHANISMS OF PHYSIOLOGICAL CONTROL OF SCPs

In a series of studies over the last 25 years, the neurophysiological basis of SCP and SCP-self-control was studied extensively (for a review see [10] and [11]). This led to a comprehensive psychophysiological model of SCP. More recent investigations used fMRI and transcranial magnetic stimulation (TMS) in healthy subjects and in patients at various stages of the learned acquisition of SCP self-control [7], [12]. The reported physiological mechanisms for SCP control might be generalized to physiological regulation of other EEG/magnetoencephalography (MEG) signals such as mu or P300, but there are, to date, no data available (see [4]).

As shown in Fig. 1, fMRI-recorded BOLD responses averaged over five trained subjects able to produce large (> 8 μV) cortical positivities and negativities. The comparable results of a larger group of subjects with a different degree of performance were described in Hinterberger et al. [7]. Subjects were trained outside the fMRI scanner for 35 sessions to produce cortical positivities and negativities of 8-s duration in the presence of a discriminative stimulus (S0) consisting of a single letter ("A" for negativity and "B" for positivity) centered on the computer screen. As a baseline for the fMRI analysis, a third condition (indicated with "C") instructed the subject to maintain viewing only without feedback. Feedback of SCP was provided over the whole 8-s period in the form of a yellow ball moving toward the illuminated goal. Each trial session included 70 trials for positivity and 70 trials for negativity. After the last training session, subjects did the training in the 1.5 T MRT scanner (Sonata,
Fig. 1. Left diagram shows the EEG slow waves during the voluntary production of cortical negativity (red), positivity (blue), and the passive viewing (green). The fMRI images on the right show highly significant areas of activation (yellow, red) during required electrocortical negativity (upper row). During required negativity BOLD-response increased in premotor areas and under the EEG electrode (vertex). During required positivity, BOLD-response decreased in medial thalamus, posterior visual areas, medial prefrontal areas, and under the EEG electrode (vertex/blu).

Siemens, Erlangen) which recorded BOLD responses during the task for performing cortical negativity, positivity, and passive viewing. (For methodological details see [7]). A reference session immediately before the fMRI session was carried out in a dummy-fMRI consisting of a tomograph without magnetic fields. (This enabled us to do the feedback session and record the EEG in the same environment as that in a real scanner without the scanning artifacts.) As shown in Fig. 1 on the left, in these reference sessions, the five subjects achieved an average differentiation of 13.3 µV (N = 620, t = 11.3). A clear pattern of differential metabolic responses of self-produced brain responses emerged: cortical negativities resulted in a general increase of metabolic activity; cortical positivity resulted in a widespread decrease. Increases during negativity were located primarily at vertex near the electrode position in the feedback training, premotor regions and precentral areas [supplementary motor area (SMA)]. Decreases during positivities were centered at vertex, thalamus, and medial precentral cortex (see Fig. 1, right). Successful regulation of cortical SCP-positivities could be predicted with an accuracy of r = 0.93 from activation of Globus pallidus and putamen and deactivation of SMA (right) with an accuracy of 0.98 from dorsomedial prefrontal areas. Negativity versus positivity was predicted with r = 0.80 from parahippocampal BOLD-activations.

These data confirm an earlier preliminary report [13] strengthening and broadening the excitation-threshold-regulation theory developed by Birbaumer et al. [10]: negative SCPs reduce neural excitation thresholds of upper cortical layers while positive SCPs increase it through a negative feedback circuit involving the basal ganglia and reticular nucleus of the thalamus. With increased cortical excitation (negativity), inhibitory striatal nuclei increase the excitation threshold of the involved cortical assemblies. Activation of these nuclei during cortical positivity not only reduces cortical excitation, but may also activate a (dopaminergic) positive reinforcement zone of the ventral striatum that is responsible for the learned stabilization and maintenance of the self-produced cortical positivity [14]. During SCP-negativity, thalamic and reticular formation is activated. Therefore, regulation of attentional modulation seems to constitute the cognitive strategy in the physiological regulation of SCPs and probably other brain responses such as mu or beta rhythms as well.

Awareness of these cognitive-attentional strategies, however, is not necessary for successful operant brain regulation. Kechouchay et al. [9] found that in successful SCP-regulators, awareness of the neural brain response, i.e. their SCPs, follows the actual (operant) control of that response and is usually delayed by several sessions. This and other results, such as absence of temporal-hippocampal involvement in the fMRI study reported previously and inconsistent verbal report data [15], clearly indicate that physiological regulation of SCP and probably other neuropsychological phenomena can be viewed as an instrumentally learned implicit-procedural response acquired through a cognitive mechanism of repetition priming [16].

III. CLINICAL OUTCOME OF TTD APPLICATION IN LOCKED-IN PATIENTS

Since our first report in this journal [1], six new patients have been trained, bringing the total to 11 patients trained over extended periods ranging from 6 mo to 6 yr. Nine of the 11 patients were diagnosed with end-stage amyotrophic lateral sclerosis (ALS) and were artificially ventilated and fed. One had subcortical hemorrhage and one was diagnosed with myeloneuropathy and Guillain-Barré syndrome and has been locked-in for five years. Four of the six new patients are completely locked in with no motor activity and no eye-movements. In these patients, locked-in syndrome was confirmed through lack of eye and lid-movements, and lack of EMG-measured face or body muscle activity. EMG measurements for anal sphincter muscle were not done. All patients satisfied cognitive-ERP detection for cognitive functioning by completing complex processing tasks. Their ERPs were intact. One of the four new locked-in patients died from pulmonary complications before achieving any communication. The remaining seven (not completely locked-in) patients were able to communicate yes-no signals only with eye or face muscles at the beginning of training. Two of these seven patients subsequently lost all motor responses and are still communicating with the TTD. None of the patients who were already completely locked-in at the beginning of training have yet been able to gain control over SCP, mu, or eye movement. Training with two of these patients is still in progress. The already substantial obstacles in trying to train these four initially completely locked-in patients are complicated by the considerable geographical distances between the home laboratory in Tuebingen, Germany, and the patients places of residence (Patient LB lived in Berlin, Germany; patient NB lives in Los Angeles, CA; patient EL lives in Lima, Peru; and patient AG, the closest, lives 120 km from the home lab). Since all patients have to be visited at home, have TTD devices installed in their homes, and have on-going training, distance presented a considerable problem. Of the remaining seven patients (who live closer to the home lab), two
currently use the TTD for communication, with an average selection speed for a letter or completed word of 1/min. The learning curves and performance of these patients can be found in [2], [17]–[20].

These results suggest that patients who learn physiological control will be able to use the spelling device and select letters and words with their brain response alone. Learning curves for acquisition of SCP control are extremely variable and rarely show exponential learning as reported for the acquisition of implicit skills or even explicit-declarative knowledge. Regression analysis of performance in five patients [21] revealed significant prediction of spelling success only in those patients demonstrating improvement during the first 30 training runs. One run consists of 70–100 single trials (see [31]).

In an effort to improve learning of physiological control of SCPs, TMS was used before each trial. In the first study [12], a single magnetic pulse was given at the vertex and at a lateral scalp position in ten healthy subjects prior to each trial of feedback-assisted differential acquisition of negative and positive SCP changes. The outcome of this study was inconclusive, main effects pointed toward a nonsignificant enhancement of negative SCP after vertex stimulation and a significant increase of positive SCP after stimulation over the lateral scalp position. An ongoing experiment, again with healthy subjects, used high-frequency TMS (15 Hz) and low-frequency TMS (1 Hz) delivered for 2 and 30 s, respectively, in a balanced sequence prior to trials of required positivity and negativity. Results clearly indicate that low-frequency TMS improved learning of SCP positivity and high-frequency TMS accelerated learning of negativity [22].

IV. QUALITY OF LIFE AND DEPRESSION IN SEVERELY PARALYZED PATIENTS

Ninety to ninety five percentage of patients diagnosed with ALS (or similar debilitating diseases) decide not to be ventilated and die under undocumented circumstances. Legal regulations concerning assisted suicide vary within Europe, from state to state in the U.S., and in other countries. Moreover, in some developing countries, common practice does not necessarily correlate with legal regulations. Most patients are not fully aware of the possible benefits of assistive communication devices and BCI, and do not have a fully accurate view of quality of life after tracheotomy and artificial respiration. Since there have been, to date, no neuropsychological and psychometric instruments for measurement of psychological variations in severely paralyzed patients, the results of published data on cognitive and emotional functioning in severely paralyzed people are unclear. The data that do exist do not confirm the negative expectations of ALS patients, families, and health professionals, but, instead, indicate satisfying or good quality of life even in artificially respirated ALS patients [23], [24].

Fig. 2 shows how a sample of 22 ALS patients rated their general quality of life, as measured by the scales to assess quality of life [25]. Patients were everything from mildly impaired to almost completely paralyzed and artificially ventilated and fed. Quality of life was not correlated with the degree of physical impairment as measured with the modified Norris Neuroscale [26]. Admittedly, these are preliminary results that await replication, but they underline the need for functioning BCIs for these groups. The data also suggest that patients’, doctors’, and family members’ fears of low quality of life and suffering in locked-in states are unfounded and question the widespread decline in choosing of artificial respiration.

V. FUTURE DEVELOPMENTS

After final tests of the common hardware and software platform for TTD and BCI-2000 developed in cooperation with the Wadsworth group (see [32]), we will conduct a controlled international study comparing acquisition and spelling between SCP- and mu-control, first in healthy persons and later in ALS patients. These studies should allow a more individualized training protocol, faster acquisition of physiological control, and reduction of dropouts. Acceleration of training of SCP- and mu-control with TMS and external dc currents [27] constitutes another priority for experimentation with healthy populations and, in case of successful completion with the healthy population, with the paralyzed. A study of metabolic and neuronal mechanisms underlying TTD-assisted acquisition of SCP control in nonrespirated ALS patients began in mid-2002.

To address issues concerning quality of life and emotional organization, a series of experiments (unpublished) using the International Affective Picture System (IAPS, [28]) will be replicated. Studies to date show that paralyzed and respirated ALS patients, patients with high spinal cord lesions, professional athletes, and healthy controls have similar neural, psychological, and autonomic processing of emotional material. These studies should allow for more efficient selection and use of positive reinforcers, and an investigation of their neural basis, in persons with extremely restricted positive reinforcers. Knowledge of the effects of remaining positive reinforcers is critical for learning of physiological self-control and BCI use.

Simultaneously with these EEG-centered BCI-approaches, two newly developed BCI systems will be tested, first in healthy subject groups and then in patients in the initial stages of ALS and other progressive neurological diseases. These include an online fMRI-BCI for physiological regulation of cortical and subcortical metabolic BOLD-responses [29] and a 151 whole-head MEG-BCI system using conditioning and physiological control of very early (<80 ms) somatosensory components and low-frequency range MEG oscillations. These invasive multisensor and multielectrode extensions of the current BCI research in humans will complement invasivemultielectrode animal BCI systems for neuroprostheses [30], [31]. For a variety of reasons, comparable precision and classification of brain states can be achieved with noninvasive methodologies for BCI such as fMRI, MEG, and high-density EEG.

In summary, BCI-research and BCI systems consist not only of clinical or engineering approaches to direct brain control, but will also open new horizons for basic systemic and behavioral neuroscience and the classification of brain states.

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Current Trends in Brain-Computer Interface Research at the Neil Square Foundation

Gary E. Birch, Steven G. Mason, and Jairine F. Borisoff

Abstract—The Neil Square Foundation (NSF) is a Canadian nonprofit organization whose purpose is to create opportunities for independence for individuals who have significant physical disabilities. Over the last ten years, our team in partnership with researchers at the Electrical and Computer Engineering Department, the University of British Columbia, has been working to develop a direct brain-controlled switch for individuals with significant physical disabilities. The NSF Brain Interface Project primarily focuses on the development of brain–computer interface switch technologies for intermittent (or asynchronous) control in natural environments. That is, technologies that will work when the User intends control but also remains in a stable off state when there is no intent to control. A prototype of such a switch has successfully been developed. This switch has demonstrated classification accuracies greater than 94%. The initial results are promising, but further research is required to improve switch accuracies and reliability and to test these switch technologies over a larger population of users and operating conditions. This paper provides an overview of the NSF brain-switch technologies and details our approach to future work in this area.

