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Perspective

Brain-Machine Interfaces beyond Neuroprosthetics

Karen A. Moxon[1,*] and Guglielmo Foffani[2,3,*]
[1]School of Biomedical Engineering, Science and Health Systems, Drexel University, 3141 Chestnut Street, Philadelphia, PA 19104, USA
[2]CINAC, HM Puerta del Sur, Hospitales de Madrid, 28938 Móstoles, and CEU-San Pablo University, 28003 Madrid, Spain
[3]Neural Bioengineering Group, Hospital Nacional de Parapléjicos, SESCAM, Finca la Peraleda s/n, 45071 Toledo, Spain
*Correspondence: karen.moxon@drexel.edu (K.A.M.), guglielmo.foffani@gmail.com (G.F.)
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The field of invasive brain-machine interfaces (BMIs) is typically associated with neuroprosthetic applications aiming to recover loss of motor function. However, BMIs also represent a powerful tool to address fundamental questions in neuroscience. The observed subjects of BMI experiments can also be considered as indirect observers of their own neurophysiological activity, and the relationship between observed neurons and (artificial) behavior can be genuinely causal rather than indirectly correlative. These two characteristics defy the classical object-observer duality, making BMIs particularly appealing for investigating how information is encoded and decoded by neural circuits in real time, how this coding changes with physiological learning and plasticity, and how it is altered in pathological conditions. Within neuroengineering, BMI is like a tree that opens its branches into many traditional engineering fields, but also extends deep roots into basic neuroscience beyond neuroprosthetics.

Introduction

The synergistic interactions between traditional engineering and basic science represent an important path toward the advance of scientific hypotheses and theories, which is supported by the continuous development of novel techniques. In turn, this development fosters the emergence of novel ideas by allowing old questions to be solved and by opening avenues for new questions to be addressed. Within neuroengineering, a good example of this path is the field of brain-machine interfaces (BMIs).

A BMI can be defined as an artificial process that allows the brain to exchange information directly with an external device. This definition reflects technological innovation, and it is typically associated with the goal of assisting, augmenting, or repairing sensorimotor or cognitive function (Figures 1A and 1B). Without entering into the nuances that differentiate between assisting, augmenting, and repairing, this is essentially the neuroprosthetic definition of BMI, in line with the utilitarian goal of improving quality of life in human beings. This neuroprosthetic definition and the applications associated with it represent the common view of BMI in both the neuroscience community and the general public. In parallel to this view, however, novel ideas that challenge existing dogma and/or extend current understanding of neural systems are emerging within the BMI context that are distinctly separate from the neuroprosthetic definition of BMI.

The unique aspect of BMI experiments is that they defy the classical object-observer duality by not respecting the separation between the observer and the object of the observation that is the hallmark of classical neuroscience. In classical neuroscience, an experiment is designed with the goal of testing a hypothesis. The experiment is then performed, and neurophysiological observations are made on the planned number of subjects. Finally, the data are analyzed and the hypothesis is rejected or corroborated. In BMI experiments, animal or human subjects are still objects of observation. However, subjects can also be viewed as indirect observers of their own neurophysiological activity because they need to interact with it, at some conscious or subconscious level, during the execution of a task.

When the experimenter is ultimately concerned with maximizing the performance of the subject in the experiment, BMI remains within the field of neuroprosthetics. When the experimenter is primarily concerned with how the subject interacts with her/his own neurophysiological activity to achieve a certain performance, then BMI takes a distinctly different tack from the field of neuroprosthetics, with the emergence of novel approaches to more deeply address old questions (e.g., about learning and neural plasticity) and/or to open new avenues of inquiry (e.g., about neural coding in health and disease) (Figure 1C). BMIs thus represent a paradigmatic example within neuroengineering of the benefits of fully integrating engineering with neuroscience to create a novel discipline.

Around the central thesis of BMI defying the classical object-observer duality, in the next sections we will provide an historical overview of the pioneering works that anticipated the BMI field, discuss the two main aspects of the central thesis at the boundaries of neuroprosthetics, and then highlight its consequences for investigating basic questions beyond neuroprosthetics.

Historical Background

Advancements in BMI were achieved after decades of basic science research into the functioning of the CNS. As early as the turn of the 20th century, hypotheses were being formulated about brain function based on insight gained from electrophysiological and anatomical experiments. For example, Sherrington (1906) and Kubie (1930) monitored the recurrent loops of excitatory transmission between regions, initially referred to as circularities, and suggested the possibility that large numbers of neurons acted in concert and influenced each other to represent information. This concept was further developed by Hebb (1949). While Hebb famously introduced the Hebbian rule to describe how the efficacy of synaptic function could be modulated by use, which now forms the basis of synaptic plasticity, he also elegantly

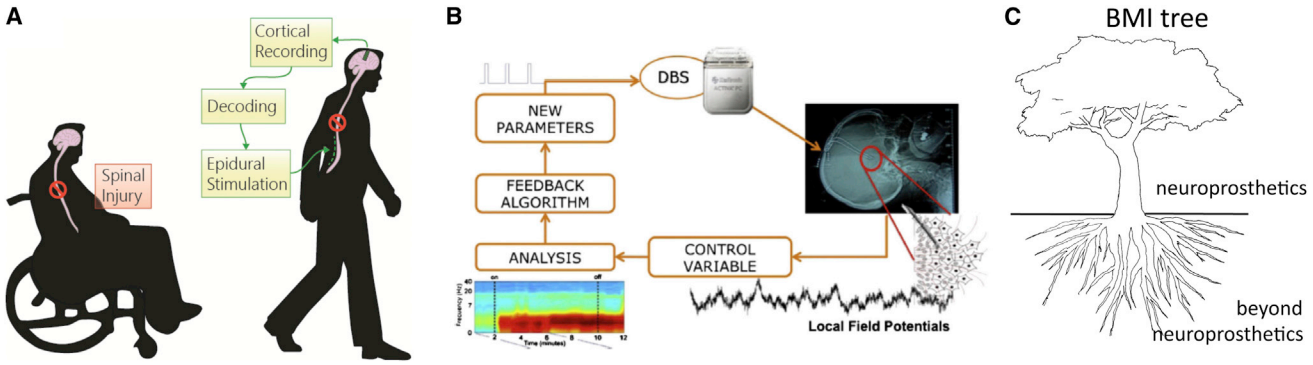

Figure 1. Invasive Brain-Machine Interface Applications

(A) Classical envisioned application of conscious BMI to extract motor information from the brain and bypass a spinal cord injury to restore voluntary motor function.

