OPINION

Brain–machine interfaces to restore motor function and probe neural circuits

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Recent studies have shown that it is possible to create functional, bidirectional, real-time interfaces between living brain tissue and artificial devices. It is reasonable to predict that further research on brain–machine interfaces will lead to the development of a new generation of neuroprosthetic devices aimed at restoring motor functions in severely paralysed patients. In addition, I propose that such interfaces can become the core of a new experimental approach with which to investigate the operation of neural systems in behaving animals.

Paralysis, one of the most common and debilitating outcomes of severe damage to the central nervous system, continues to cast a long shadow of hopelessness on millions of lives worldwide. Despite the significant strides made by basic and clinical research, few (if any) therapeutic options are available at present for restoring voluntary motor control of the limbs in patients suffering from extensive traumatic or degenerative lesions of the motor system.

The prevalence of severe body paralysis is high, particularly among young adults. For instance, among the leading causes of permanent paralysis, traumatic spinal cord injuries — produced by traffic accidents, acts of violence or falls — account for nearly 11,000 new cases each year in the United States alone[1]. In all, more than 200,000 patients in the United States live with the motor sequelae of similar injuries[1]. About half of these patients are quadriplegic, which means that, owing to injury to the cervical spinal cord, they cannot move any of their limbs or any other muscle below the neck. Quadriplegics depend on continuous assistance to accomplish even the simplest of motor acts. Whereas most of us take for granted our ability to breathe, eat and drink, a quadriplegic patient usually cannot do any of these without the assistance of a machine (such as a ventilator) or a carer. For this reason, restoring even the smallest of motor skills in these patients can have a profound effect on their quality of life.

Several new experimental approaches to the restoration of motor function lost as a result of spinal cord injuries have been proposed[2]. Most focus on ways to repair the damaged axons that normally mediate communication between cortical (and subcortical) motor neurons and pools of interneurons and α-motor neurons in the grey matter of the spinal cord. Despite promising results, this approach faces large challenges given the difficulty involved in guiding large numbers of severed axons to re-establish their original connections.

Parallel to these efforts to repair spinal cord connectivity, recent experimental demonstrations in rodents[3,4], primates[5–7] and patients[8–11] have raised interest in the proposition that neuroprosthetic devices — designed to bypass spinal cord lesions — could be used to restore basic motor functions in patients suffering from severe body paralysis. This approach, first proposed by the neurophysiologist Edward Schmidt[12], assumes that voluntary motor commands can be extracted in real time from the collective electrical activity of populations of cortical or subcortical neurons spared by the underlying illness, and then used to enact motor function either by directly stimulating the patient's musculature or by controlling the movements of artificial actuators, such as robot arms. FIGURE 1 shows the general design of a cortical neuroprosthetic device aimed at restoring upper limb movements in quadriplegic patients. This device relies on chronic intracranial recordings to obtain large-scale brain activity from motor areas in the cortex. A real-time mathematical model is responsible for extracting a few motor control commands from the raw electrical brain activity. An artificial actuator (in this case, a multi-joint robot arm), controlled by the output of the real-time mathematical model, is used to reproduce the subject's upper limb movements. Because the robot arm provides continuous feedback information to the subject (not shown), this neuroprosthetic device operates through a closed control loop. Recent review articles discuss this design in greater detail[13,14].

The device shown in FIG. 1 is also defined by the neurophysiological approach chosen to extract the raw brain activity from which the motor control signals are derived. Over the years, distinct sources of neuronal signals, ranging from scalp electroencephalograms (EEGs)[8,10] to intracranial single-unit recordings[5,9,13], have been proposed as potential sources of control signals to drive various neuroprostheses. The advantages and disadvantages of each of these and other neurophysiological approaches have been reviewed[13]. Regardless of the type of brain signal selected, several studies have now indicated the feasibility of building functional interfaces between living brain tissue in experimental animals and various electronic, mechanical and computational devices[3–7]. To a limited degree, clinical applications of this approach, notably those based on EEG recordings, have also been implemented[10].