Index Terms—Assistive technology, asynchronous control, brain-computer interface (BCI), functional model, intent, intermittent control, neuroprosthesis, pattern recognition, standards, statistical signal processing, taxonomy.

I. INTRODUCTION

The Neil Square Foundation (NSF)—in partnership with the Electrical and Computer Engineering Department, the University of British

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Learning to Control a Brain–Machine Interface for Reaching and Grasping by Primates

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Reaching and grasping in primates depend on the coordination of neural activity in large frontoparietal ensembles. Here we demonstrate that primates can learn to reach and grasp virtual objects by controlling a robot arm through a closed-loop brain–machine interface (BMIC) that uses multiple mathematical models to extract several motor parameters (i.e., hand position, velocity, gripping force, and the EMGs of multiple arm muscles) from the electrical activity of frontoparietal neuronal ensembles. As single neurons typically contribute to the encoding of several motor parameters, we observed that high BMIC accuracy required recording from large neuronal ensembles. Continuous BMIC operation by monkeys led to significant improvements in both model predictions and behavioral performance. Using visual feedback, monkeys succeeded in producing robot reach-and-grasp movements even when their arms did not move. Learning to operate the BMIC was paralleled by functional reorganization in multiple cortical areas, suggesting that the dynamic properties of the BMIC were incorporated into motor and sensory cortical representations.

Introduction

Traumatic lesions of the central nervous system as well as neurodegenerative disorders continue to inflict devastating and so far irreparable, motor deficits in large numbers of patients. Every year, spinal cord injuries alone are responsible for the occurrence of about 11,000 new cases of permanent paralysis in the United States (Nobunaga et al. 1999). These cases add up to an already sizeable population of patients, estimated at 200,000 in the United States (Nobunaga et al. 1999), who have to cope with partial (as in the case of paraplegics) or almost total (i.e., quadriplegia) body paralysis.

Until very recently, the main thrust of basic research on restoration of motor functions after spinal cord injuries focused on reconstructing the connectivity and functionality of damaged nerve fibers (Ramon-Cueto et al. 1998; Uchida et al. 2000; Bomze et al. 2001; Bunge 2001; Schwab 2002). While this repair strategy has produced encouraging results, such as limited restoration of limb mobility in animals, the goal of restoring complex motor behaviors, such as reaching and grasping, remains a major challenge.

Two decades ago, an alternative method for restoring motor behaviors in severely paralyzed patients was proposed (Schmidt 1980). This approach contends that direct interfaces between spared cortical or subcortical motor centers and artificial actuators could be employed to “bypass” spinal cord injuries so that paralyzed patients could enact their voluntary motor intentions. Initial experimental support for a cortically driven bypass came from the studies conducted by Fetz and collaborators (Fetz 1989; Fetz and Finocchio 1971, 1975; Fetz and Baker 1973), who demonstrated that macaque monkeys could learn to selectively adjust the firing rate of individual cortical neurons to attain a particular level of cell activity if provided with sensory feedback that signaled the level of neuronal firing.

Recent studies in rodents (Chapin et al. 1999; Talwar et al. 2002), primates (Wessberg et al. 2000; Serruya et al. 2002; Taylor et al. 2002), and human subjects (Birbaumer 1999) have rekindled interest in using brain–machine interfaces (BMIs) as a potential alternative for spinal cord rehabilitation. These experiments have demonstrated that animals can learn to utilize their brain activity to control the displacements of computer cursors (Serruya et al. 2002; Taylor et al. 2002) or one-dimensional (1D) to three-dimensional (3D) movements of simple and elaborate robot arms (Chapin et al. 1999; Wessberg et al. 2000).

Despite these initial results, several fundamental issues regarding the operation of BMIs, ranging from basic electrophysiological issues to multiple engineering bottlenecks, remain a matter of considerable debate (Nicolelis 2001, 2003; Donoghue 2002). For example, although most agree that a BMI designed to reproduce arm/hand movements will require long-term and stable recordings from cortical (or subcortical) neurons through chronically implanted electrode arrays (Nicolelis 2001, 2003; Donoghue 2002), there is considerable disagreement on what type of brain signal (single unit, multiunit, or field potentials [Pesaran et al. 2002])

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Abbreviations: BMI, brain–machine interface; BMIC, closed-loop brain–machine interface; 1D, one dimensional; 3D, three dimensional; DOF, degree of freedom; DTC, directional tuning curve; DTD, directional tuning depth; DTE, directional tuning of neural ensemble; EMG, electromyogram; GF, gripping force; HP, hand position; HV, hand velocity; M1, primary motor cortex; MIP, medial intraparietal area; ND, neuron dropping; PETH, peri-event time histogram; PMd, dorsal premotor cortex; PP, posterior parietal cortex; S1, primary somatosensory cortex; SMA, supplementary motor area

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would be the optimal input for a such a device. Research groups that propose the use of single-unit activity also diverge on the assessments of whether small (eight to thirty) (Serruya et al. 2002; Taylor et al. 2002) or substantially larger (hundreds to thousands) numbers of single units may be necessary to operate a BMI efficiently for many years (Wessberg et al. 2000; Nicolelis 2001).

The issues of what signal to use and how much neuronal tissue to sample are linked to the question of what type of motor commands may be extracted from brain activity. Up to now, animal studies have demonstrated the capability of extracting a single motor parameter (e.g., hand trajectory, position, direction of movement) from brain activity in order to operate a BMI (Wessberg et al. 2000; Taylor et al. 2002). While it is well known that cortical neuronal activity can encode a variety of motor parameters (Fetz 1992; Messier and Kalaska 2000; Johnson 2001), it is not clear which cortic areas would provide the best input for a BMI designed to restore multiple features of upper-limb function. A couple of laboratories have focused on the primary motor cortex (M1) (Serruya et al. 2002; Taylor et al. 2002), while another group has selected the parietal cortex as the main input to a BMI (Pesaran et al. 2002). Our previous studies have suggested that, because of the distributed nature of motor planning in the brain, neuronal samples from multiple frontal and parietal cortical areas ought to be employed to operate such devices (Wessberg et al. 2000; Nicolelis 2001, 2003; Donoghue 2002). Another important issue that has received little attention is how the interposition of an artificial actuator (such as a robot arm) in the control loop impacts the BMI and the subject's performance. Two previous studies have reported that macaque monkeys learn to operate a closed-loop BMI (BMIC) using visual feedback (Serruya et al. 2002; Taylor et al. 2002), but the animals in these studies did not control a real mechanical actuator.

Finally, more data are needed to evaluate the extent, relevance, and behavioral meaning of cortical reorganization that can be triggered by operation of a BMIC. A possibility of such reorganization is supported by results in plasticity in M1 neurons in a force-field adaptation task (Li et al, 2001) and by an initial report of changes in directional selectivity in a small sample of M1 neurons during BMIC operation (Taylor et al. 2002).

In this paper, we present the results from a series of long-term studies in macaque monkeys to address several of the fundamental issues that currently shape the debate on BMIs. In particular, we demonstrate for what we believe is the first time the ability of the same ensemble of cells in closed-loop mode to control two distinct movements of a robotic arm: reaching and grasping. In addition, we demonstrate how the monkeys learn to control a real robotic actuator using a BMIC. We also report on how they overcome the robot dynamics and return to the same level of performance without modification of the task. Finally, we quantitatively compare the contribution of neural populations in multiple cortical areas needed to create this control and analyze changes in these contributions during learning.

**Results**

Using the experimental apparatus illustrated in Figure 1A, monkeys were trained in three different tasks: a reaching task (task 1; Figure 1B), a hand-grasping task (task 2; Figure 1B), and a reach-and-grasp task (task 3; Figure 1B).

We used multiple linear models, similar to those described in our previous studies (Wessberg et al. 2000), to simultaneously extract a variety of motor parameters (i.e., hand position [ HPx, HPy, HPz], velocity [ HVx, HVy, HVz], and gripping force [GF]) and multiple muscle electromyograms (EMGs) from the activity of cortical neural ensembles. Although all these parameters were extracted in real time on each session, only some of them were used to control the BMIC, depending on each of the three tasks the monkeys had to solve in a given day. In each recording session, an initial 30-min period was used for training of these models. During this period, monkeys used a hand-held pole either to move a cursor on the screen or to change the cursor size by application of gripping force to the pole. This period is referred to as “pole control” mode. As the models converged to an optimal performance, their coefficients were fixed and the control of the cursor position (task 1 and 3) and/or size (task 2 and 3) was obtained directly from the output of the linear models. This period is referred to as “brain control” mode. During brain control mode, animals initially produced arm movements, but they soon realized that these were not necessary and ceased to produce them for periods of time. To

**Figure 1.** Experimental Setup, Behavioral Tasks, Changes in Performance with Training, EMG Records during Pole and Brain Control, and Stability of Model Predictions

(A) Behavioral setup and control loops, consisting of the data acquisition system, the computer running multiple linear models in real time, the robot arm equipped with a gripper, and the visual display. The pole was equipped with a gripping force sensor. Robot position was translated into cursor position on the screen, and feedback of the gripping force was provided by changing the cursor size.

(B) Schematics of three behavioral tasks. In task 1, the monkey's goal was to move the cursor to a visual target (green) that appeared at random locations on the screen. In task 2, the pole was stationary, and the monkey had to grasp a virtual object by developing a particular gripping force as instructed by two red circles displayed on the screen. Task 3 was a combination of tasks 1 and 2. The monkey had to move the cursor to the target and then develop a gripping force necessary to grasp a virtual object.

(C–E) Behavioral performance for two monkeys in tasks 1–3. The percentage of correctly completed trials increased, while the time to conclude a trial decreased with training. This was true for both pole (blue) and brain (red) control. Horizontal (green) lines indicate chance performance obtained from the random walk model. The introduction of the robot arm into the BMIC control loop resulted in a drop in behavioral performance. In approximately seven training sessions, the animal's behavioral performance gradually returned to the initial values. This effect took place during both pole and brain control.

(F) Stability of model predictions of hand velocity during long pole-control sessions (more than 50 min) for two monkeys performing task 1. The first 10 min of performance were used to train the model, and then its coefficients were frozen. Model predictions remained highly accurate for tens of minutes.

(G) Surface EMGs of arm muscles recorded in task 1 for pole control (left) and brain control without arm movements (right). Top plots show the X-coordinate of the cursor; plots below display EMGs of wrist flexors, wrist extensors, and biceps. EMG modulations were absent in brain control.

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Figure 2. Performance of Linear Models in Predicting Multiple Parameters of Arm Movements, Gripping Force, and EMG from the Activity Frontoparietal Neuronal Ensembles Recorded in Pole Control
(A) Motor parameters (blue) and their prediction using linear models (red). From top to bottom: Hand position (HPx, HPy) and velocity (HVx, HVy) during execution of task 1 and gripping force (GF) during execution of tasks 2 and 1.
(B) EMGs (blue) recorded in task 1 and their prediction (red).
(C) Contribution of neurons from the same ensemble to predictions of hand position (top), velocity (middle), and gripping force (bottom). Contributions were measured as correlation coefficients ($R^2$) between the recorded motor parameters and their values predicted by the linear
model. The color bar at the bottom indicates cortical areas where the neurons were located. Each neuron contributed to prediction of multiple parameters of movements, and each area contained information about all parameters.

(D–F) Contribution of different cortical areas to model predictions of hand position, velocity (task 1), and gripping force (task 2). For each area, ND curves represent the average prediction accuracy ($R^2$) as a function of number of neurons needed to attain it. Contributions of each cortical area vary for different parameters. Typically, more than 30 randomly sampled neurons were required for an acceptable level of prediction.

(G–I) Comparison of the contribution of single units (blue) and multunits (red) to predictions of hand position, velocity, and gripping force. Single units and multunits were taken from all cortical areas. Single units' contribution exceeded that of multunits by approximately 20%.