(B) Example of subconscious BMI to perform closed-loop brain stimulation based on an electrophysiological biomarker; in this case it is adaptive deep brain stimulation controlled by local field potentials to treat Parkinson's disease. From Priori et al. (2013), with permission.

(C) BMI is like a tree that not only opens its branches toward neuroprosthetic applications, but also extends its roots outside the limits imposed by the classical object-observer duality, allowing fundamental neuroscience questions to be answered beyond neuroprosthetics.

outlined how populations of neurons could work together as assemblies of activity to represent and, ultimately, store information. Hebb's view of cell assemblies allowed him to postulate that information was redundant, diffusely represented in composite cortical regions, and that only a fraction of the entire assembly needed to be active to recall the information.

Hebb's theory of cell assemblies combined with his theories of synaptic plasticity opened up a plausible explanation for how information could be represented with novel patterns of activity and stored in structural synaptic changes. This addressed a controversy at the time surrounding the physical underpinnings of learning and memory, namely whether all learning requires plasticity (i.e., physical changes to the underlying anatomy) or can emerge as novel patterns of activity. Now, one might suggest it is just a matter of degree, but strong arguments were made on each side, with important contributions being provided by lesion studies. For example, Lashley (1950) demonstrated that any part of the region associated with a learned task was equally effective in storing the memory for that task (theory of equipotentiality) and that the more tissue devoted to a task, the better the system could perform (theory of mass action). Lashley concluded that information was diffusely represented, with the particular set of cells that fired at a given time not being nearly as important as their spatiotemporal relationships. The idea was taken up by John (1972), who proposed that memory traces are stochastically diffuse, redundant, and primarily related to function rather than anatomy, suggesting that a particular organized temporal pattern of activity in a population of cells can represent a specific memory (convey information) regardless of the identity of the cells momentarily activated. This is in contrast to more deterministic views of how information was tied to specific connections between cells (McCulloch and Pitts 1943). Today, our understanding in the BMI field is somewhere in between John's purely statistical view and the purely deterministic view. The implications of these theories are still being argued today and are relevant for the complex relation between BMI and neuroplasticity.

In parallel, anatomical studies were addressing questions on how information was represented in the brain. Predating Hebb, Lorente de No (1939), building on the precise anatomical work of cortical organization by the school of Ramón y Cajal, suggested that although anatomical connections may form a substrate upon which information can be represented, they do not define the information. Lorente de No's work discovered the modular organization of the cortex and showed that cells were grouped in patterns that repeated across large cortical areas. Building on this and on the early work of Mountcastle (1957) and others, Szentágothai (1975) defined a cortical column as the basic functional block that could support the representation of information. Eccles (1981), taking advantage of these earlier works, suggested that the complexity and interconnectivity of cortical modules allows them, rather than single cells, to act as the functional unit of spatiotemporal patterns of activity representing information. Eccles goes even further, suggesting that cortical modules rather than single neurons form the fundamental unit from which consciousness emerges, which could be intriguingly relevant for BMI experiments.

Technology has also played a key role in the advances in our understanding of the representation of information in the brain and in the development of BMI. From simultaneous recordings of multiple cells, John emphasized that "the response of a single neuron to a specific stimulus was not reliable, but the average response of many neurons to a single stimulus was as invariant as the average response of a single neuron to multiple presentation of the same stimulus" (John, 1967), a fundamental premise for BMI decoding algorithms. On the sensory side, investigators were using neuronal activity simultaneously recorded from multiple neurons to examine the details of Hebb's cell assemblies (Gerstein and Perkel, 1969; Gerstein et al., 1978). On the motor side, Evarts (1966, 1968) demonstrated a relationship between specific limb movements under applied forces and the resulting modulations in the spiking activity of single neurons in the motor cortex of the monkey. These works are relevant for the development of decoding algorithms for BMI experiments.