The recent increase in interest in this field of research — commonly referred to as neuroengineering — has been driven by the expectation that various powerful clinical implementations of direct brain–machine interfaces (BMIs) might emerge in the near future. Support for this contention is provided by the tangible success of a variety of implantable brain stimulators, such as cochlear implants for restoring auditory function, deep brain stimulators for pain management and control of motor disorders (such as Parkinson's disease), and vagal nerve stimulators for treating chronic epilepsy. As more patients have benefited from this approach, the interest in brain stimulation technology has grown significantly. Indeed, investments in a new generation of these devices are rapidly fuelling the emergence of an incipient brain-based biomedical industry. In essence, this process is similar to the phenomenon that led to the translation of basic science discoveries into revolutionary clinical applications in the field of cardiology. That translational process helped to create the backbone of a heart-based biomedical engineering industry, which today generates billions of dollars in revenue. At present, it is not possible to predict the economic impact that a brain-based industry will have in the future. However, judging by present trends, it seems fair to say that brain actuators will have a prominent role in the further development of this industry.

Although these arguments might encourage some neurophysiologists to become entrepreneurs, a word of caution is justified. Most BMIs tested in experimental animals are not yet ready to be translated into practical clinical applications. Much basic research must be done to ensure that this approach is safe and can provide sufficient benefits to justify the type of surgical intervention that might be required for BMIs to become fully operational. Furthermore, significant engineering bottlenecks have yet to be overcome[13]. These include substantial work in the areas of microelectrode array design and testing, biocompatibility of chronic brain implants, microelectronics (for example, miniaturization of hardware for multichannel neural signal conditioning and telemetry), power management, real-time computational modelling and robotics (a new generation of actuators and sensors). These engineering developments are prerequisites for moving the field from experimental demonstrations to clinical implementations that can achieve the therapeutic benefit envisioned for such devices.

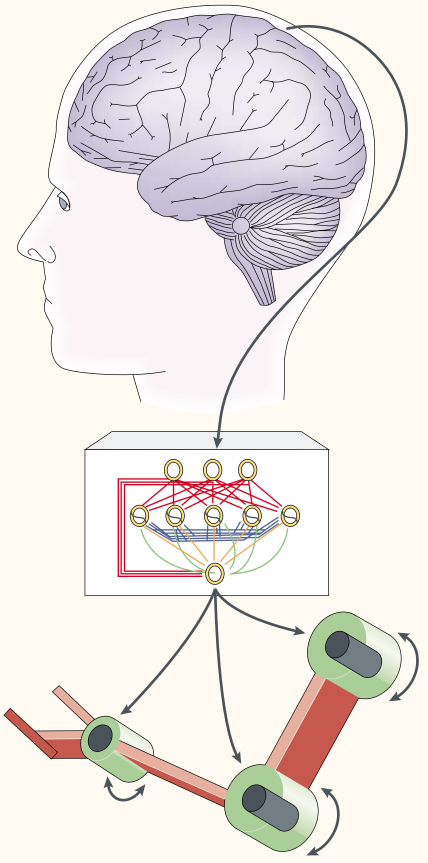

Figure 1 | **Schematic representation of a cortical neuroprosthetic device.** In the general design shown, intracranial recordings are used to sample the extracellular activity of a few hundred neurons in frontal and parietal cortical areas that are involved in the planning of arm and hand movements. The combined activity of these neuronal populations is processed, in real time, by a series of simple mathematical models designed to extract motor-control parameters from the raw brain signals. The outputs of these models are used to control the movements of a robot arm that has been designed to allow the patient to enact fundamental upper limb movements.

BMIs and fundamental research

Because of their potential clinical relevance, the potential contribution of BMIs to basic brain research is often neglected. For example, recent findings indicate that BMIs might lead to the definition of various new experimental models, aimed at investigating the real-time operation of neural circuits in behaving animals[15]. The continuing refinement of electrophysiological, computational and engineering methods for establishing functional interfaces between living brain tissue and artificial devices has the potential to influence experimental models in several other fields of inquiry, such as cellular, computational and cognitive neuroscience[4,5,16]. A few examples of what the future might bring are already present in the literature. These include the use of experimental BMIs to investigate how different populations of neurons in a neural circuit contribute to the encoding of motor parameters[5,17,18], and an *in vitro* implementation of hybrid biological and artificial networks to study the cellular properties of complex neural circuits[16]. In addition, recent findings show that a BMI could be used to optimize the operant training of experimental animals[4].