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systematically study this phenomenon, we removed the pole after the monkey ceased to produce arm movements in a session. In each task, after initial training, a 6 DOF (degree-of-freedom) robot arm equipped with a 1 DOF gripper was included in the BMic control loop. In all experiments, visual feedback (i.e., cursor position/size) informed the animal about the BMic's performance. When the robot was used, cursor position indicated to the animal the X and Y coordinates of the robot hand. The cursor size provided feedback of the force measured by the sensors on the robot's gripper. The time delay between the output of the linear model and the response of the robot was in the range of 60–90 ms.

For each task, training continued until the animal reached high levels of performance in brain control mode. During this learning period, both the animal's and the BMic's performance were assessed using several measures. Chance performance was assessed using Monte Carlo simulations of random walks. Contributions of individual neurons and the overall contribution of different cortical areas to the prediction of multiple motor signals were evaluated. In addition, changes in directional tuning of the neurons that resulted from using the BMic were quantified.

Behavioral Performance during Long-Term Operation of a BMic

Figure 1C–1E illustrates procedural motor learning as animals interacted with the BMic in each of the three tasks. Improvement in behavioral performance with the BMic was indicated by a significant increase in the percentage of trials completed successfully (Figure 1C–1E, top graphs) and by a reduction in movement time (Figure 1C–1E, bottom graphs). For task 1, both monkeys had some training in pole control of task 1 (data not shown) several weeks before the series of successive daily sessions illustrated in Figure 1C. For both tasks 1 and 2, after a relatively small number of daily training sessions, the monkeys' performance in brain control reached levels similar to those during pole control (Figure 1C and 1D). For tasks 2 and 3, all behavioral data are plotted, given that in both cases pole and brain controls were used since the first day of training. Behavioral improvement was also observed in task 3, which combined elements of tasks 1 and 2 (Figure 1E).

In all three tasks, the levels of performance attained during brain control mode by far exceeded those predicted by a random walk model (dashed and dotted lines in Figure 1C–1E). Moreover, both animals could operate the BMic without any overt arm movement and muscle activity, as demonstrated by the lack of EMG activity in several arm muscles (Figure 1G). The ratios of the standard deviation of the muscle activity during pole versus brain control for these muscles were 14.67 (wrist flexors), 9.87 (wrist extensors), and 2.77 (biceps).

A key novel feature of this study was the introduction of the robot equipped with a gripper into the control loop of the BMic after the animals had learned the task. Figure 1C shows that because the intrinsic dynamics of the robot produced a lag between the pole movement and the cursor movement, the monkeys' performance initially declined. With time, however, the performance rapidly returned to the same levels as seen in previous training sessions (Figure 1C). It is critical to note that the high accuracy in the control of the robot was achieved by using velocity control in the BMic, which produced smooth predicted trajectories, and by the fine tuning of robot controller parameters. These parameters were fixed across sessions in both monkeys. The controller sent velocity commands to the robot every 60–90 ms. Each of these commands was compensated for potential position errors of the robot hand that resulted from previous commands.

In all experiments, the animals continuously received visual feedback of their performance. Unlike previous results in owl monkeys from experiments in which an open-loop BMI was implemented (Wessberg and Nicolelis 2003), after the model parameters were fixed, its predictions did not drift substantially from initial best performance, even during 1-h recordings. As shown in the examples of Figure 1F, prediction of grasping force (mean ± SEM, $R = 0.84 ± 5 \times 10^{-5}$) in monkey 1, as well as hand position ($R = 0.63 ± 3 \times 10^{-5}$) and velocity ($R = 0.73 ± 5 \times 10^{-5}$) in monkey 2, remained very stable despite some transient fluctuations (slopes for black, magenta, and cyan lines are, respectively, $-2.16 \times 10^{-4}$, $-5.15 \times 10^{-4}$, and $-1.1 \times 10^{-3}$). One possibility is that the presence of continuous visual feedback helped to stabilize model performance.

Which Motor Parameters Can Be Extracted in Real Time?

Throughout learning of all three behavioral tasks, populations of neurons distributed in multiple frontal and parietal cortical areas exhibited task-related modulations of their firing rates. Using multiple linear models running in parallel, several motor signals were extracted from those modulations. To evaluate the performance of the models in extracting different motor parameters, the models were first trained using 15 min of pole control data and then subsequent data were predicted. Figure 2A shows representative 1-min records of such predictions of hand position (HPx, HPy), hand velocity (HVx, HVy), and gripping force (GF). Figure 2B shows the model prediction of EMG activity. In well-trained animals, the linear models accounted for up to 85% of the variance of hand position, 80% of hand velocity, 95% of gripping force, and 61% of multiple EMG activity. These results show that elaborate hand movements, such as the ones required to solve task 3, could be predicted from brain activity using a BMic with the simultaneous application of multiple linear models.

What Cortical Areas to Sample? How Many Neurons to Record From? What Type of Neuronal Signal to Use?

Several analytical tools were used to address these fundamental questions. By measuring the correlation between neuronal firing and each of the predicted parameters (Figure 2A), we observed that single neurons located in
frontal and parietal areas contributed to real-time predictions of all motor parameters analyzed (Figure 2C). Although cortical areas are known to have functional specializations (Wise et al. 1997; Burnod et al. 1999), our sample of M1, dorsal premotor cortex (PMd), supplementary motor area (SMA), posterior parietal cortex (PP), and primary somatosensory cortex (S1) cells provided information, albeit at different levels, for predictions of hand position, velocity, gripping force, and multiple EMGs.

For each motor parameter analyzed, increasing the size of the neuronal population improved the quality of prediction. The effect of sample size on predictions was clearly shown using neuron-dropping (ND) analysis (Figure 2D–2F). ND plots indicate the number of neurons that are required to achieve a particular level of model prediction for each cortical area. Although all cortical areas surveyed contained information about any given motor parameter, for each area, different numbers of neurons were required to achieve the same level of prediction. For example, the sample of M1 neurons (33–56 cells) taken alone (Figure 2D–2F) was the best predictor for all motor variables (73% of the variance for hand position, 66% for velocity, 83% for gripping force). The sample of SMA neurons (16–19 cells) produced high predictions of hand position (51%) and velocity (51%), but poor prediction of gripping force (19%). The activity of PMd (64 cells) or S1 (21–39 cells) ensembles predicted hand position (48% for both PMd and S1) and velocity (46% for PMd and 35% for S1) reasonably well, but yielded lower predictions of grip (29% for PMd neurons and 15% for S1). Meanwhile, the sample from PP (63–64 cells) yielded very accurate predictions of gripping force (73%) and hand velocity (52%), but not hand position (25%). Ensemble predictions of gripping force in most cases were more accurate than those obtained from the same population for hand position and velocity. In addition, the ND analysis revealed that predictions of any motor parameter based on combined neural ensemble activity were far superior to those obtained based only on the mean contribution of single neurons.

Another interesting finding emerged from the comparison of the contribution of single-unit versus multiunit activity to the performance of the linear models. Overall, up to 90 single units and 95 multiunits were simultaneously recorded in monkey 1 and 75 single units and 175 multiunits in monkey 2. The cell population was stable not only during the length of the recording sessions but across sessions. The vast majority of the population remained stable for several weeks and, in some cases, months (Nicolleli et al. 2003).

Figure 2G–2I shows that the linear predictions of hand position, velocity, and gripping force were somewhat better when single units were used (by 17%, 20%, and 17%, respectively). That difference could be compensated by increasing the number of channels. For example, as seen in Figure 2G, around 30 additional multiunits compensate for the difference in prediction of hand position provided by 20 single units. That difference was, however, not critical, as the animals could still maintain high levels of BMI performance in all tasks using multiunit activity only. Thus, in contrast to previous studies (Serruya et al. 2002; Taylor et al. 2002) that dealt with fewer motor parameters and a simpler task, we observed that large neuronal samples were needed to achieve a high level of real-time prediction of one or more motor parameters and, consequently, high behavioral proficiency in operating the BMic.

Functional Cortical Reorganization during Operation of BMic

The achievement of high proficiency in the operation of the BMic by the monkeys was consistent with procedural motor learning. Since cortical ensemble recordings were obtained during behavioral training in all three tasks, it was possible to examine the neurophysiological correlates of this learning process. Both short (within a recording session) and long-term (across recording sessions) physiological modifications took place.

Long-term functional changes in multiple cortical areas were evident in both animals. For instance, the average contribution of single neurons to model performance increased with learning. Figure 3A shows changes in the contribution of single cortical neurons (measured in terms of correlation coefficient, R, color-coded, where blue shows low R; red, high R) from five cortical areas (PMd, M1, S1, SMA, and M1 ipsilateral) to the linear model that predicted hand position in task 1. Data from 42 recording sessions are shown. In these sessions, predictions of hand position (HPx, HPy) were used to control the cursor on the screen. By the end of the training, very accurate predictions of hand position and velocity were obtained (mean R ± SEM; HPx = 0.75 ± 0.04, HPy = 0.72 ± 0.04, HVx = 0.70 ± 0.03, and HVy = 0.71 ± 0.02). These high values were reached through a significant increase in contribution of individual neurons to the linear model. When the mean contribution of single neurons was plotted as a function of their cortical area location, differences across cortical areas were found (Figure 3B–3E). The change was higher in SMA (Figure 3E; R = 0.81, slope = 0.01, p < 0.001) than in PMd (Figure 3B; R = 0.81, slope = 1 × 10⁻³, p < 0.001), S1 (Figure 3D; R = 0.67, slope = 4 × 10⁻², p < 0.001), and M1 (Figure 3C; R = 0.50, slope = 3 × 10⁻³, p < 0.001). Note that from the beginning of training, M1 neurons (Figure 3C) provided the highest mean contribution. By the end of 42 sessions, however, the mean contribution of neurons located in other cortical areas (e.g., SMA, PMd, and S1) was as high as that of M1. It is noteworthy that the significant enhancement in contribution occurred for the model predicting hand position (average of all cortical areas, R = 0.80, slope = 4 × 10⁻², p < 0.001), but not the one predicting hand velocity (R = 0.05, slope = 2.2 × 10⁻⁴). This selectivity coincided with the use of a position model in the BMic during these 42 sessions. Thus, long-term training with the BMic using a particular model could result in selective enhancement of the mean contribution of neurons to that model, but not the others.

Changes in Neuronal Direction Tuning during Operation of a BMic

As animals learned to operate the BMic, we also observed short-term changes in neuronal directional tuning, within a single recording session, after switching the BMic mode of operation from pole to brain control. Directional tuning curves (DTCs) reflected dependency of the neuronal firing rate on movement direction of either the pole or the cursor. DTCs were normalized by dividing average firing rates for particular movement directions by the standard deviation of the whole firing rate record and then subtracting the DTC mean. Using that normalization, changes in firing rate with
movement direction were compared with the overall variation of firing rate. Average directional tuning of neural ensembles (DTE) was also assessed, and the spread of the preferred tuning directions was evaluated as the ensemble average of the angles between preferred directions in pairs of neurons. Color-coded population histograms (Figure 4A–4D) displayed the DTCs of all recorded neurons. Polar plots (magenta figures in Figure 4A–4D) showed the DTE and preferred direction spread. Figure 4A–4D shows that DTCs and DTEs for the same neural ensemble had distinct features during pole control (Figure 4A), during brain control with the presence of arm movements (Figure 4B and 4D), and during brain control without arm movements (Figure 4C). Even if the animal was still making arm movements after switching to brain control and direction tuning was calculated in relation to pole movements (compare Figure 4A with 4D), DTC and DTE changed significantly when compared to curves obtained during pole control ($R = 0.57$ using pole movements as a reference direction, $R = 0.70$ using cursor movements as a reference). The changes in DTC and DTE became greater as the animal ceased to produce arm movements in brain control (Figure 4C) ($R = 0.48$). Notice, however, that the pattern for brain control without arm movements (Figure 4C) was also distinct from that for brain control with arm movements (Figure 4B) ($R = 0.57$). These findings suggest that both the cursor and pole movements influenced the definition of directional tuning profiles in multiple cortical areas.