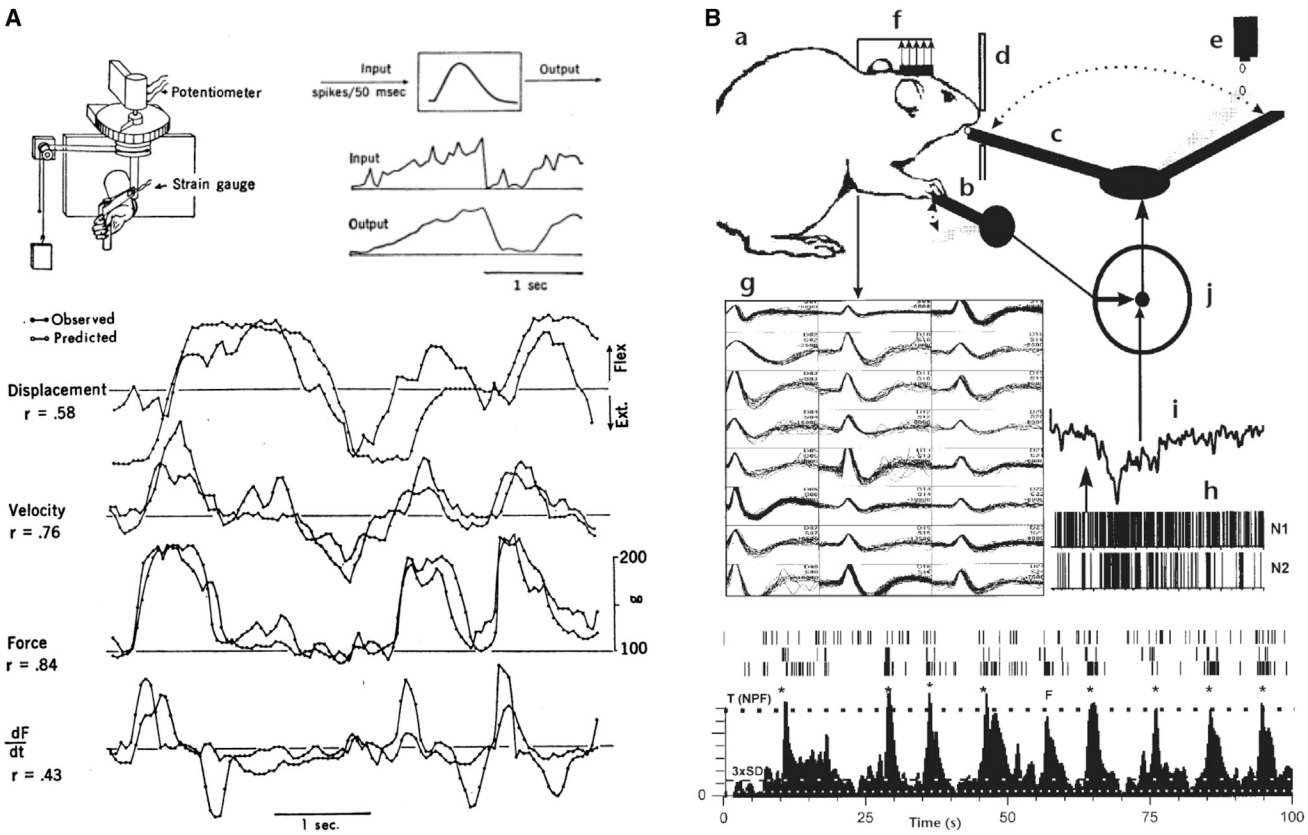

Figure 2. Historical Foundations of Invasive BMI

(A) By simultaneously recording small populations of neurons in the motor cortex while monkeys performed controlled arm movements (upper left) and properly smoothing the recorded signals (upper right), it was possible to nicely predict both kinematic and dynamic aspects of movement execution. Adapted from Humphrey et al. (1970) with permission.

(B) In the first demonstration of invasive BMI, rats (a) were trained to press a lever (b) that proportionally moved a robot arm (c) from a rest position (d) to a water dropper (e) in order to receive a water reward. The task was then switched to neurorobotic control (f) so that the robot arm became controlled by the activity of populations of motor cortex neurons (g), with the spike trains of multiple single units (h) being combined into a neural population function (NPF) (i) (j indicates the switch from movement control to neural control). Under neurorobotic control (lower panel), animals were able to successfully bring the NPF (and thus the robotic arm) above a threshold T to receive water reward (asterisks). Adapted from Chapin et al. (1999) with permission.

Around the same time, two key studies were performed that define present-day BMI. First, Humphrey et al. (1970) demonstrated that even small populations of simultaneously recorded neurons in the motor cortex could predict displacement, velocity, or force produced by a monkey trained to grasp a handle and alternatively flex and extend its wrist. The authors concluded that "by simply weighting and summing the discharge frequencies of each cell in the set we were able to predict the time course of certain response measurements with unexpected accuracy." Even more relevant for recent BMI experiments, the authors go on to speculate that their results suggest that the neural substrates of information "may well depend not only on the types of units observed, but also on whether or not they are observed simultaneously so that the important temporal relations between their discharge patterns can be taken into account."

Second, Fetz (1969) used operant conditioning to train animals to modulate their firing rate based on a reward. The monkeys viewed their neural activity in real time and were rewarded if they were able to increase their neuron's firing rate above a threshold. This work anticipated the potential of BMI to defy the classic object-observer duality, demonstrating that the subject can interact with its own neurophysiology in a causal way.

The pioneering work of Humphrey et al. (1970) and Fetz (1969) and accompanying technological advances laid the foundation for the first demonstration of invasive BMI in rats (Chapin et al., 1999), which documented that signals produced by an ensemble of neurons could be recorded from the brain while the animal was performing a motor task and be used to substitute for the animal's motor behavior to control a robotic arm (Figure 2B), forming a direct causal link between neural activity and functional outcome. Interestingly, the investigators found that, with time, the neural activity became decorrelated from the actual movements such that the animal no longer needed to move its limb to produce a neural signal about the intention to move. Demonstrating the feasibility of brain-driven control of robotic arm and uncovering a surprising degree of plasticity in the neural code, this early BMI anticipated both the neuroprosthetic application of BMI and its potential to provide novel insights into basic brain function.

Brain-Behavior Causality in BMI

A critical limit of the classical object-observer duality in neurophysiological in vivo experiments is that observations are always incomplete: both the neurophysiological activity and the behavior performed by the subject are objects of observation, but the observed neurophysiological activity is only a small fraction of the possible neurophysiological activity that could cause the behavior. This implies an epistemological difficulty of going beyond correlative evidence to establish genuinely causal relationships between neurophysiological activity and behavior. Within this framework, only indirect approximations to brain-behavior causality can be achieved by disrupting neural activity with an external intervention and observing the consequent change in behavior. The very concept of BMI, even in its neuroprosthetic definition, offers a more direct path for overcoming the epistemological difficulty: a key element of subjects being indirect observers of their own neurophysiological activity is that their observation is complete. Consequently, the relationship between neurophysiological activity and BMI behavior can be genuinely causal.

Much of the early BMI work focused on the problem of moving a cursor on a computer screen, following the early work on operant conditioning by Fetz. For example, Kennedy and Bakay (1998) showed that neurons could be trained to control a cursor on a computer screen in patients with amyotrophic lateral sclerosis, in the hope this could be used to access a communication system. The authors presented their technology as "an invasive alternative to externally applied brain-computer interface (BCI) devices" (Kennedy et al., 2000), because relatively simple control of a cursor on a computer screen was achieved with non-invasive EEG recordings in humans at least since the early nineties (Wolpaw et al., 1991). Non-invasive BCI continues to be an important avenue of study, developing new options of communications and rehabilitation for humans with severe disabilities (Wolpaw and McFarland, 2004; Wolpaw, 2007; Millán et al., 2010; Ramos-Murguialday et al., 2013; Chavarriaga et al., 2014).

A key advance of the work by Chapin et al. (1999), presented above, was that the BMI controlled not a cursor on a computer screen, but a physical robotic arm in real space: a completely observed set of neurons causally controlled the behavior of a physical object. This invasive neurorobotic BMI approach opened a new avenue of possibilities and challenges for operating clinically relevant neuroprosthetic devices.

After the first demonstration of invasive BMI in the rat, the technology was quickly translated to monkeys. Task complexity of BMI studies rapidly advanced from 2D and 3D control of a cursor on a computer screen (Serruya et al., 2002; Taylor et al., 2002) to the control of more natural behaviors, such as reaching and grasping (Carmena et al., 2003), self feeding (Velliste et al., 2008), and bimanual arm movements (Ifft et al., 2013). These remarkable increases in task complexity were achieved through both advances in hardware from the technology industry and advances in the development of decoding and control algorithms (Santhanam et al., 2006; Gilja et al., 2012; Hwang et al., 2013). These advances are critical for ultimately bridging the gap between more traditional neuroprosthetics on healthy animals and their translation to the clinical population (Hochberg et al., 2006, 2012; Collinger et al., 2013).