These examples illustrate a new approach to investigation of the brain, which I call real-time neurophysiology[15]. The uniqueness of this approach is that theories of brain function can be tested under the demanding constraints imposed by the need to perform efficiently in real time, or at the same timescale as the animal's behaviour. An example of this approach is shown in FIG. 2, which illustrates a new experimental platform that is being used in our laboratory to address questions on both neural population coding and neuroprosthetic design. In this system, monkeys learn to produce complex hand movements in response to arbitrary sensory cues. Chronically implanted microwire arrays are used to simultaneously record the extracellular activity of hundreds of single neurons distributed across several cortical and subcortical structures. Using this neurophysiological approach, the dynamics of several neural circuits can be measured simultaneously. Moreover, because neuronal recordings remain stable for long periods[5], this approach also allows one to quantify the physiological changes that take place in different components of a neural circuit as animals learn various sensorimotor and cognitive tasks.

In this type of experimental apparatus, several real-time models can be used to extract various motor-control parameters — such as direction of hand movement, gripping force, hand velocity, acceleration, three-dimensional position and so on — from the parallel streams of neuronal activity that are recorded as the animal executes various arm movements. The outputs of these models are then used to control the movements of a multi-jointed robot arm, so that one can investigate the type of real-time computation that is required to reproduce the animal's arm movements in a robot arm. Although successful replication of the animal's arm movements in a robot does not imply that the motor system works in the way proposed by the real-time model tested in these studies, this experimental apparatus can be a useful tool in ongoing efforts to dissociate motor variables through behavioural training. I envisage that this can be achieved by modifying the strategy used to close the control loop between the robot and the animal (see later discussion).