After the mode of operation was switched to brain control, pole and cursor movements became dissociated. Further, as animals started controlling the BMc without producing overt hand movements, directional tuning primarily reflected...
Figure 4. Directional Tuning in Frontoparietal Ensemble during Different Modes of Operation in Task 1

(A–D) Directional tuning during pole control (A), brain control with arm movements (tuning assessed from cursor movements) (B), brain control without arm movements (tuning assessed from cursor movements) (C), and brain control with arm movements (tuning assessed from pole movements) (D). In each of the color-coded diagrams (red shows high values and blue low values; see color scale), the rows depict normalized directional tuning for individual cells. Because of the high directional tuning values of some cells (e.g., that shown in (H)), a color scale limit was set at 0.3 to allow color representation of the largest possible number of cells. Each tuning curve contains eight points that have been interpolated for visual clarity. Correspondence of tuning patterns under different conditions has been quantified using correlation coefficients (shown near lines connecting the diagrams). The highest correspondence was between tuning during pole control and brain control with arm movements, with lower similarity between brain control without arm movements and brain control with arm movements. Polar plots near each diagram show average directional tuning for the whole neural ensemble recorded. They indicate an average decrease in tuning strength and shifts in the preferred direction of tuning as the operation mode was switched from pole to brain control. Spread of preferred directions (90° corresponds to uniformly random distribution) is indicated near each polar plot.

(E–G) Scatterplots comparing DTD (maximum minus minimum values of tuning curves) during pole control versus brain control with and without arm movements. DTD during brain control was consistently lower than during pole control. This effect was particularly evident during brain control without arm movements.

(H–J) Changes in directional tuning for individual neurons under different conditions. Blue shows pole control; red, brain control with arm movements (tuning assessed from pole movements); and green, brain control without arm movements. The first illustrated cell (H) was tuned only when the monkey moved its arm, more so during pole control. The second cell (I) had similar tuning during all modes of operation, but tuning depth was the highest for pole control and the lowest for brain control without arm movements. The third cell (J) was better tuned during brain control.

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cursor movements. Interestingly, during the transition from pole to brain control, directional tuning depth (DTD) was reduced for most cells. Figure 4E–4G shows this effect by comparing the DTD in individual neurons during pole control (Y axis of Figure 4E–4G) and brain control (X axis). Notice that the reduction in tuning depth was more pronounced when no arm movements were produced during brain control (Figure 4G). Reduction in directional tuning during brain control with no movements characterized 68% of the sampled neurons and included neurons from all cortical areas (see color dots in Figure 4E–4G and examples of Figure 4H and 4I). A small percentage of neurons (14%) did not show such change. Perhaps more surprisingly, a fraction of neurons (18%) enhanced their directional tuning during the switch from pole to brain control (see Figure 4J). These neurons correspond to the dots that are located to the right of the main diagonal in Figure 4E–4G.

Operating the BMIC without making movements was characterized by an appearance of peculiar patterns of directional tuning at the population level. Figure 5A and 5C displays the evolution of DTC and DTE for the same neural ensemble during four task 1 sessions with the robot in the loop. Whereas in each case DTCs during brain control resembled those in pole control, they evolved toward a more organized distribution. Although certain diversity in DTCs remained, clear groups of neurons sharing similar DTCs appeared as a result of training (Figure 5C). Quantitatively, this effect was manifested by a decrease in the spread of preferred directions. This effect was also evident in the polar plots showing population-average tuning (i.e., DTE). The DTE became progressively sharper and rotated clockwise. Throughout the four sessions depicted in Figure 5, tuning depth remained higher during pole than brain control operation of the BMIC (Figure 5B).

Further analysis revealed that significant changes in directional tuning also occurred within a single recording session during brain control (Figure 5D). The session illustrated in Figure 5D was characterized by a gradual improvement in behavioral performance during brain control without arm movements, as evident from measurements made every 5 min (Figure 5E). The population histograms of Figure 5D show that the distribution of DTCs, although variable, became on average tighter across all cortical areas, defining a vertical band across the population histogram. This tightening was manifested by a decrease in the spread of preferred directions (Figure 5F). Moreover, average tuning depth gradually increased (Figure 5G), but remained lower than that observed during pole control.

Similarity of DTCs during brain control indicated that particular movement directions were associated with simultaneous increases in activity in many neurons; i.e., firing rates of these neurons became more correlated. Indeed, we found increases in broad correlation (100 ms time window) in neuronal firing within and between cortical areas. Thus, during the transition from pole to brain control in task 1, the average correlated firing between pairs of cortical neurons, measured in terms of correlation coefficient (mean ± SEM), increased from 0.02 ± 1×10⁻⁵ to 0.06 ± 2×10⁻⁵, a 3-fold rise that was highly significant (Wilcoxon signed rank test, p < 0.0001). All cortical areas tested (M1, PMD, SMA, S1, and M1 ipsilateral) showed increases in correlated firing. The highest within-area increases from pole to brain control were observed in M1 (ΔBrain-Pole = 0.07), S1 (ΔBrain-Pole = 0.05), and PMd (ΔBrain-Pole = 0.03). The highest between-area increases were observed between M1–S1 (ΔBrain-Pole = 0.06), M1–PMD (ΔBrain-Pole = 0.04), PMd–S1 (ΔBrain-Pole = 0.04), M1–SMA (ΔBrain-Pole = 0.02), and M1contra–M1ipsi (ΔBrain-Pole = 0.02).

Changes in average firing rates of the neurons during switching from pole to brain control were insubstantial. Firing rates of individual cells ranged from 0.1 to 40 spikes/s (8 ± 8 spikes/s; mean ± SD). After the mode was switched to brain control and the monkey continued to move the arm, firing rates increased on average by 4% from pole-control level. When the monkey controlled the BMI without moving the arm, the average neuronal firing rates decreased 2.5% from pole-control level.

Real-Time Prediction of Gripping Force

In addition to reproducing hand trajectories with great accuracy, linear models also allowed the reconstruction of fine variations in gripping force produced by both monkeys in tasks 2 and 3. Figure 8A shows that during execution of task 2, most of the recorded cortical neurons contained information about gripping force. In this figure, normalization was achieved by dividing the firing rate of each individual neuron by its standard deviation. In this way, force-related modulations are expressed relative to the
Figure 5. Plasticity of Directional Tuning during Training in Brain Control without Arm Movements

Conventions are as in Figure 4.
(A) Directional tuning profiles during four sessions in pole control (task 1). Percentages of correctly performed trials are indicated for each session.
(B) Scatterplots comparing directional tuning during pole versus brain control for the same sessions. For each day, DTD was on average higher in pole control.
(C) Directional tuning during brain control for the same sessions as in (A). Note the emergence of a population pattern in which a group of neurons (with some exceptions) exhibits a similar preferred direction. This is manifested as a decrease in the spread of preferred directions shown near polar plots. Notice also a gradual rotation of the population preferred direction (see polar plots) with training.
(D) Gradual changes in DTE during one representative session of brain control without arm movements. This 60-min session was split into 5-min periods, five of which are shown.
(E) Improvement in behavioral performance during a single session (same as in [D]).
(F) Decrease in the spread of preferred directions during that session.
(G) Increase in average tuning depth during the same session.
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overall variability of the neuron's firing rate. Both monkeys mastered task 2 in seven to eight sessions. Figure 6B displays the evolution of the average contribution of neurons from different areas of monkey 1 to model predictions during this period. Contribution of contralateral M1 (R = 0.77, slope = 0.02, p < 0.05) and S1 (R = 0.85, slope = 0.02, p < 0.002) increased significantly, while that of PMd (R = 0.19, slope = 2 × 10^-10), SMA (R = 0.34, slope = 0.01), and ipsilateral M1 (R = 0.38, slope = -0.01) did not change substantially. For the whole ensemble combined, there was a significant increase in contribution in both monkey 1 (R = 0.95, slope = 0.02, p < 0.001) and monkey 2 (R = 0.54, slope = 0.01, p < 0.05). By comparing Figure 3B–3F and Figure 6B, we can see that while M1 and S1 neurons showed changes during both tasks 1 and 2, PMd and SMA neurons showed changes in task 1, but not in task 2. This may reflect the greater involvement of these cortical areas in learning visuomotor spatial relationships than in the production of muscle force.

Switching from pole to brain control did not affect neuronal firing rate correlations in task 2. This could be related to saturation of this parameter because the average firing rate correlation observed during pole control when monkeys performed task 2 (0.056) was already higher than that observed during task 1 (0.022, p < 0.001, Wilcoxon rank sum test).

Using a BMiC to Reach and Grasp Virtual Objects

Our experiments demonstrated, to our knowledge for the first time, that monkeys can learn to control a BMiC to produce a combination of reaching and grasping movements to locate and grasp virtual objects. The major challenge in task 3 was to simultaneously predict hand position and gripping force using the activity recorded from the same neuronal ensemble. This problem could not be reduced to predicting only hand position as in task 1 or gripping force in task 2, because the animal had to sequentially reach and grasp the target.

The DTD of cortical neurons, measured during pole control, increased almost linearly during the learning of task 3 (Figure 6C). Although this effect was significant in all cortical areas tested, its magnitude varied across areas. The most prominent increase in DTD was observed in M1 (red dots in Figure 6C; R = 0.81, slope = 0.02); Neurons in S1 (green dots in Figure 6C; R = 0.82, slope = 0.02) and ipsilateral M1 (magenta dots in Figure 6C; R = 0.81, slope = 0.02) exhibited the next largest increase. Relatively smaller DTD increases were observed in PP (cyan dots in Figure 6C; R = 0.73, slope = 0.01), SMA (black dots in Figure 6C; R = 0.63, slope = 0.01), and PMd (blue dots in Figure 6C; R = 0.51, slope = 0.01). Similar to task 1, tuning depth was higher during pole control than during brain control. As in task 1, the DTC and DTE patterns changed during training (data not shown). Improvements in model performance occurred as well. Figure 6D and 6E show the evolution in accuracy of real-time predictions of hand position, velocity, and grip force during 14 sessions for both monkeys. During this period, real-time predictions of both hand position and velocity improved with training while predictions of grip force remained high and stable in two monkeys (monkey 1, mean ± SD, R = 0.86 ± 0.04; monkey 2, R = 0.79 ± 0.03).

The monkeys' performance in brain control in task 3 approximated that during pole control, with characteristic robot displacement (reach) followed by force increase (grasp). Figure 6F and 6G shows several representative examples of reaching and grasping during pole and brain control in task 3 by monkey 1. Hand position (X, Y) and gripping force (F) records are shown. In the display of hand trajectories, the size of the disc at the end of each hand movement shows the gripping force produced by the monkey (Figure 6F) or by the BMiC (Figure 6G) to grasp a virtual object. The reach (r) and grasp (g) phases are clearly separated, demonstrating that the monkeys could use the same sample of neurons to produce distinct motor outputs at different moments in time. Thus, during the reaching phase, X and Y changed, while F remained relatively stable. However, as the monkey got closer to the virtual object, F started to increase, while X and Y stabilized to maintain the cursor over the virtual object. Thus, our goal to train the monkey to reproduce coupled sequences of reach-and-grasp movements using the BMiC was accomplished.

Discussion

Reliable, long-term operation of a BMiC was achieved by extracting multiple motor parameters (i.e., hand position, hand velocity, and gripping force) from the simultaneously recorded activity of frontoparietal neural ensembles. Macaque monkeys learned to use the BMiC to reach and grasp virtual objects with a robot even in the absence of overt arm movements. Accurate performance was possible because large populations of neurons from multiple cortical areas were sampled. Thus, the present study shows that large ensembles are preferable for efficient operation of a BMiC. This conclusion is consistent with the notion that motor programming and execution are represented in a highly distributed fashion across frontal and parietal areas and that
Figure 6. Ensemble Encoding of Gripping Force, Plasticity of Directional Tuning, and Neuronal Contribution to Model Performance during Learning to Control the BMI for Reaching and Grasping

(A) Perievent time histograms (PETHs) in task 2 for the neuronal population sampled in monkey 1. The plots on top are color-coded (red shows high values; blue, low values). Each horizontal row represents a PETH for a single-neuron or multunit activity. PETHs have been normalized by subtracting the mean and then dividing by the standard deviation. PETHs are aligned on the gripping force onset (crossing a threshold). Plots at the bottom show the corresponding average traces of gripping force. Note the general similarity of PETHs in pole (left) and brain (right) control in this relatively easy task. Cortical location of neurons is indicated by the bar on the top left. Note the distinct pattern of activation for different areas.