BMI control is typically achieved and optimized in well-controlled experimental conditions, in which animals are trained to perform a single task—or at most few different tasks—using the activity of neurons recorded from the motor cortical areas. The translation of neuroprosthetic BMIs to more everyday life conditions, where extreme multitasking is the rule, represents an important challenge (Orsborn et al., 2014). In this direction, several studies have explored the potential of recording neurons in different cortical areas for BMI applications (Wessberg et al., 2000; Carmena et al., 2003). For example, the premotor cortex can be targeted to separate movement planning from movement execution (Santhanam et al., 2006; Shanechi et al., 2012). Alternatively, the posterior parietal cortex can be targeted to decode higher-level discrete control signals, such as the goals of movements (Musallam et al., 2004), together with continuous control signals related to movements themselves (Mulliken et al., 2008; Hauschild et al., 2012). At the same time, resting—which is a critical component of everyday life multitasking—can be directly decoded in the motor cortex (Velliste et al., 2014). The concept of multitasking in a BMI context thus brings the study of brain-behavior causality to the multivariate level.

In neurorobotic BMI, brain-behavior causality is not between the brain and the body, but between the observed neurophysiological activity within the brain and an external device outside the body. In parallel to the impressive achievements obtained with neurorobotic BMI, a number of studies have attempted to implement a neurosomatic BMI that, instead of actuating an external device, stimulates back into the organism to reanimate the limbs (Moritz et al., 2008; Ethier et al., 2012; Powers et al., 2013; Shanechi et al., 2014). In particular, Miller and colleagues (Ethier et al., 2012) performed a reach-to-grasp study in monkeys where the motor nerve was anesthetized, preventing limb movement, and then the brain signal was used to intramuscularly stimulate grasping in order for the animal to grab a ball and place it in a tube (Figure 3A). In spinal cord injury studies, the limbs of paralyzed animals were reanimated when the brain signal was used to activate epidural or intraspinal stimulation below the injury (Nishimura et al., 2013; Powers et al., 2013; Figure 3B). These approaches will likely be improved by integrating recent advances in the control of spinal sensorimotor circuits (Bamford and Mushahwar, 2011; Wenger et al., 2014).

Finally, in both neurorobotic and neurosomatic applications, complementing causal brain-behavior control with explicit addition of somatosensory feedback (O'Doherty et al., 2011; Tabot et al., 2013) will likely provide the subject with a more natural—and thus more acceptable—experience. At the same time, novel BMI experiments that modulate, perturb, or even disrupt the feedback could be designed to start investigating the very nature of brain-behavior causality.

Conscious versus Subconscious Self-Observation in BMI

According to the classical object-observer duality, the observer designs an experiment to manipulate the object of observation, but the act of observing is not supposed to interfere with the experiment. After obtaining the results of the observations, the observer designs new experiments to manipulate the object, and the process repeats. To say that in BMI experiments

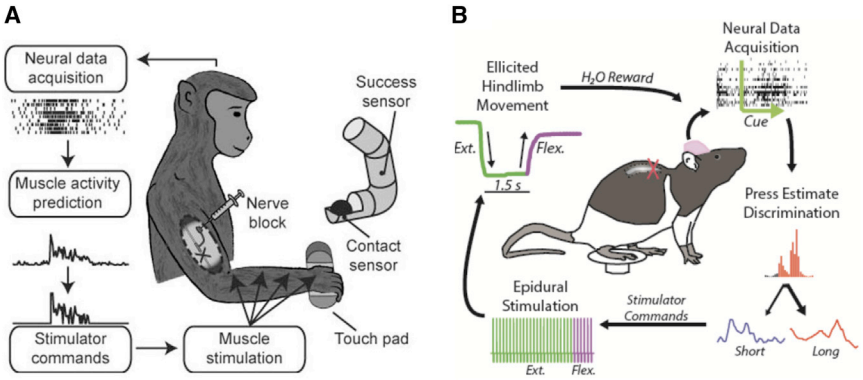

Figure 3. Neuroprosthetic BMIs

(A) Example of neurosomatic BMI in monkeys, in which the motor nerve was anesthetized to prevent limb movement, and then the brain signals were used for electrical muscle stimulation in order to restore the animal's ability to perform a functional grasping task (grab a ball and drop it in a tube). From Ethier et al. (2012), with permission.

(B) Example of neurosomatic BMI in rats in which the spinal cord was transected and the intention to press a pedal with the hindlimb (short or long duration) was decoded from the hindlimb sensorimotor cortex and used to control epidural electrical stimulation over the lumbar spinal cord below the lesion to restore task-dependent hindlimb movements.

"subjects can also be viewed as indirect observers of their own neurophysiological activity" implies that the above process is already occurring at the subject level. The key aspect is that it is occurring in real time: when provided with some form of feedback of the brain-behavior causality, the subjects are continuously using the results of their "observation" to manipulate their own neurophysiological activity to improve BMI performance.

This concept of self-observation in BMI is tightly linked to the well-known engineering concept of feedback in closed-loop control. Indeed, neuroprosthetic control is almost always a closed-loop control, even if no tactile/proprioceptive feedback is explicitly provided to the brain. In fact, the subject is typically provided with continuous visual feedback about its performance. This visual feedback enhances the ability of the observed neuronal populations to control the neurorobotic or neurosomatic BMI by both activating physiological circuits responsible for visuo-motor integration and inducing functional and/or anatomical changes that modulate the encoding for neural control. Even though the self-observation in neuroprosthetic BMI is typically conscious, in the sense that the subject is aware of the feedback, it is not a necessary condition. This reflection about conscious versus subconscious self-observation allows inclusion within the BMI branches of two broad experimental paradigms: neurofeedback and closed-loop brain stimulation.