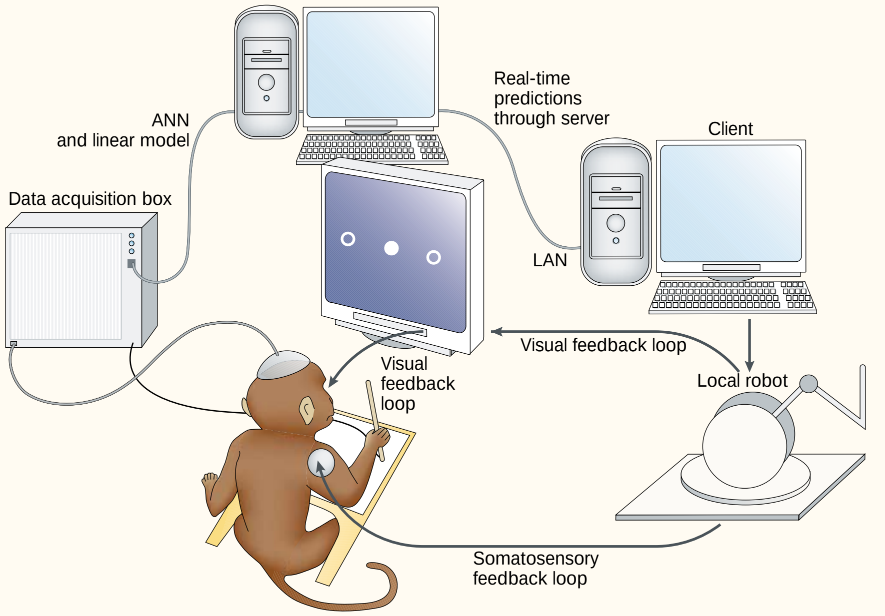

Figure 2 | **Experimental design used to test a closed-loop control brain–machine interface for motor control in macaque monkeys.** Chronically implanted microwire arrays are used to sample the extracellular activity of populations of neurons in several cortical motor regions. Linear and nonlinear real-time models are used to extract various motor-control signals from the raw brain activity. The outputs of these models are used to control the movements of a robot arm. For instance, while one model might provide a velocity signal to move the robot arm, another model, running in parallel, might extract a force signal that can be used to allow a robot gripper to hold an object during an arm movement. Artificial visual and tactile feedback signals are used to inform the animal about the performance of a robot arm controlled by brain-derived signals. Visual feedback is provided by using a moving cursor on a video screen to inform the animal about the position of the robot arm in space. Artificial tactile and proprioceptive feedback is delivered by a series of small vibromechanical elements attached to the animal's arm. This haptic display is used to inform the animal about the performance of the robot arm gripper (whether the gripper has encountered an object in space, or whether the gripper is applying enough force to hold a particular object). ANN, artificial neural network; LAN, local area network.

To complete a closed-loop control BMI, information describing the performance of the robot arm is relayed back to the animal, using artificially generated visual and 'proprioceptive/tactile' feedback signals. Visual feedback is delivered on a monitor in front of the animal, and proprioceptive/tactile information can be relayed through an array of vibrotactile elements attached to the animal's contralateral arm. As microelectrode arrays are implanted in neural circuits that process sensory feedback generated by arm movements, intracranial microstimulation can be used to deliver to the animal feedback information that describes the robot's performance (not shown).

When a BMI is in a closed-loop configuration, the experimenter can manipulate the feedback information that the animal receives in several ways. These manipulations can be designed to permit neuroscientists to address key questions regarding the dynamics of sensory and motor information encoding by distinct populations of neurons. For example, does learning allow a population of neurons that normally contributes little to the encoding of a given movement parameter to enhance its contribution? This question could be addressed by first comparing the performance of populations of neurons from distinct cortical areas in controlling the movements of a robot arm. Then, by selecting only neurons from a given cortical area to feed into the real-time model, one could measure whether the contribution of these neurons can be enhanced by visual and/or tactile feedback, which are used to indicate the error between the movements of the animal's arm and the robot arm.

This apparatus could also be used to measure how fast changes in the kinematic properties of the motor actuator (robot arm) or in the task contingency affect the encoding of motor information by distinct populations of neurons[19]. For example, suppose that animals are rewarded for using their brain activity to make a robot arm move in the same direction as their own hand. By introducing a rotation in the output of the model that converts the animal's brain activity into robot arm movements, and using visual and tactile feedback to illustrate the mismatch between the robot arm and the animal's hand movements, one can test whether populations of neurons that encode information about hand movements adapt to account for the transformation of the model's output. Results obtained at the single-neuron level indicate that this would occur[19–21].

The use of sensory feedback or reward in operant conditioning of neural activity has a long tradition in neuroscience[20–24]. Indeed, the concept of building a BMI to restore motor function was heavily influenced by the early studies of Fetz and colleagues[20,21,23,24]. These landmark experiments showed that monkeys could learn to increase the firing rate of individual cortical neurons if they were provided with visual or auditory feedback — which signalled the unit firing rate — combined with a food reward for attaining high rates. This conditioning occurred over a few training sessions so that when overtraining was achieved, monkeys could readily increase the firing rates of newly isolated cortical neurons to levels 50–500% higher than their normal rates[23]. Fetz also showed that removal of feedback and reward led to the return of normal firing rate levels[23].

The experimental apparatus illustrated in FIG. 2 also makes it possible to test the hypothesis that, with adequate visual and proprioceptive/tactile feedback, animals could not only learn to operate a robot arm efficiently, but they could also incorporate such an artificial device into the body representations that are present in motor and somatosensory cortical and subcortical structures[13,25,26]. Theoretically, such an assimilation could occur as a result of experience-dependent plastic reorganization, and could lead to significant improvement in the operation of a neuroprosthetic device. Such a demonstration would not only have considerable clinical relevance, but would also raise intriguing neurobiological and robotic questions[27].