B

C

D

E

F

G


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each of these areas contains neurons that represent multiple motor parameters. We suggest that, in principle, any of these areas could be used to operate a BMI, provided that a large enough neuronal sample was obtained. While analysis of ND curves (see Figure 2D–2F) indicates that a significant sample of M1 neurons consistently provides the best predictions of all motor parameters analyzed, neurons in areas such as SMA, S1, PMd, and PP contribute to BMI performance as well.

Our argument for using large neuronal samples is also supported by the fact that some neurons can be lost during chronic recordings, either due to electrode malfunction, modification of electrode tip properties, or simple cell death. Then, a BMI that relies on only very small samples of neurons (e.g., 8–30 cells) (Serruya et al. 2002; Taylor et al. 2002), all derived from a single cortical area, would not be able to provide a broad variety of motor outputs, handle changes in cortical properties, or cope with alterations in the neuronal sample over time.

Another important finding of this study is that accurate real-time prediction of all motor parameters as well as a high level of BMI control can be obtained from multitui signals. This observation is essential because it eliminates the need to develop elaborate real-time spike-sorting algorithms, a major technological challenge, for the design of a future cortical neuroprosthesis for clinical applications.

Our experiments also demonstrate that the initial introduction of a mechanical device, such as the robot arm, in the control loop of a BMI significantly impacts learning and task performance. After the robot was introduced in the control loop, the monkey had to adjust to the dynamics of this artificial actuator. As a result, there was an immediate drop in performance (see Figure 3G). With further training, however, the animals were able to overcome the difficulties. Thus, the simple utilization of the output of a real-time model to move a cursor on a computer screen (Serruya et al. 2002; Taylor et al. 2002) does not fully test the limitations and challenges involved in operating a clinically relevant BMI. Instead, such testing must include the incorporation in the apparatus of the mechanical actuator designed to enact the subject’s motor intentions and training the subject to operate it.

As was proposed recently (Nicolelis and Ribeiro 2002), multi-site, multi-electrode recordings (Nicolelis et al. 2003) also allowed us to quantify neurophysiological modifications occurring in cortical networks, as animals learned motor tasks of different complexity. At a single-neuron level, one modification observed was a reduction in the strength of directional tuning as animals switched from pole to brain control of the BMI, an effect that reached its maximum as animals ceased to produce overt arm movements. This finding touches directly on the ongoing debate of two opposing views of what the motor cortex encodes (Mussa-Ivaldi 1988; Georgopoulos et al. 1989; Kakei et al. 1999; Todorov 2000; Johnson et al. 2001; Scott et al. 2001). At the first glance, the reduction in tuning depth in the absence of arm movements could be interpreted as providing support to the notion that directional tuning in the motor cortex is highly influenced by movement dynamics. Thus, the elimination of proprioceptive feedback during brain control could explain the significant reduction in directional tuning. However, a smaller but significant decrease in directional tuning was also observed during brain control while animals still used their hands to move the pole. This suggests that directional tuning reflects neither movement dynamics nor abstract motor goals alone, but rather their combination. Additional findings support this contention. For example, a small fraction of M1 and S1 neurons became better directionally tuned when the monkey did not make hand movements during brain control (see Figure 4Ba–4Bd and Figure 5G). Moreover, during brain control there was a significant increase in pairwise-correlated firing and a tendency for groups of neurons to exhibit rather similar DTCs (see Figures 4 and 5). Increases in tuning depth accompanied improvements in performance during brain control, although values observed during pole control were never reached (see Figure 5E and 5G). All together, these physiological changes suggest that as animals learn to operate the BMI during brain control, visual feedback signals representing the goal of movement, rather than information about arm movements per se, become the main guiding signal to the cortical neurons that drive the BMI. Thus, we hypothesize that, as monkeys learn to formulate a much more abstract strategy to achieve the goal of moving the cursor to a target, without moving their own arms, the dynamics of the robot arm (reflected by the cursor movements) become incorporated into multiple cortical representations. In other words, we propose that the gradual increase in behavioral performance during brain control of the BMI emerged as a consequence of a plastic reorganization whose main outcome was the assimilation of the dynamics of an artificial actuator into the physiological properties of frontoparietal neurons. This hypothesis is consistent with previous observations in paralyzed humans who learned to move a cursor on the screen using cortical activity (Kennedy and King 2000). It is also supported by the results that cortical neurons may modulate their firing rate either during use of tools (Iriki et al. 1996), according to cursor movement on the screen rather than underlying arm movements (Alexander and Critchley 1990; Shen and Alexander 1997), or in relation to the orientation of spatial attention (Lebedev and Wise 2001).

Our results on cortical reorganization are very distinct from a previous claim of plastic changes in directional tuning of cortical cells during the use of BMI (Taylor et al. 2002). First, in that previous report, the population vector model yielded poor predictions when applied to activity of a small sample ($n = 18$) of M1 cells. Introduction of visual feedback improved the subject’s performance to a point in which
monkeys could use a BMI to produce stereotypic center-out movements of a cursor. The authors claimed that changes in cell-preferred direction occurred after switching to brain control. However, preferred directions were derived not from the real-movement directions of the hand or the cursor, but rather from ideal directions defined by target locations. In addition, a wide 420–990 ms time window was used to measure firing rates. This window was comparable to movement duration. Therefore, differences in movement trajectories and duration between hand and brain control, rather than true differences in cell directional tuning, could lead to different estimates of preferred direction. The report also claims that tuning strength increased with training in brain, but not hand, control. However, tuning depth was evaluated by measuring covariation between firing rate modulations and target locations, rather than actual movement trajectories. Because during training, cursor trajectories gradually approached a straight line connecting the starting point and the target, the observed improvement in covariation between target locations and neuronal firing rate modulations could simply reflect the improvement in movement accuracy. These considerations should be taken into account to decide how much of the plasticity reported by Taylor et al. (2002) reflects real cortical reorganization instead of resulting from the improvement in the animal's behavioral performance during the task used to measure directional tuning.

In the present study, all the changes in firing and tuning properties of neuronal ensembles were related to the actual trajectories produced by the monkeys during pole and brain control. Moreover, the relationship between the neuronal firing and movement patterns was evaluated continuously. Thus, the cortical changes reported here more closely reflected the relationship between neuronal signals and motor behaviors that they underlie.

Overall, the present findings demonstrate that it is reasonable to envision that a cortical neuroprosthesis for restoring upper-limb movements could be implemented in the future, following the basic BMIC principles described here. We propose that long-term operation of such a device by paralyzed subjects would lead, through a process of cortical plasticity, to the incorporation of artificial actuator dynamics into multiple brain representations. Ultimately, we predict that this assimilation process will not only ensure proficient operation of the neuroprosthesis, but it will also confer to subjects the perception that such apparatus has become an integral part of their own bodies.

Materials and Methods

Behavioral training and electrophysiology. Two adult female monkeys (Macaca mulatta) were used in this study. All procedures conformed to the National Research Council’s Guide for the Care and Use of Laboratory Animals (1996) and were approved by the Duke University Animal Care and Use Committee.

At the time of surgery, animals had completed a period of chair training, and one of them (monkey 2) was familiarized with the requirements of task 1 (a large target size was used in this preliminary training). Multiple arrays containing 16–64 microelectrodes each (separation between adjacent microwires = 300 μm) were implanted in several frontal and parietal cortical areas in each animal (Nicolelis et al. 2003) (96 in monkey 1 and 320 in monkey 2). Implanted areas included the dorsal premotor cortex (PMd), supplementary motor area (SMA), and the primary motor cortex (M1) in both hemispheres. In monkey 1 an implant was placed in the primary somatosensory cortex (SI). In monkey 2, the medial intraparietal area (MIP) of the posterior parietal cortex (PP) was also implanted. The monkeys performed the tasks with their left arms, which were contralateral to the areas with the best cell yield. Upon recovery from this surgical procedure, animals were transferred to the experimental apparatus illustrated in Figure 1A and started behavioral training.

Monkeys were seated in a primate chair facing a computer monitor. They were trained to perform three different tasks using a hand-held pole equipped with a pressure transducer (PCB Piezotronics Inc., Depew, New York, United States) for measuring grasping force. The position of the monkey's hand was obtained from an infrared marker located on top of the pole. The marker was monitored by an optical tracking system (Optotak, Northern Digital, Waterloo, Ontario, Canada). In the first task, the monkey was shown a small disk (the "cursor") and a larger disk (the "target"). They had to use the pole to put the cursor over the target and remain within it for 150 ms. Should the monkey cross the target too fast, the target disappeared and the trial was not rewarded. Each trial began with a target presented in a random position on the screen. The monkeys had 5 s to hit the target and get a juice reward. In the second task, the monkeys were presented with the cursor in the center of the screen and two concentric circles. The ring formed by these two circles instructed the amount of gripping force the animals had to produce. The pole was fixed, and the cursor grew in size as the monkey gripped the pole, providing continuous visual feedback of the gripping force. Force instruction changed every trial. The third task contained elements of tasks 1 and 2. In this task, the monkeys were presented with the cursor, the target, and the force-instructing ring and were required to manipulate the pole to put the cursor over the target and match the ring size by developing the proper amount of gripping force, while staying inside the target. The monkeys received juice rewards for correct performance. In task 1, the monkeys were initially trained without the robot in the loop, but after a certain number of sessions, the robot was incorporated to the loop. In tasks 2 and 3, the robot was always part of the loop.

A 512-multichannel acquisition processor (Plexon Inc., Dallas, Texas, United States) was employed to simultaneously record from single neuron and multunit activity during each recording session. EMG signals were recorded from the skin surface just above the belly of the wrist flexors, wrist extensors, and biceps muscles using gold disc electrodes (Grass Instrument Co., West Warwick, Rhode Island, United States) filled with conductive cream. These signals were amplified (gain, 10,000X), high-pass filtered, rectified, and smoothed (kernel convolution).

Linear model. Hand position, velocity, and gripping force were modeled as a weighted linear combination of neuronal activity using a multidimensional linear regression or Wiener filter, the basic form of which is

\[ y(t) = b + \sum_{u} a(u)x(t-u) + \epsilon(t) \]

In this equation, \( x(t-u) \) is an input vector of neuronal firing rates at time \( t \) and timelag \( u \), \( y(t) \) is a vector of kinematic and dynamic variables (e.g., position, velocity, gripping force) at time \( t \), \( a(u) \) is a vector of weights at timelag \( u \), \( b \) is a vector of y-intercepts, and \( \epsilon(t) \) are residual errors. The linear in the summation can in general be negative (in the past) or positive (in the future) with respect to the present time \( t \). We only considered lags into the past. This equation can be recast in matrix form as

\[ Y = XA \]

here each row in each matrix is a unit of time and each column is a data vector. Note that matrix \( X \) contains lagged data and thus has a column for each lag multiplied by the number of channels; e.g., 100 channels and 10 lags imply 1000 columns. The y-intercept is handled by prepending a column of ones to matrix \( X \). Matrix \( A \) is then solved by

\[ A = inv(X'X)X'Y \]

Real-time predictions of motor parameters. Predictions of hand trajectory and grasping force were generated using the Wiener filter described above. Neuronal firing rates were sampled using 100 ms bins, and 10 bins preceding a given point in time were used for training the model and predicting with it. Models were trained with 10 min of data and tested by applying them to subsequent records. In individual neuron analysis, a model was trained using single-unit/multunit activity only and then tested for predictions of motor parameters. In velocity mode, the model was trained using velocity
derived from position measurements by digital differentiation. During brain control, predicted velocity was digitally integrated to provide an output position signal. To avoid slow drifts, this signal was high-pass filtered with a first-order Butterworth filter (cutoff frequency of 2 Hz). The linear models independently predicted X, Y, and Z hand position coordinates. However, because the three tasks reported in this study took place in the X–Y plane, the predictions of position and velocity along the Z axis were not used. Several alternative decoding algorithms were tested offline, including a Kalman filter, normalized least-mean squares filter, and a feed-forward backpropagation artificial neural network. None of these methods could consistently outperform the Wiener filter.