Neurofeedback is a special case of conscious BMI in which a subject is trained to gain conscious control of otherwise subconscious brain activity by receiving proper sensory feedback. Neurofeeback is not only a special case, but also a precursor of BMI, as we already acknowledged when we discussed Fetz's work with operant conditioning of neural firing rates in monkeys (Fetz, 1969, 2007). At the same time, similar neurofeedback experiments were being performed to train human subjects to consciously control EEG alpha rhythms (Kamiya et al., 1969). The potential of EEG-based neurofeedback was rapidly recognized for both increasing normal cognitive performance (Beatty et al., 1974) and improving mood disorders (Hardt and Kamiya, 1978) and is still being actively studied and applied today (Ros et al., 2014). The recent resurgence of neurofeedback (Schafer and Moore, 2011) has also been supported by the development of fMRI-based protocols, which provide unprecedented spatial resolution to non-invasively gain control of brain activity (Bray et al., 2007; Shibata et al., 2011; Greer et al., 2014). With fMRI technology, neurofeedback has again been investigated to improve normal functions, such as visual attention (Scharnowski et al., 2012), or to treat brain disorders, such as Parkinson's disease (Subramanian et al., 2011). Of course, if the neurofeedback itself is considered as an actuator (e.g., the classical cursor on a computer screen), then the conceptual line between neurofeedback and BMI becomes very subtle (Birbaumer et al., 2009), possibly depending only on the type of signal used to close the loop.

Closed-loop brain stimulation is a paradigmatic example of subconscious BMI, which is being tested in at least two clinically relevant settings that are not classically considered within the BMI field: Parkinson's disease and epilepsy. In Parkinson's disease, deep brain stimulation (DBS) has emerged as a widely accepted non-pharmacological therapy in which electrodes are neurosurgically implanted into specific subcortical targets—typically in the subthalamic nucleus (STN)—and then connected to a subcutaneous stimulator that continuously delivers high-frequency stimulation, like a "brain pace-maker" (Limousin et al., 1995). Of course, standard DBS is not a BMI, because the implanted electrodes are only used to deliver stimulation without receiving any information from the brain. However, the same electrodes can also be used to record deep brain activity (Brown et al., 2001; Levy et al., 2002; Foffani et al., 2003; Priori et al., 2004). This opens the possibility of continuously adapting the stimulation parameters (amplitude, frequency, etc.) based on ongoing brain activity (Priori et al., 2013), thereby effectively closing the loop similarly to neuroprosthetic BMI applications. However, in closed-loop DBS, the subject is not aware of the feedback used to control the stimulation. Recent works in animals (Rosin et al., 2011) and humans (Little et al., 2013) suggest that closed-loop DBS could be more effective than standard DBS for the treatment of Parkinson's disease. Given the range of disorders for which DBS is effective (Krack et al., 2010), subconscious BMIs open a broad range of potential new neuroprosthetic applications.

A second neurological disorder where subconscious neural control of brain stimulation offers promising results is epilepsy (Fountas and Smith, 2007; Stypulkowski et al., 2014). Epilepsy is not a movement disorder, but a pathological state resulting in periods of hyper-synchronous activity in the brain. Similar to Parkinson's disease, continuous delivery of high-frequency electrical stimulation has provided some effectiveness at reducing

symptoms (Salanova et al., 2015). But continuous stimulation does not seem to be necessary (Bergey et al., 2015): if stimulation is tied to neural signals recorded from the brain and only applied when specific changes in the signal are identified, the neural stimulation is at least as effective as continuous stimulation. In this direction, recent studies are exploring the futuristic variant of using closed-loop optogenetic stimulation protocols to stop seizures (Armstrong et al., 2013; Krook-Magnuson et al., 2013).

The distinction between conscious and subconscious self-observation in BMI clarifies that future BMI applications are not limited to the control of conscious actions but could be extended to the control of subconscious functions, aiming toward either functional repair or augmentation. For example, the simple, yet fascinating, possibility of controlling cortical plasticity by using action potentials recorded from one electrode to deliver electrical stimulation at other cortical locations (Jackson et al., 2006) has already been implemented to restore function in a rat model of focal brain injury (Guggenmos et al., 2013). In another example, a hippocampal neuroprosthetic (Hampson et al., 2013) was used to facilitate memory via electrical stimulation to improve performance on a delayed match to sample task. Finally, auditory close-loop stimulation phase-locked to slow oscillations during sleep has been suggested to enhance memory (Ngo et al., 2013). In general, the interplay between conscious and subconscious BMIs is likely to play a primary role in the present and future of neuroprosthetics (Jackson and Zimmermann, 2012; Potter et al., 2014).

BMI to Study Plasticity

The two foundational aspects of BMI discussed above, brain-behavior causality and self-observation, offer the opportunity not only to develop neuroprosthetic applications, but also to gain basic insights into brain function beyond neuroprosthetics. We stated above that in BMI experiments, "when provided with some form of feedback of the brain-behavior causality, the subjects are continuously using the results of their 'observation' to manipulate their own neurophysiological activity to improve BMI performance." Where the classical engineer sees the opportunity to achieve futuristic neuroprosthetic performances, the basic neuroscientist sees the opportunity to observe the self-observation, to study how the causality between neurophysiological activity and behavior changes with learning: a unique window into world of brain plasticity.

The definitions of brain plasticity have changed over the years as experimental technology has allowed greater insight into the underlying mechanisms. Plasticity had been defined by the level at which it operates (Buonomano and Merzenich, 1998): (i) synaptic plasticity, which reflects changes in synaptic properties at the sub-cellular level, (ii) cellular conditioning, which refers to changes in receptive field or tuning properties of individual neurons, and (iii) representational plasticity, which indicates changes in representational maps across large neuronal populations. However, with new understanding of the molecular mechanisms underlying plasticity, the term plasticity can be specifically applied to define structural changes at the synaptic-to-cellular level or more loosely used to describe changes in receptive field or tuning properties of neurons at the cellular-to-population level. This goes back to the fundamental questions about the nature of plasticity raised by Hebb and John, reviewed above. BMI experiments can spectacularly manipulate cellular-to-population tuning curves, but the role of plasticity at the synaptic-to-cellular level (i.e., physical changes in synaptic structure) in these manipulations largely remains to be investigated (Legenstein et al., 2010; Koralek et al., 2012; Orsborn and Carmena, 2013; Orsborn et al., 2014).

In the first BMI study in the rat, already mentioned several times (Chapin et al., 1999), it did not take long for the animals to start dissociating BMI control from motor control, i.e., they started controlling the robotic arm without any overt movement. This relatively fast dissociation between BMI control and motor control was confirmed in subsequent studies in non-human primates (Taylor et al., 2002; Carmena et al., 2003). It is important to acknowledge that a similar dissociation between the activity of motor cortex cells and arm muscles was previously observed during control of neural activity achieved with operant conditioning (Fetz and Finocchio, 1975). The dissociation might suggest some form of plasticity, but the same neurons could in principle be coding for both movement imagination and execution, so the animal could be progressively switching from execution to imagination without changing the tuning properties of the recorded cells. However, BMI studies suggest that this is not necessarily the case (Lebedev et al., 2005) because the tuning properties of neurons remarkably change during training and execution of BMI tasks (Taylor et al., 2002; Carmena et al., 2003; Manohar et al., 2012; Figures 4A and 4B). Furthermore, experimental perturbations of the task, such as changing from controlling cursor to controlling a robot (Carmena et al., 2003) or rotating the tuning functions of the decoding model (Jarosiewicz et al., 2008), lead to drops in performance that are quickly compensated for with subsequent training. Overall, these findings establish that BMI learning is associated with changes in tuning properties at the cellular-to-population level, but they do not clarify whether these changes are associated with physical plasticity at the synaptic level.