BMIs and distributed neural coding

The examples described above indicate that BMIs could become useful tools for studying the dynamic and distributed nature of neural population coding in behaving animals. The concept of distributed coding has a long history in neuroscience. The initial formulation of this theoretical model — which guides most of the present thinking behind attempts to develop a neuroprosthetic device for restoring motor function — dates back to the work of the eclectic nineteenth-century English physician and Cambridge physicist, Thomas Young[28]. Young is perhaps best known for the double slit experiment, which led to the

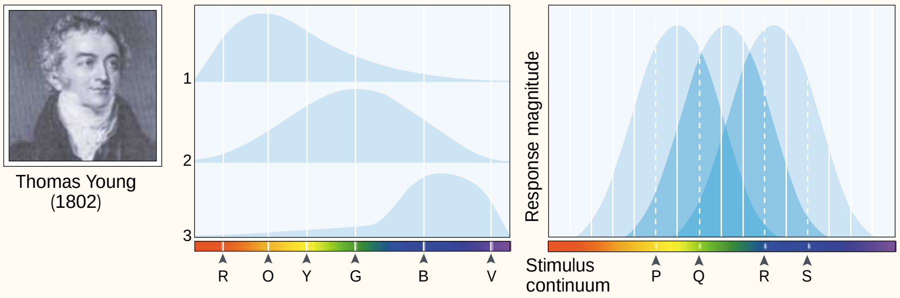

Figure 3 | **Distributed neural coding in colour vision.** In 1802, Thomas Young (left) introduced the concept of distributed neural coding in his classic trichromatic theory of colour vision. In his formulation, the combined response profile of only three retinal receptors (middle), tuned to respond to a broad spectrum of light wavelength (right), can account for the representation of any colour in the visible spectrum. P, Q, R, S, colour stimuli.

proposition of the principle of light interference, for his fundamental contributions to the theory of elasticity of materials, and for his efforts to decipher Egyptian hieroglyphics. His sole contribution to neuroscience was of equal stature to his other intellectual adventures. In a paper published in 1802 (REF. 28), Young proposed the trichromatic theory of colour vision (FIG. 3). With no anatomical or functional evidence, Young proposed that the combined action of just three classes of light receptor in the retina (later known as cones) could account for the complete spectrum of colour sensation experienced by humans. Young indicated (FIG. 3) that although these receptors could be specialized to respond maximally to the presence of one of the three main colours (red, blue and yellow), each would also be able to respond, albeit less strongly, to light of different wavelengths. In other words, each receptor would be broadly tuned to a large wavelength spectrum.

Young's formulation predicted that the collective or distributed response pattern of these three retinal receptors could be used to represent the wavelength (or colour) of any light stimulus in the visual spectrum unambiguously. Despite lacking any insight into the structure of the retina or the brain, Young's ingenious formulation gave rise to the concept of distributed neural coding. In this scheme, the electrical activity of large and spatially distributed populations of neurons — rather than single cells — is responsible for representing the attributes of incoming sensory stimuli, or for generating the motor commands required for the production of a voluntary act.

After Young, many neuroscientists contributed to the elaboration of the concept of distributed neural coding. Perhaps the most influential was Donald Hebb. In his classic book *The Organization of Behavior*[29], published in 1949, Hebb provided a cellular analogue to Young's formulation by describing the brain entity that, according to him, would be responsible for the 'grunt' work of computing, storing and representing information in the central nervous system. Hebb proposed that these functions would be carried out by:

> "...the cell assembly, a diffuse structure comprising [brain] cells in the cortex and diencephalon, capable of acting briefly as a closed system, delivering facilitation to other such systems..."

The main reason that one can seriously consider using neuroprosthetic devices to restore motor function in paralysed patients is that motor information is widely distributed in populations of neurons in the primary motor cortex[30] and other motor cortical areas[5,17,18]. This widespread dispersion of information within and between cortical areas might explain why random samples of relatively small populations of single neurons can provide enough information to reconstruct continuous three-dimensional hand trajectories produced by monkeys that were trained in simple motor tasks[5,7].