**Robotic arm and gripper.** A 6 DOF robotic arm equipped with a 1 DOF gripper (The ARM, Exact Dynamics, Didam, The Netherlands) was used in this study. The gripper was sensorized with pressure transducers (Flexforce, Tekscan, Boston, Massachusetts, United States) of 1 lb (2.2 kg) force range for providing grasping force feedback. Position feedback of the robot was obtained through the built-in joint encoders. Both the commands for controlling the robot and the feedback were in Cartesian coordinates. The communication between the client computer and the robot was performed via the CAN bus (National Instruments, Austin, Texas, United States) (sampling period, 60 ms). For the tasks involving grasping, the gripper had a light object inserted made of foam material. This object was squeezed by the gripper in proportion to either the force applied by the monkey in the pole or to the brain signal.

**Data analysis.** The monkeys' behavior was continuously monitored and videotaped throughout each recording session. The percentage of correctly performed trials and the time to accomplish each trial, during both pole and brain controls, were used as measures of performance. Chance performance for each task was determined using Monte Carlo simulations of a random walk with 2, 1, and 3 DOF (for task 1, task 2, and task 3, respectively). The velocity of the random walk was varied from 1 to 500 mm/s, with 10,000 trials for each velocity. For tasks 1 and 3, this was the velocity of the cursor; for task 2, velocity corresponded to the rate in change of the cursor radius. Because each monkey operated the pole at different speeds, predictions shown in Figure 1C–1E are based on the average velocity across all sessions for a given monkey.

Random neuron-dropping (ND) technique was implemented as described by Wesberg et al. (2000). Population data (10 min) were used to fit a linear model, which was used to predict motor parameters from the subsequent record. A single neuron was then randomly removed from the population, the model retrained, and new predictions generated. This process was repeated until only one neuron remained. The average squared linear correlation coefficient ($R^2$) as a function of number of neurons was obtained by repeating this procedure 30 times for each ensemble. Curves were obtained with populations of neurons segregated from M1, PMd, S1, SMA, and PP and for single units and multisite.

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**Conflicts of Interest.** The authors have declared that no conflicts of interest exist.

**Author Contributions.** JMC and MALN conceived and designed the experiments JMC, MALN, and MALN performed the experiments. JMC integrated the robotic interface. JMC and MALN analyzed the data. JEO and CSH contributed Beowulf cluster simulations and analyses. REC contributed the initial stages of this study. JMC, DMS, and MALN recorded the EMGs. DFD performed the surgeries, JMC, MALN, REC, PGP, and MALN assisted in the surgeries, JMC, MALN, and MALN wrote the paper.

**References**


Information Conveyed Through Brain-Control: Cursor Versus Robot

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Abstract—Microwire electrode arrays were implanted in the motor and premotor cortical areas of rhesus macaques. The recorded activity was used to control the three-dimensional movements of a virtual cursor and of a robotic arm in real time. The goal was to move the cursor or robot to one of eight targets. Average information conveyed about the intended target was calculated from the observed trajectories at 30-ms intervals throughout the movements. Most of the information about intended target was conveyed within the first second of the movement. For the brain-controlled cursor, the instantaneous information transmission rate was at its maximum at the beginning of each movement (averaged 4.8 to 5.5 bits/s depending on the calculation method used). However, this instantaneous rate quickly slowed down as the movement progressed and additional information became redundant. Information was conveyed more slowly through the brain-controlled robot due to the dynamics and noise of the robot system. The brain-controlled cursor data was also used to demonstrate a method for optimizing information transmission rate in the case where repeated cursor movements are used to make long strings of sequential choices such as in a typing task.

Index Terms—Brain–computer interface (BCI), brain–machine interface (BMI), information rates, information theory, neural prosthetics, neurocontrollers, prosthetics, robots, virtual reality.

I. INTRODUCTION

Many types of brain–computer interfaces (BCIs) have been developed for assisting the disabled [1]–[7]. Possible functions include choosing letters to spell words [1]–[4], moving a cursor to select from a menu, and mentally directing the motion of a robot, a wheelchair, or a neuromuscular prosthesis [5], [6]. Such diversity of output tasks makes it difficult to compare the performance of one BCI with another. However, letter selection, movement direction, and menu choice can all be quantified into bits—the number of binary digits—or yes-or-no questions needed to specify the action.

Here, we measured the information conveyed with a BCI that uses the firing rates of a population of single cells and multicell clusters recorded from microwire electrode arrays implanted in the motor and premotor cortical areas of rhesus macaques [7]. We compared the information transferred when the cortical signals were used to control a three-dimensional (3-D) virtual cursor versus a six-degree-of-freedom robotic arm (Zero2Zebra). In both cases, the task was a 3-D center-out task where the brain-controlled cursor or robot had to move from a center start position to targets that appeared at one of eight corner positions of an imaginary cube. In this analysis, we only evaluated the information conveyed about the intended target and not about the details of the movement trajectory itself. Information about the intended target was calculated at the output end of each system (i.e., the cursor movement and the robot movement) as opposed to the input end (i.e., the information imbedded in the cortical activity itself). Although information may be encoded in many aspects of the cortical activity, some of that information will be lost when using simplistic algorithms to translate cortical activity into 3-D movements. Additional information will be lost when the calculated 3-D movements are further translated into physical movements due to variability and noise in the physical system. Here, we calculate the information about intended target conveyed through the brain-controlled cursor and robot to compare the functional information transmission rate through each of these complete systems.

Georgopoulos and Massey [8] have shown that more information about intended target direction can be obtained from neural activity of the motor cortex than from the actual arm movement itself during the initial part of the movement. This suggests that information is naturally lost through the motor system during volitional movement. This also suggests that, if enough motor cortex cells are used, controlling a computer cursor directly from the motor cortex may produce more accurate movements than controlling a cursor by physically moving a mouse. In the Georgopoulos study, motor cortex information was calculated by predicting intended targets from a population vector [9] that combined the simulated activity of up to 253 motor cortex cells. Their results showed that the information conveyed by the population vector exceeded that conveyed by arm movements once the number of cells used in the population vector reach between 40 and 50. Their simulated cell activity was modeled after cells which where recorded one at a time using a movable electrode. These acute electrodes allowed them to optimally place the electrode near each cell body and record large well-isolated waveforms. The recording quality is likely to be lower in chronic cortical implants where arrays of electrodes are fixed in place. With chronic electrodes, the recorded cell waveforms are often poorly isolated or too small in amplitude to be completely separated from the system noise. Therefore, the number of recorded units needed to exceed the information conveyed with actual arm movements is likely to be higher with chronic implants than what the Georgopoulos study suggests. In our study, cursor and robot movements were controlled by the activity of 39 ± 2 cortical units which consisted of a more typical sampling of the quality of recordings seen in fixed chronic implants.

II. METHODS

In the first experiment, rhesus macaques controlled the 3-D movements of a cursor in a virtual workspace while both arms were restrained. The animals’ cortical activity was translated into cursor movements in real time. Full details of the experimental design and cortical decoding algorithm have been reported elsewhere [7].
Fig. 1. Examples of brain-controlled cursor trajectories. Trajectories to all eight 3-D targets are plotted in two groups of four for easier viewing. Corner circles indicate target locations. Trajectory shading matches the shading of the intended target. The three letters indicate the 3-D target position in the following order: left-or-right, upper-or-lower, proximal-or-distal.

In a second experiment, a robot was added into the control loop. The animal still viewed the task through the same virtual cursor interface. However, instead of controlling the cursor directly from the brain activity, the robot was controlled directly from the brain activity, and a position sensor on the end of the robot determined the position of the cursor in the monkey’s virtual workspace. The monkey did not see the actual brain-controlled robot, but did see the robot’s movements via the 3-D virtual cursor.

These series of experiments were designed to evaluate the use of cortical activity for directional control of an upper-limb neural prosthesis. Therefore, the task required that the subjects make trajectories to each target and hold the cursor or robot at the target to get a reward. Although this is appropriate for evaluating the naturalness of the hypothesized prosthetic limb movement, these full trajectories resulted in the transfer of redundant information about the intended targets. Enough information was usually conveyed early on in the trajectory to determine the intended target well before reaching it. In this type of task, with a limited number of discrete goals, a smart controller could predict the intended target early on in the movement and complete the movement for the subject without the need for further information.

Fig. 1 demonstrates this point. Five minutes of brain-controlled cursor trajectories to all eight targets are shown. In this example, all intended targets could be predicted two-thirds of the time into the movement because there was no overlap of the trajectory distributions after that point. Therefore, three bits of information (which of the eight possible targets) were transmitted in the first two-thirds of the movement. The additional trajectory information would not provide any more information about which target the subject was aiming for (although it did provide qualitative information about the form of the trajectories).

To evaluate the target-related information conveyed over the time course of the movements, predictions of intended targets were made at 30-ms intervals along each trajectory recorded from 15 days of brain-controlled cursor data and six days of robot data from one animal (about 15 min/day). At each time interval, the intended target was predicted using two different methods. The first method assumed the closest target was the intended target. Therefore, classification boundaries were equally spaced between neighboring targets. However, on some days, trajectories to one or more targets showed a consistent curvature or would consistently hit one side of a target over the other. Therefore, shifting the classification boundaries to reflect these consistent deviations should result in greater prediction accuracy. In the second method, target predictions were made by first defining a “typical” movement path for each target, then placing the classification boundaries equal distance between these paths. These “typical” movement paths were calculated as the median of each day’s trajectories to each particular target. However, in order to avoid the unfair advantage of including the trajectory that is being classified in the calculation of its own classification boundaries, these boundaries were recalculated for each trajectory with that particular trajectory eliminated from the boundary calculation.

Information theory [10], [11] was used to measure average information conveyed each day at various stages of the movement. For a system with eight possible discrete targets, the average information conveyed about the target can be calculated as

\[ I = \sum_{T_p=1}^{8} P(T_p) (S[T_a] - S[T_a|T_p]) \]  

(1)

where \( I \) is average information conveyed about the intended target, \( P(T_p) \) is the probability of predicting target \( T_p \), \( S[T_a] \) is the entropy in the distribution of actual targets, and \( S[T_a|T_p] \) is the entropy of the conditional distribution of the actual targets, \( T_a \), given the predicted target was \( T_p \).

The two entropy terms are defined as

\[ S[T_a] = - \sum_{T_a=1}^{n} P(T_a) \log 2 (P(T_a)) \]  

(2)

\[ S[T_a|T_p] = - \sum_{T_a=1}^{n} P(T_a|T_p) \log 2 (P(T_a|T_p)) \]  

(3)

Here, \( P(T_a) \) is the probability of the actual target being \( T_a \). In the case where all eight targets are equally likely, this would simply be \( 1/8 \), and \( S[T_a] \) would equal three bits. \( P(T_a|T_p) \) is the conditional probability that the actual target was \( T_a \) given the target predicted by the observed trajectory was \( T_p \).

This form of the information equation is a weighted average of what is learned about the actual target when each of the eight targets is predicted from the observed trajectories. The entropy term \( S[T_a] \) measures the number of bits needed to describe the full range of the possible intended targets \( T_a \). The term \( S[T_a|T_p] \) measures the number of bits needed to describe the more limited range of possible values of \( T_a \) given that target \( T_p \) is predicted. The difference between the two is the information gained about \( T_a \) by the prediction of target \( T_p \). The information gain from predicting each specific target \( T_p \) is then weighted by the probability of actually getting a prediction of \( T_p \). These values are then summed across all possible targets to get the average information conveyed about the intended targets.