Studying changes in neuronal tuning properties during learning is complicated by the fact that there is an implicit assumption that neuronal tuning properties remain stable in the absence of learning. However, this point is controversial. In the motor cortex, it is not clear whether tuning properties are stable at the level of single cells (Chestek et al., 2007), stable at the level of neuronal ensembles (Serruya et al., 2003; Carmena et al., 2005), or relatively unstable (Rokni et al., 2007), continuously changing as demand for specific tasks increases or decreases. The ability of BMI experiments to retain brain-behavior causality allows for novel avenues of exploration. For example, BMIs with constant decoders were used in monkey studies to demonstrate that new neural representations can consolidate into stable cortical maps for neuroprosthetic control (Ganguly and Carmena, 2009). Moreover, this consolidation was not limited to a single cortical map: a second map could be learned and stored, allowing for either map to be recalled, pointing toward the possibility to investigate the dynamics of motor memories (Ganguly and Carmena, 2009). Recent work clarified that this ability to consolidate new cortical maps for neuroprosthetic control is constrained by the existing network structure (Sadtler et al.,

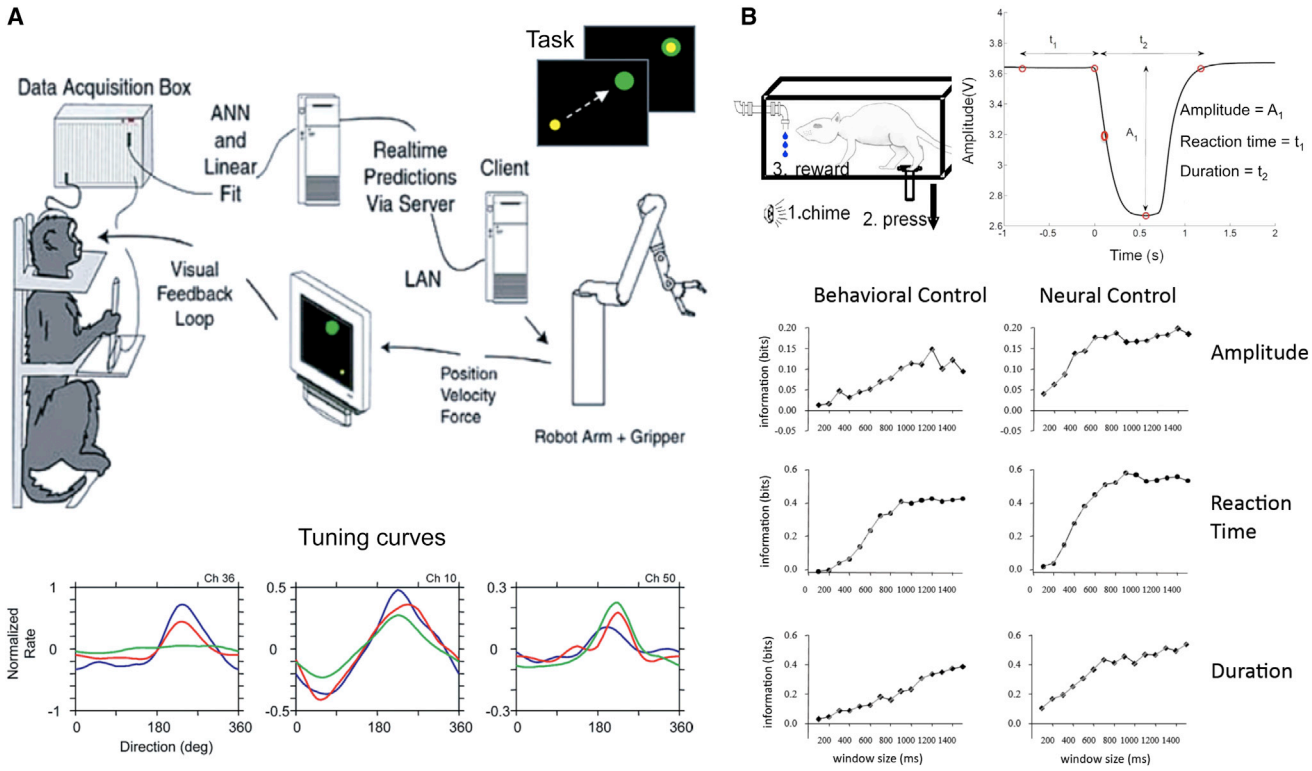

Figure 4. BMI to Study Plasticity

(A) Monkeys were trained to use a pole to control a robot arm whose position was translated into cursor position on a computer screen. In a task in which the monkeys had to move the cursor to a visual target appearing at random locations (upper right), the directional tuning curves of cortical neurons (three examples in lower plots) were different in pole control (blue) versus brain control with arm movements (red) versus brain control without arm movements (green). Note that the left cell was directionally tuned only when the animal moved the arm, particularly in pole control, the central cell was similarly tuned in the three conditions, whereas the right cell was better tuned during brain control. Adapted from Carmena et al. (2003).

(B) Rats were trained to press a pedal with the hindlimb after hearing a chime to obtain a water reward, while the activity of populations of neurons were recorded in the hindlimb sensorimotor cortex. Animals were rewarded either for the appropriate press (behavioral control) or based on the neural activity during the task (neural control). The information about the kinematics of hindlimb movement was actually higher under neural control compared to behavioral control. Adapted from Manohar et al. (2012).

2014). BMI experiments are therefore particularly helpful for shedding light into the relative role of stable cortical maps versus cellular/population plasticity during motor learning.