Further experimental evidence indicates that cortical and subcortical neural ensembles can simultaneously represent multiple motor and sensory parameters[31–33]. Although there is debate on how this multiplexing is achieved, preliminary results in our laboratory indicate that by sampling a few hundred neurons simultaneously and differentially weighting their contribution, one can extract multiple control signals from the same population of recorded neurons. Further studies using BMIs in experimental animals could help to answer this and other fundamental questions in neural ensemble physiology.

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Converging on applications

Because BMIs offer a new way to study distributed neural processing, and because addressing some of these basic questions might influence the design of future neuroprosthetic devices, research on BMIs offers a unique opportunity for promoting convergent areas of investigation for both basic and applied neuroscientists. For example, there is much discussion in the literature regarding how many neurons need to be sampled to build a clinically viable BMI for restoring upper limb movements. Although the original studies suggested that a few hundred neurons could provide an ideal sample for driving such a BMI[5], a couple of laboratories have used small neuronal samples (8–30 neurons) to drive experimental BMIs with some success[6,7].

Clearly, this question is as pertinent to neuroscientists that are interested in how motor information is encoded in the brain as it is to biomedical engineers that are interested in designing and implementing a clinically relevant BMI. An appropriate answer requires the analysis of a number of factors. Three main arguments challenge the notion that small samples of neurons could be used to drive a clinically relevant BMI. First, to be considered as a viable therapeutic alternative, BMIs will have to produce a significant improvement in the patient's quality of life. Before now, studies based on reduced samples of neurons have led to limited experimental demonstrations of motor control[6,7,9]. These include using cortical neuronal activity to control the movements of a computer cursor[9] or to reproduce the direction and trajectory of hand movements for brief periods of time[6,7]. A recent study reported that monkeys operating a closed-loop control BMI driven by the combined activity of about 18 cortical neurons correctly completed 50% or fewer of the task trials[7]. As control of computer cursors can be achieved with non-invasive methods, such as EEG recordings and electromyogram activity[8,10], proponents of BMIs based on small samples of neurons would have to demonstrate much more elaborate and reliable levels of motor control to justify subjecting patients to the neurosurgical procedure that is required to render these neuroprostheses functional.

A second argument against the potential clinical relevance of these BMIs is that any small reduction in the original population of recorded cells could impede the reliable function of the neuroprostheses. For instance, any minor postsurgical disruption in electrode properties, leading to an inability to record from the full original population of neurons, could render this type of BMI useless. Natural loss or death of just a couple of neurons could produce a similarly catastrophic effect. Indeed, the normal time-dependent reduction in neuronal yield that characterizes some methods for chronic multi-electrode recordings would lead to the same outcome.

Third, relatively small changes in the physiological properties of these small samples of neurons (such as changes in tuning properties) could also reduce the effectiveness of such BMIs. Although adaptive learning algorithms can be used to counteract these changes[5,7], variations in patterns of neuronal firing due to changes in attention or arousal can prove difficult to handle in real time, particularly if the sample of cells used to derive a neural population signal is very small. It could be argued that patient training using visual, auditory and tactile feedback signals might enhance the information content of individual neurons or small populations of cells. Even though sensory feedback will probably improve the performance of BMIs and reduce the overall neuronal sample required to operate them, the crucial demonstration that BMIs based on small populations of neurons can maintain high performance for months or years, despite losing a few neurons, is still lacking. As BMIs based on brain implants would have to maintain a high level of daily performance for many years, this important drawback alone almost certainly limits the clinical application of a design based on a small sample of neurons.

Neural coding theory and BMI design

Ultimately, I believe that the design of a successful BMI for restoring control of upper limb movements will have to take into account general physiological principles of how motor signals underlying these movements are encoded in the primate brain. Moreover, instead of aiming solely to restore motor functions by controlling a computer cursor, these BMIs must be able to restore fundamental hand or arm movements by using either the patient's limbs (the most difficult goal) or artificial devices — such as robot arms and specially designed exoskeletons[34] — as their motor actuators. Including a gripper in these artificial actuators would also be essential. Although these requirements make it more difficult to build these devices, the successful implementation of such a BMI would lead to significant benefits for severely paralysed patients, while providing undisputed clinical justification for the need for surgical intervention.