Finally, in addition to movements to the eight corners of a cube, both the brain-controlled cursor and robotic were used in a task that required movements from the center to random target positions throughout the workspace, and then back to the center start position. This was done to verify that the control algorithm, which was optimized for the eight-target center-out task, would also allow the subject to make movements to all parts of the workspace and make 180° real-time changes in movement direction.

All experiments were approved and monitored by Arizona State University’s Institutional Animal Care and Use Committee. The guidelines put forth by the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) and the Society for Neuroscience were followed.

III. RESULTS

Fig. 2 shows the mean and standard deviation (std) across days of the average information conveyed by the brain-controlled cursor and
robot trajectories at successive time intervals within the movement. The dark-gray lines and light-gray areas reflect information conveyed by the brain-controlled cursor position. The black lines and hatched areas reflect information conveyed by the brain-controlled robot position. For both the robot and cursor movements, using the classification boundaries based on "typical" trajectories depicted in Fig. 2(a) resulted in a slightly faster gain of information than using classification boundaries evenly spaced between the targets depicted in Fig. 2(b).

In both the robot and cursor tasks, the total information gained per movement began to saturate around 1–1.5 s into the movement. This demonstrates that most of the information about the intended target was conveyed early on in the movements. Therefore, most information in the later part of each trajectory was redundant and did not provide new information. Each day's average information per movement seldom reached the full 3 b needed to specify which of the eight targets the animal was trying to hit. This is because not all trajectories went to their intended targets. Periodically, the cursor or robot would tend to wander randomly about the workspace. This was most likely due to the animal's occasional inattention to the task since the errors tended to occur in blocks and did not show any particular relation to the targets. These blocks were often associated with distracting noises outside the experiment room and/or the animal looking away from the screen. If the target was not hit within 3 s in the cursor task or 4.5 s in the robot task, the cursor or robot would be returned back to the center start position and the next target would appear. The daily average percentage of targets hit was 83 ± 6% in the cursor task and 92 ± 4% in the robot task.

For the brain-controlled cursor, the highest information transmission rate, i.e., the slope of \( I(t) \), occurred in the earliest part of the cursor movement. The information gained at this stage was about 1.5 b in 0.275 s (5.5 b/s) when using classification boundaries based on typical trajectories, or 1.5 b in 0.31 s (4.8 b/s) when using classification boundaries based on target distance. The brain-controlled robot had a fairly irregular information transmission rate at the beginning of the movement, but achieved an information transmission rate similar to the cursor once the movement got underway.

In the final tests, the subject had to move from the center to random 3-D target positions and then return to the center target, the animal was equally successful hitting the new random target positions as it had been hitting the eight well-practiced targets. In addition, the animal readily changed movement directions to return the cursor or robot to the center after hitting an outer target. However, there were qualitative differences in the round-trip trajectories of the cursor versus the robot. Fig. 3 shows examples of these trajectories. The light-gray dots indicate when an outer target was hit. The dark-gray dots indicate when the center target was hit on the return path. Dots are 30 ms apart in time. The robot moved more slowly than the cursor and was allowed more time to complete each movement.

IV. DISCUSSION AND CONCLUSION

In the center-out task, the goal of each movement was simply to get to one of eight possible targets. Reaching the targets could have represented selecting letters or groups of letters in a communication task, selecting options from a menu of environmental controls, or choosing between several predefined hand configurations for controlling stimulation of a paralyzed limb [12]. In this analysis, we were only looking at how much information was transmitted about the intended target. Therefore, the total information could not exceed 3 b because there were only eight targets. However, the initial information transmission rate was 4.8–5.5 b/s for the brain-controlled cursor. It may be possible for a subject to work at this higher information transfer rate in a free-form drawing task which is not defined by a preset number of goals. By identifying this potential information transmission rate and using Fitts' Law [13], one could determine the gain of the system needed to produce the desired accuracy level in free-form brain-controlled movements.

In most BCIs, cursor movement is used to choose between a fixed number of discrete choices. As was shown here, redundant information may be produced if the cursor goal can be predicted fairly accurately before the end of each movement. In BCI tasks where long sequences of selections are made in a row, such as selecting letters in a typing task, shortening duration to minimize redundant information should increase the net information transferred over a longer fixed time period. Shorter duration will allow more selections to be made in a given time period. However, the proportion of those selections that are correct will often also be reduced. In the typing example, cutting movement duration in half could result in typing a two-page letter with five typos in the same amount of time as typing a one page letter with no typos. In spite of the increased percentage of errors, the total information transmitted during that time period will have increased.

A high information transfer rate needs to be balanced against the functional "cost" of this higher percentage of errors (i.e., how important is it to correct the errors and how much time does the correction process take). If the task is to choose between menu options for putting your brain-controlled car into park, reverse, neutral, or drive, then the cost of an incorrect choice could be quite high. In that case, the movement duration should be set long enough to guarantee that all information is received before executing the action. However, if the task is to shoot down alien invaders in a video game where laser direction is under brain-control, then the extra number of incorrect selections (i.e., shooting empty space) at the higher information transmission rate may
Fig. 4. Movement duration’s effect on (a) total information conveyed per minute, (b) proportion of targets incorrectly selected $P(\text{Error})$, (c) number of selections made per minute $S$, and (d) number of corrected selections made per minute $N_c$.

have little or no “cost” in the game. Using a shorter duration between firings should still allow more “hits” per unit time giving the player the best chance of saving the earth.

In communication BCIs, where letters or words are selected, the cost of an incorrect selection is simply the extra time it takes to cancel the selection and remake the selection. The process of optimizing movement duration based on functional cost can be demonstrated using the cursor data from the eight-choice task shown in Fig. 2(a) (gray line). Suppose the selection task was to choose between seven choices or a “cancel-previous-selection” option. Then the number of correct selections per minute $N_c$ would be approximately

$$N_c = S - (2S \cdot P(\text{Error}))$$

where $S$ is the number of selections per minute, and $P(\text{Error})$ is the probability the selection would be incorrect. $2SP(\text{Error})$ represents the number of movements per minute that did not produce a correct selection. This term is comprised of all incorrect movements, $SP(\text{Error})$, plus an equal number of “cancel-previous-selection” movements. Note, $N_c$, $P(\text{Error})$, and $S$, as well as total information, are all functions of movement duration. Fig. 4 plots these functions using the cursor data from the experiment where the intended target was predicted using classification boundaries based on “typical” trajectories. Although the total information transferred is highest at the shortest time durations [Fig. 4(a)⁴], the proportion of incorrect selections is also highest [Fig. 4(b)]. This can be reconciled by understanding that the short duration results in a “noiser” signal, but the speed at which it is sent [number of selections per minute, Fig. 4(c)] more than makes up for the excess noise. The time “cost” of removing the excess noise $-2SP(\text{Error})$ makes the shortest time durations inefficient in spite of the higher information transmission rate. Fig. 4(d) shows $N_c$, the number of correct selections that could be made per minute once the time to remove the errors is accounted for. In this task, setting movement duration to 0.57 s would be the most efficient way to produce an error-free sequence of choices. At this duration, the subject could make about 47 correct choices per minute with each choice being one of seven options. This is equivalent to correctly typing 47 digits of a base-seven code per minute (equivalent to about 2.2 b/s).

The method shown here is intended to illustrate how to choose a movement duration that will maximize the practical function of a BCI. However, the calculations in this example simply used the proportion of targets missed at each duration. Average information conveyed was never used. Note that the transmission rate of corrected bits per second was about 2.2 in this example, where as the actual information transmission rate at the same movement duration was 2.1 b in 0.57 s or 3.7 b/s [see Fig. 2(a)]. This discrepancy can be accounted for by the fact that some of the information is imbedded in the structure of erroneous target predictions. For example, when a target is selected in error, the actual intended target is usually the one nearest the selected target. This information will be lost unless a smart controller makes use of it when correcting erroneous selections.

The 2.2 b/s value calculated previously does not include any additional time that may be needed between movements in order to transition between brain states. In the center-out experiments, we arbitrarily set the intertrial-interval to 500 ms, and included a 200 ms delay between the time the target appeared and the time the cursor was allowed to move. The targets were presented in random order, and this delay ensured the subjects had time to perceive and react to the targets. Including this arbitrary 700-ms delay between selections reduces the maximum corrected information transfer rate down from 2.2 to 1.1 b/s. However, additional studies need to be done to pinpoint the true minimum time needed between movements in order to transition between brain states in the case where the subject knows ahead of time the choice sequence he or she is trying to make.

Less target information was conveyed through the brain-controlled robot than cursor. Although the cursor went exactly where the cortical decoding algorithm dictated, the robot, like virtually all physical systems, has its own dynamics and inherent noise. The robot accelerated more slowly than the cursor resulting in smaller initial movements. Jitter and vibration hindered target prediction most in the beginning of the movements when the trajectories had not yet progressed very far toward the targets. However, once the movement got under way, the information transmission rate of the robot was similar to that of the cursor.

Fig. 3 also demonstrates the richness of the robot’s dynamics on the movements. With the brain-controlled cursor, the animal tended to make relatively sharp 180° changes in direction when returning the cursor to the center target. However, when controlling the robot, the animal tended to make wider loops through the targets. The robot’s mass and inertial properties may have made it difficult to perform sharp changes in movement direction. However, the animal adjusted to the physical properties of the robot system and was still able to successfully perform the task. This demonstrates that brain-control skills acquired in a computer-based environment can be applied to the control of practical physical devices, although the control strategies may need adjusting, and the quality of the performance may degrade when information is lost with the physical system.

REFERENCES


Multimodal Neuroelectric Interface Development


Abstract—We are developing electromyographic and electroencephalographic methods, which draw control signals for human-computer interfaces from the human nervous system. We have made progress in four areas: 1) real-time pattern recognition algorithms for decoding sequences of forearm muscle activity associated with control gestures; 2) signal-processing strategies for computer interfaces using electroencephalogram (EEG) signals; 3) a flexible computational framework for neuroelectric interface research; and 4) noncontact sensors, which measure electromyogram or EEG signals without resistive contact to the body.

Index Terms—Brain-computer interfaces (BCI), electroencephalogram (EEG), electric field sensors, electromyogram (EMG), neuroelectric interfaces.

I. INTRODUCTION

We define a system that couples the human nervous system electrically to a computer as a neuroelectric interface—a sensing and processing system that can use signals from the brain or from other parts of the nervous system, such as peripheral nerves, to achieve device control. We regard brain–computer interfaces (BCIs) [1] as a subset of neuroelectric interfaces. Our current focus is on using features from electroencephalograms (EEGs) and electromyograms (EMGs) as control signals for various tasks, such as aircraft or vehicle simulations and other graphic displays.

Our long-term goals are to: 1) develop new modes of interaction that cooperate with existing modes such as keyboards or voice; 2) augment human–system interaction in wearable, virtual, and immersive systems by increasing bandwidth and quickening the interface; and 3) enhance situational awareness by providing direct connections between the human nervous system and the systems to be controlled. Our near-term goals include: 1) a signal acquisition and processing system for real-time device control; 2) automatic EMG-based recognition and tracking of human gestures; and c) feasibility testing of EEG-based control methods.

In this paper, we will survey selected results and demonstrations of EMG- and EEG-based neuroelectric interfaces. We will describe an EMG-based flight stick, an EMG-based numeric keypad, an EEG-based interface for smooth, continuous control of motion in a graphic display, and comparison of algorithms for modeling the EEG patterns associated with real and imagined hand motion. Finally, we will discuss recent developments of noncontact electric field sensors for EMG and EEG recording.

Our approach is to describe a body of developmental research, which is still in progress, and to indicate methods that have potential for engineering development. Given the BCI focus of this Special Issue, descriptions of purely EMG-based interfaces will be brief. We will describe the EEG results and the new sensor developments in more detail.