An intriguing aspect of cortical plasticity at the cellular/population level is its spatial scale. By using only a subset of the recorded neurons to perform BMI control and monitoring changes in tuning properties of the other neurons, it was possible to show that changes in tuning curves extended to neurons beyond those that are causally involved in BMI control (Ganguly et al., 2011), suggesting that BMI-induced changes in tuning properties have a certain level of global impact. However, it is clear that neurons involved in BMI control (Arduin et al., 2013) or selectively perturbed during BMI control (Jarosiewicz et al., 2008) undergo greater modifications during BMI learning, suggesting that BMI-induced changes in tuning properties are also locally selective. In agreement with this view, recent BMI experiments with two-photon imaging in mice showed that learning is associated with alterations of correlated activity at fine scales (Clancy et al., 2014).

To further investigate the relationships between changes in tuning properties and plasticity, it is feasible to propose new paradigms that combine BMI with other techniques that modulate cortical plasticity at a more global level, such as pharmacological interventions (Maya Vetencourt et al., 2008; Ganzer et al., 2013), exercise (Cotman et al., 2007; Graziano et al., 2013), or electromagnetic neuromodulation with either direct current stimulation (Bindman et al., 1964; Márquez-Ruiz et al., 2012; Filmer et al., 2014) or static magnetic field stimulation (Oliviero et al., 2011; Aguila et al., 2014). With these combined paradigms, the causality of BMI could be exploited to clarify the mechanisms by which interventions inducing changes in plasticity at a broad population level can affect tuning properties at the cellular level and ultimately behavior.

BMI to Study Neural Coding

In addition to plasticity, the brain-behavior causality and self-observation that characterizes BMI paradigms can provide invaluable insights into the basic principles of neural coding. Many important questions remain open to fully understand how the brain encodes sensory information from the outside world into an internal language, how it integrates external and internal information to produce cognitive/emotional representations,

and how it generates and executes motor programs. In this area, BMI research made critical contributions to the maturity of the ideas about population coding that were introduced by Hebb 50 years earlier (Nicolelis, 2003; Nicolelis and Lebedev, 2009). Theoretical concepts like distributed coding (i.e., information is distributed among large populations in various cortical areas), multiplexing (i.e., the same population of neurons can perform different tasks, serially or simultaneously), and redundancy (i.e., different populations of neurons can perform the same task) were transformed from theoretical possibilities into testable realities during BMI experiments (Nicolelis and Lebedev, 2009). The key aspect is that any BMI decoder employed to establish the causal relationship between the neurophysiological activity and behavior necessarily assumes one or more neural coding principles. This very concept allows new BMI experiments to be designed to address specific questions about neural coding.

In the field of sensory coding, a classical debate is whether the basic element of the neural code is the frequency of firing of individual neurons (rate coding) or the precise timing when spikes occur (temporal coding) (Huxter et al., 2003; Kumar et al., 2010). Even though one might argue that the problem is just a matter of temporal scale, the very existence of the debate hides a more fundamental methodological dilemma: it is relatively easy to show that a particular element of the code (e.g., spike-timing) conveys significant information about a set of external stimuli (Panzeri et al., 2001; Foffani et al., 2009); it is much more challenging to experimentally demonstrate that the brain actually uses that information. Correlative evidence can be collected, but convincing causal evidence is lacking. Here is where the brain-behavior causality of BMI could be useful: the question "is spike-timing information behaviorally relevant?" becomes "is spike-timing information sufficient to perform BMI control?" In other words, instead of asking ourselves whether the brain uses spike-timing information based on analyses, we could require the brain to directly use spike timing and evaluate the outcome. Similar reasoning could be applied in a variety of classical neural coding problems, from the informational contribution of variability at the cellular level (Scaglione et al., 2011), to the role of correlations at the population level (Shamir, 2014), to the implications of theta-gamma oscillations (Lisman and Jensen, 2013; Bieri et al., 2014) and synchrony at higher network levels (Singer, 1999; Ratté et al., 2013). A proof of principle of this approach is already provided by the ability of monkeys to learn to generate gamma oscillations associated with spike synchrony in the motor cortex to control a BMI (Rouse et al., 2013; Engelhard et al., 2013; Figure 5A), the ability of rats to separately increase either firing rates and neural synchrony at cortico-hippocampal level to obtain a reward during operant conditioning (Sakurai and Takahashi, 2013) or, at non-invasive level, the ability of human subjects to modulate EEG power, frequency, phase, or even complexity in neurofeedback experiments (Brunner et al., 2006; Angelakis et al., 2007; Wang et al., 2011; So et al., 2014). The impact of these different coding schemes on behavioral performance could provide important insight into their relative contribution to the neural code.

Another opportunity offered by BMI from a neural coding perspective is the possibility to dissociate different aspects of movement control from movement itself. For example, BMI experiments in patients with spinal cord injury allowed the physiology of movement intention in the primary motor cortex to be studied without the confounding effects of somatosensory feedback (Truccolo et al., 2008). A more recent study used a BMI paradigm in rats to demonstrate that information about a more subtle aspect of movement, movement timing, is present in the primary motor cortex in absence of motor output and despite a loss of somatosensory feedback due to experimental spinal cord injury (Knudsen et al., 2014; Figure 5B). With the fast progresses being made in providing artificial somatosensory feedback (O'Doherty et al., 2011; Tabot et al., 2013), it will soon be possible to design sophisticated BMI paradigms to dissociate and dissect the different components of sensorimotor integration.

BMI to Study Pathophysiology

An exciting frontier is the possibility of exploiting the brain-behavior causality and self-observation of BMI to investigate basic pathophysiological questions about specific neurological disorders.

In the field of spinal cord injury (and cortical deafferentation in general), BMI experiments are particularly appealing for rigorously investigating the impact that pathological alterations of plasticity at the population level (Moxon et al., 2014) might have on plasticity and coding at the cellular level. In addition, BMI paradigms could be introduced to investigate and modulate cortico-spinal plasticity in order to dig into the mechanisms underlying the variability of functional recovery independent of spared fibers. An important issue in this case would be to determine the possible contribution of plasticity above the level of the lesion to recovery below the level of the lesion (Fagg et al., 2007; Kao et al., 2009; Courtine et al., 2009; Graziano et al., 2013).