"Ultimately, I believe that the design of a successful BMI for restoring control of upper limb movements will have to take into account general physiological principles of how motor signals underlying these movements are encoded in the primate brain."

Recently, I proposed a neuroprosthetic design that could overcome the three problems identified in the discussion of BMIs based on small neuronal samples[13]. This design was based on five 'physiologically inspired' principles. The first principle proposes that motor information related to hand movements is represented in a distributed way in several cortical and subcortical structures that define the motor system. The second principle purports that, within each of these areas, multiple motor parameters (position, velocity, force, direction and so on) can be extracted in real time from the electrical activity of populations of neurons. This principle assumes that multiplexing of information by neural ensembles is a ubiquitous property of motor cortical areas in the frontal and parietal lobes. The third principle contends that to reproduce a given hand trajectory in a robot arm, one might need to sample from a small fraction (a few hundred) of all the neurons (several million) in each cortical motor area (and across the entire motor system) that modulate their firing rate before the onset of a hand movement[5]. As mentioned above, several independent empirical observations support this contention. These findings also raise the hypothesis that there is considerable redundancy in the encoding of motor parameters in each cortical area. In this context, one could conceive a potential coding scheme in which the minimal neuronal mass required to generate an appropriate arm/hand movement in a given trial is selected from a large pool of cortical neurons that modulate their firing before the onset of a hand movement (Principle 1). As this minimal neuronal mass could be defined by different combinations of individual neurons (Principle 5, below) such a coding scheme would ensure that reliable motor outputs would continue to be produced, even if significant numbers of neurons were lost owing to lesions of the motor system.

The fourth principle states that the physiological properties of cortical ensembles are adaptive and can change as a function of experience and training, so the existence of cortical and subcortical plasticity must be taken into account in the design of an efficient BMI. Finally, the fifth principle asserts that the same hand/arm movements can be produced by distinct spatiotemporal patterns of neural ensemble firing. In other words, on a single-trial basis, different combinations of single neurons from several cortical areas, producing distinct spatiotemporal sequences of neuronal firing, can encode the same movement. Experimental evidence supports three of these principles; the third and fifth principles are still hypothetical. However, preliminary evidence obtained in our laboratory indicates that they have merit and should be investigated further.

A BMI design that takes into account these five principles would use chronic implants of high-density microwire arrays to sample the extracellular activity of 100–200 neurons from each of 3–5 cortical areas simultaneously. Using this approach, several motor control parameters could be simultaneously extracted from the recorded neuronal sample, enabling patients to achieve more elaborate control of artificial actuators — such as robot arms and grippers — to recreate various arm/hand movements aimed at increasing their independence (for example, feeding without assistance) or at improving their ability to interact with their surrounding environment (for example, controlling a wheelchair). Additional improvements in the ability to control actuators located in remote environments (such as robots in different rooms) could further improve quality of life for these patients.

Overall, this BMI design would increase the chances of achieving robust, continuous performance and long-term reliability. By sampling from a large neuronal population from the onset, the performance of such a BMI would be much less affected by eventual problems with individual electrodes, reductions in neuronal samples or changes in the physiological properties of individual neurons. Indeed, loss of all but one of the implants could still provide enough information for the continuous operation of such a cortical neuroprosthesis.

Conclusions

During the last five years, a series of experimental studies has demonstrated the feasibility of building neuroprosthetic devices to restore basic motor functions in patients suffering from catastrophic body paralysis. As obstacles to bringing these devices to the clinical arena are overcome, further research on BMIs is also likely to spur the development of various new models to investigate the operation of the neural circuits that will be used as a source of brain signals to drive a new generation of neuroprostheses. The confluence of these two outcomes might lead to profound contributions to the study of distributed neural coding, and the design of new brain-controlled actuators aimed at minimizing the devastating motor impairments that are caused by a large repertoire of neurological disorders.

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