II. EMG INTERFACES

A. EMG-Based Flight Stick

In our first demonstration, a computer transformed EMG signals recorded from four bipolar channels placed on the forearm of a subject into control signals for an aircraft simulator. Thus, the processed EMG signals controlled an imaginary flight stick [2]. EMG samples were processed in real time using a flexible signal-processing framework developed in our laboratory. Our feature extraction procedures included routines to filter out redundant and meaningless channels with a mutual information metric [3]. The features were moving averages of the EMG signal from overlapping windows, where the data within a window are nearly stationary. Our model for mapping EMG signal features to gestures uses mixtures of Gaussians within a hidden Markov model context. We tested and validated this system with many trials over a two-year period in three subjects, who flew and landed high-fidelity simulations of a Boeing F-15 Eagle or a Boeing 757-200 freighter aircraft. Control of both aircraft was adequate for normal maneuvers. For the 757, a real-time landing sequence under neuroelectric control was filmed at NASA Ames Research Center (see on-line demos [4] and [5]).

B. EMG-Based Numeric Keypad

We have also found that EMG signals from the arm can distinguish typing of one key from another on a "virtual keyboard." In this demonstration,

1We used overlapping moving averages of the rectified, unfiltered EMG signal, sampled at either 500 (joystick task) or 2000 Hz (typing task). The windows contained 128 points and overlapped preceding windows by 96 points. We tried other types of features such as autoregressive coefficients, wavelets, and short-time Fourier transforms, but the moving averages provided the most robust response for everyday use.
Research report

On the translation of directional motor cortical commands to activation of muscles via spinal interneuronal systems

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Abstract

I discuss in this paper some of the neural mechanisms by which directional motor cortical commands could be potentially translated into multi-muscle activations to generate a directed force (and initial movement) in space. Specifically, I review the results of recent studies in the motor cortex of monkeys and the spinal cord of the frog, and propose a possible mechanism by which these results could be formally connected. It is suggested that spinal mechanisms of the kind described in the spinal frog could serve as substrates for the operation of directionally tuned motor cortical activity to produce an appropriately directed motor output by the limb.

Keywords: Motor cortex; Spinal cord; Direction in space; Monkey; Frog; Force

1. Introduction

Much effort has been expended during the past thirty odd years in investigating the relations between single cell activity in the motor cortex and static force exerted by behaving animals about single joints [23]. In contrast, the relations between motor cortical cell activity and changes in force have been studied only occasionally, and usually within studies of the relations to static force. Most of the studies addressing the cortical mechanisms of dynamic motor function have been focused on movements as experimental paradigms [6, 7]. Similarly, there is a wealth of information on the relations between spinal mechanisms and movements in locomotion [15]. Studies in monkeys [8] and frogs [14] have addressed questions relating to the development of dynamic force under isometric conditions. These studies used very different methods: the work in monkeys used recording of the activity of single cells in the behaving animal, whereas the work in frogs used microstimulation in spinalized preparations. However, both sets of studies addressed the question of how a change in force could be generated. These studies also shared another common aspect, namely that the force monitored was exerted in a two-dimensional (2D) space by the distal end of the limb. Although there are substantial differences in species and methods used, it may nevertheless be useful to speculate on how the results of these two kinds of studies could be related. Indeed, that what follows is an initial attempt to connect speculatively these two disparate sets of studies. I summarize first the relevant data and then develop the ideas concerning their interaction.

2. Motor cortical commands for directed, dynamic, isometric force

2.1. Directional tuning of single cells

The activity of single cells in the motor cortex is directionally tuned with respect to movement [13] or dynamic isometric force [8], in that cell activity is highest for a given direction ('preferred direction') of movement (or isometric force) and decreases gradually with directions farther and farther away from the preferred one. The tuning is broad and usually unimodal. Typically, the frequency of cell discharge is a linear function of the cosine of the angle formed between the direction of a particular movement (or force) and the cell's preferred direction.
2.2. Directional coding by neuronal populations

The population vector hypothesis [9] allows for the calculation of an unambiguous signal by a population of broadly tuned neurons. It was first applied to the coding of the direction of arm movements [9,11,12], and was subsequently extended to the coding of the direction of dynamic isometric force [8]. The calculation is a vectorial summation of a population of cell vectors pointing in their preferred direction with a strength proportional to the change in their firing rate, for a particular case. This weighted vector sum of the neuronal contributions is the 'population vector':

\[ P_i = \sum_{i=1}^{N} w_i c_i \]  

Fig. 1. A hypothetical scheme for the translation of directionally tuned motor cortical command to the activation of muscles by spinal interneuronal systems. See text for explanation.
where $P_1$ is the population vector for movement direction $l$, $w_{ij}$ is the weight for the $i^{th}$ cell and $l$ movement, and $C_i$ is the preferred direction of the $i^{th}$ cell. The population vector has been found to point in the direction of movement [9,11,12] and dynamic isometric force [8].

3. Spinal cord studies of isometric force production

In general, the neural signals from the motor cortex do not activate muscles directly but ultimately influence the activity of motoneurons through the spinal cord. In certain cases, the corticospinal axons terminate within the motor nuclei, as is the case, for example, for the motoneurons innervating distal muscles of the limb in adult primates [23], but in the vast majority of cases the influence on the motoneuronal pools is exerted through intercalated interneurons. These interneurons are found at the segmental level as well as at upper cervical (C3–C4) levels. The latter system has been investigated extensively in the cat and its intricate inputs from central and peripheral sources partially elucidated [18].

A detailed analysis of how spinal interneuronal systems can influence the spinal motor output in space has been carried out recently in the spinal frog [2,14,21]. In these studies, the technique of microstimulation was used to determine the effects of activation of interneuronal populations on the direction and magnitude of the force in space developed by the limb of the spinalized frog. There were three major findings of these studies. First, microstimulation at a particular interneuronal zone in the spinal cord elicited the development of force by the limb, the direction and magnitude of which differed depending on the position of the limb in space. The set of these forces define a ‘force field’. In the absence of microstimulation, there were passive forces due to the resistance to stretch of the tissues of the limb; during microstimulation, active forces were developed which, when added to the passive ones, resulted in the total force exerted by the limb. In the experiment, the total and the passive forces were measured, and the passive subtracted from the total to obtain the ‘active’ force field. It was found that microstimulation in a given area resulted in an active force field in which the force vectors converged on a particular point in space at which the force developed was zero; this was called the ‘equilibrium point’ of that field. In many cases, the force field predicted the limb motion when the limb was allowed to move; therefore, these fields can be regarded as underlying movement primitives [14]. The second finding was that only a few (3–4) clusters of equilibrium points were found by a detailed and systematic microstimulation of extensive areas of the spinal cord; each equilibrium point was represented at different locations in the spinal cord. Finally, concomitant microstimulation at any two sites produced a new force field which was the result of a point-by-point linear summation of the force field produced at each of the two stimulation sites; thus new equilibrium points were created [21]. These findings suggest possible mechanisms by which supraspinal commands could be translated into motor action as follows.

4. Translation of supraspinal commands

First, since microstimulation will activate an appreciable number of neurons [22], these intrinsic spinal motor mechanisms involve populations of neurons and summation of influences from potentially separate neuronal ensembles. Second, it is likely that these ensembles are the targets of supraspinal influences. For example, a common characteristic of pyramidal tract axons is their appreciable divergence in the spinal cord with collaterals to various spinal segments [23]. Although spinal microstimulation studies have not been performed in primates, it is reasonable to hypothesize a similar plan of spinal organization. Then this divergence of the pyramidal tract axons would enable central motor commands to address concomitantly a number of the spinal populations associated with different force fields, that is with different movement primitives. Third, this organization could provide the background for the translation of the motor cortical command, as understood at the single cell and neuronal population level, to motoneuronal activation (see [5]). This is illustrated in Fig. 1. Consider movement $M_i$ in direction $l$, starting from point A. When the hand is in position A, various force fields can act on it, depending on the spinal interneuronal population activated. Let us assume that there are four force fields ($K = 4$) potentially acting on the hand at position A and producing movement primitives $m_j$ ($j = 1$ to $K$) with magnitudes $U_{ji}$, that are proportional to the intensity of activation of the underlying spinal neuronal ensemble, appropriate for movement $M_i$. Assuming that the directions of the force fields are fixed for a given position of the hand, then movement direction $M_i$ should be the result of adjusting the magnitudes $U_{ji}$ so that

$$M_i = \sum_j U_{ji} m_j$$  \hspace{1cm} (2)

We assume that $N$ motor cortical cells converge on all $m_j$'s, and that for $M_i$ the influence of the $i^{th}$ cell on the $j^{th}$ force field $m$ is composed of two parts: one ($v_{ij}$) reflects the hard-wired connection strengths, and the other ($w_{ij}$) reflects the activation of the cell during movement $M_i$. Then $U_{ji}$ can be re-expressed as:

$$U_{ji} = \sum_i w_{ij} v_{ij}$$ \hspace{1cm} (3)

Substituting in Eq. (2) we get:

$$M_i = \sum_j \left( \sum_i w_{ij} v_{ij} \right) m_j$$ \hspace{1cm} (4)
and by rearranging:

$$M_i = \sum_{i}^{N} w_{ij} \left( \sum_{j}^{K} v_{ij} m_j \right)$$  \hspace{1cm} (5)$$

As discussed above, the population vector $P_i$ (equation 1) points in the direction of movement $M_i$ (equation 5); therefore:

$$\sum_{i}^{N} w_{ij} C_i = \sum_{i}^{N} w_{ij} \left( \sum_{j}^{K} v_{ij} m_j \right)$$  \hspace{1cm} (6)$$

and

$$C_i = \sum_{j}^{K} v_{ij} m_j$$  \hspace{1cm} (7)$$

Equation 7 connects the concept of the preferred direction $C_i$ of the $i$th cell to that of the movement primitive generator $m_j$, as mentioned above; the weights $v_{ij}$ can be regarded as the hardwired connection strengths of the $i$th cell on the ensemble of movement primitive generators $m_j$, and then the vector sum of these influences will point at the cell's preferred direction.

Equation 3 implies two important assumptions: namely, (i) that there exist hardwired connections ($v_{ij}$) between motor cortical cells and spinal neurons, and (ii) that the activity of a motor cortical cell ($w_{ii}$) can vary independently of its spinal connectivity pattern. Both of these assumptions are supported by the results of experimental studies of corticospinal influences, investigated by using the technique of postspike facilitation (see [23] for a review). Especially important is the observation that for different motor tasks, the cell activity can vary but the pattern of postspike facilitation remains the same [20]. Although these observations are for putative monosynaptic projections of motor cortical cells to motoneurons, it is reasonable to extend them to the more general case in which the effect is mediated, as in intercalated interneurons such as those making up the movement primitive generator $m_j$.

5. Concluding remarks: control of the limb as a whole

The results of the studies reviewed above suggest that spinal and supraspinal motor structures regard the limb as a functional whole. Recent studies [3] indicate that afferent systems may do the same. In these experiments single cell activity was recorded in the Clarke's column, the nucleus of origin of the dorsal spinocerebellar tract. Cells were antidromically identified as projectors to the cerebellum and their activity recorded during peripheral stimulation of the hindlimb in anesthetized cats. Although single cells received mono- and polysynaptic convergent inputs from various kinds of receptors and parts of the limb, their activity varied in an orderly fashion with the orientation of the limb in space and with the direction of limb movement in space, when the limb was moved passively. This shows that the converging information onto single cells can meaningfully reflect spatial aspects of the status of the limb as a whole. Convergence of peripheral inputs on spinal interneurons has been described in several cases, including the C3–C4 propriospinal interneurons mediating central commands to proximal motoneurons [16]. It would be interesting to know whether the activity of these neurons similarly reflects spatial aspects of limb posture and/or movement.

Additional support for the idea that the limb may be controlled as a multi-joint unit comes from the results of recent studies in which microstimulation or ablation of central nervous structures were used. First, microstimulation of the motor cortex in the monkey elicited concomitant activation of various muscles [4]. Second, reversible inactivation of the motor cortex in the cat affected multi-joint, reaching movements of the limb but not single joint movements about the elbow [19]. And third, lesion of the dentate nucleus in the monkey also differentially affected reaching but not single joint movements [17]. These findings are in accord with the suggestion of the original single cell recording studies [10] that the motor cortex controls reaching movements. The close interaction between the motor cortex and the cerebellum [1] suggests that both of these structures may share this common feature of whole-limb motor control.

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