In the fields of epilepsy and Parkinson's disease, among others, BMI protocols could be used to gain control over supposedly pathological oscillatory neural activities, such as fast-ripples (Foffani et al., 2007; Zijlmans et al., 2012) or beta oscillations (Brown et al., 2001; Priori et al., 2004), in order to search for definitive answers about their possible causal role (i.e., beyond the extensive correlative evidence) in the generation of certain clinical symptoms. Gaining conscious control over subconscious pathological activity might even be sufficient for patients to learn to control their symptoms, without any stimulation involved. Proof of concept of this idea is already provided by the fMRI-neurofeeback study cited before (Subramanian et al., 2011). In Parkinson's disease, the self-observation characterizing the BMI paradigm seems particularly appealing to experimentally test the provocative hypothesis of a specific loss of habitual control versus goal-directed control (Redgrave et al., 2010) and to elucidate its underlying neural mechanisms. In epilepsy, the BMI paradigm could test the relative importance of identified biomarkers that appear specific for seizure generation (Grasse et al., 2013).

More in general, BMI experiments could address many other interesting questions in neurological and neuropsychiatric conditions. BMI experiments could even be used to define new models of neurological and neuropsychiatric conditions by

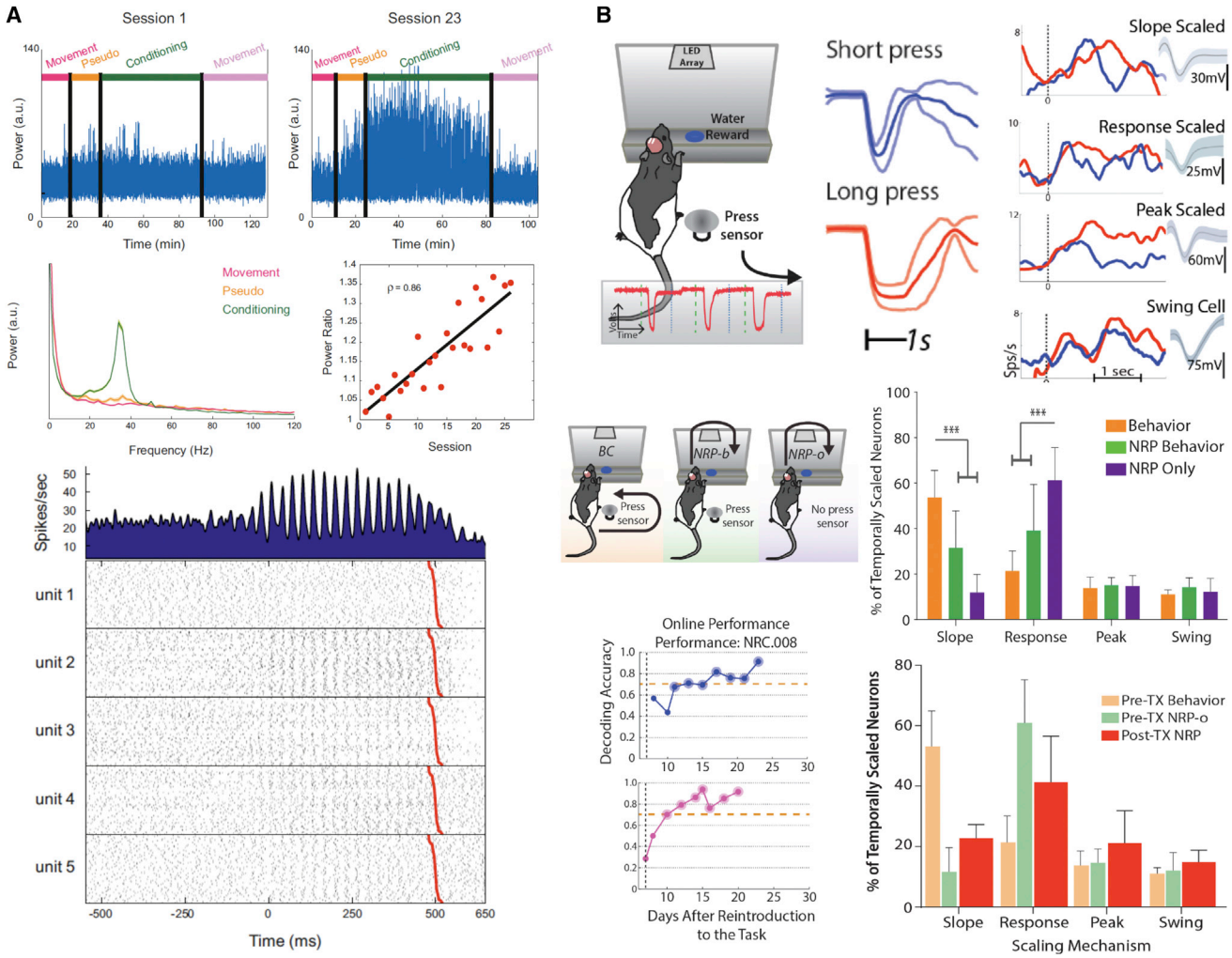

Figure 5. BMI to Study Neural Coding

(A) Throughout sessions of operant conditioning, monkeys learned to increase cortical gamma activity to move a cursor to obtain a reward (upper and central plots). Populations of neurons became evidently synchronized at gamma frequencies prior to reward delivery (red line in lower plot). Adapted from Engelhard et al. (2013) with permission.

(B) Rats were trained to perform short or long pedal presses with the hindlimb to obtain a water reward. Animals were rewarded either for the appropriate press (behavior) or based on the neural activity of the motor cortex during the task (neural reward paradigm, NRP), either with (NRP-b) or without the pedal (NRP-o), before and after complete thoracic transection of the spinal cord (TX). Neurons were classified into four different time-scaling mechanisms (slope scaled, response scaled, peak scaled, swing cell). Temporal scaling changed between behavior and NRP. NRP decoding accuracy dropped after TX but was recovered with additional training. Movement timing information was still present in the primary motor cortex after the loss of motor output and of afferent feedback due to spinal cord injury. Data are presented as mean values ± SD. Adapted from Knudsen et al. (2014) with permission.

cleverly altering the self-observation or interfering with the brain-behavior causality. The door is open.

Conclusions

The past 15 years have witnessed tremendous advancements in the field of BMI with high impact not only in the development of neuroprosthetics, but also in our basic understanding of brain function. The BMI approach is expanding the landscape of neuroscientific inquiry by defying the classical object-observer duality in neuroscience. Specifically, the main characteristics of self-observation and brain-behavior causality make the BMI paradigm particularly appealing for investigating fundamental questions on how information is encoded and decoded by neural circuits in real time, how this coding changes with physiological learning and plasticity, and how it is altered in pathological conditions. Overall, BMI can be seen as a tree of neuroengineering that not only opens its branches into traditional engineering, but also extends deep roots into basic neuroscience beyond neuroprosthetics.

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