Perspective

Combining Decoder Design and Neural Adaptation in Brain-Machine Interfaces

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Brain-machine interfaces (BMIs) aim to help people with paralysis by decoding movement-related neural signals into control signals for guiding computer cursors, prosthetic arms, and other assistive devices. Despite compelling laboratory experiments and ongoing FDA pilot clinical trials, system performance, robustness, and generalization remain challenges. We provide a perspective on how two complementary lines of investigation, that have focused on decoder design and neural adaptation largely separately, could be brought together to advance BMIs. This BMI paradigm should also yield new scientific insights into the function and dysfunction of the nervous system.

Introduction

Millions of people suffer from disabling neurological injuries and diseases. Examples include spinal cord injury, amputation, stroke, and amyotrophic lateral sclerosis (ALS). For people with paralysis, one of the most desirable clinical outcomes is recovering a sense of independence by restoring arm movements or the ability to communicate (e.g., Anderson, 2004).

The advancement of brain-machine interface (BMI) medical systems over the past 15 years has brought a sense of hope and enthusiasm because of its potential to provide new assistive devices and neurorehabilitative approaches. As illustrated in Figure 1A, BMIs convert neural signals from the brain into control signals for guiding computer cursors, prosthetic arms, exoskeletons, and other assistive devices. This conversion involves the design of decode (control) algorithms as well as an understanding of how neurons reflect movement information. Closed-loop BMI control is established by providing the subject with visual feedback, and potentially other sensory modalities, of the prosthetic actuator. For a recent review, see Bensmaia and Miller (2014).

Designing and implementing BMI systems in the preclinical (laboratory) and clinical settings requires many factors to be considered (e.g., Borton et al., 2013; Collinger et al., 2013; Gilja et al., 2013, Soc. Neurosci., abstract; Hochberg et al., 2006, 2012; Kim et al., 2008, 2011; Nuyujukian et al., 2014, Soc. Neurosci., abstract; Pandarinath et al., 2014, American Society for Stereotactic and Functional Neurosurgery, abstract; Pandarinath et al., 2014, Soc. Neurosci., abstract; Ryu and Shenoy, 2009; Simeral et al., 2011). Describing each of these is beyond the scope of this Perspective piece, which focuses on the proposition of combining "decoder design" and "neural adaptation" (terms defined below) to arrive at potentially better BMIs. However, a few factors are worth noting as they describe the context we envision. First, a major distinction in BMI systems is the type and location of electrodes used to record neural signals. Here we consider intracortical recordings of action potentials from individual neu-

rons with an array of permanently implanted electrodes. Recent articles review the tradeoffs among the various approaches (e.g., Millán and Carmena, 2010; Moran, 2010). Second, BMIs are comprised of several subsystems including low-power neural recording, wireless communication, and other hardware components (e.g., Homer et al., 2013). Finally, decoder design and neural adaptation, considered separately, and overall system operation, have been reviewed recently (e.g., Baranauskas, 2014; Bensmaia and Miller, 2014; Green and Kalaska, 2011; Kao et al., 2014).

Despite these many advances, barriers remain. If these barriers are unaddressed they will substantially limit the prospect of intracortically based BMIs having a broad and important clinical impact. These barriers can be grouped into two main categories: making the implantable neural interface viable for a person's lifetime (e.g., Durand et al., 2014; Judy, 2012) and achieving a clinically viable level of performance, robustness, and utility. Here we focus on the latter. More specifically, we highlight a largely unexplored approach to BMIs that relies on the inherent closed-loop control nature of BMIs: the combination of decoder design and neural adaptation. Understanding how to best employ decoder design and engage neural adaptation, such that they cooperate optimally, is a potentially major opportunity for BMIs as well as for basic neuroscience (e.g., Orsborn and Carmena, 2013).

Our operational definition of decoder design is the pursuit of algorithms that convert neural activity into the desired prosthetic actuator movements. Decoder design includes (1) algorithms informed by estimation and control principles (i.e., general decoder design), (2) algorithms that are informed by an understanding of the closed-loop BMI context (i.e., decoder design informed by a closed-loop perspective), and (3) algorithms that employ neural and/or behavioral data collected during closed-loop BMI operation to retrain the decoder (i.e., decoder adaptation, also referred to as closed-loop decoder adaptation [CLDA]). The goal of decoder design is to minimize the need for neural

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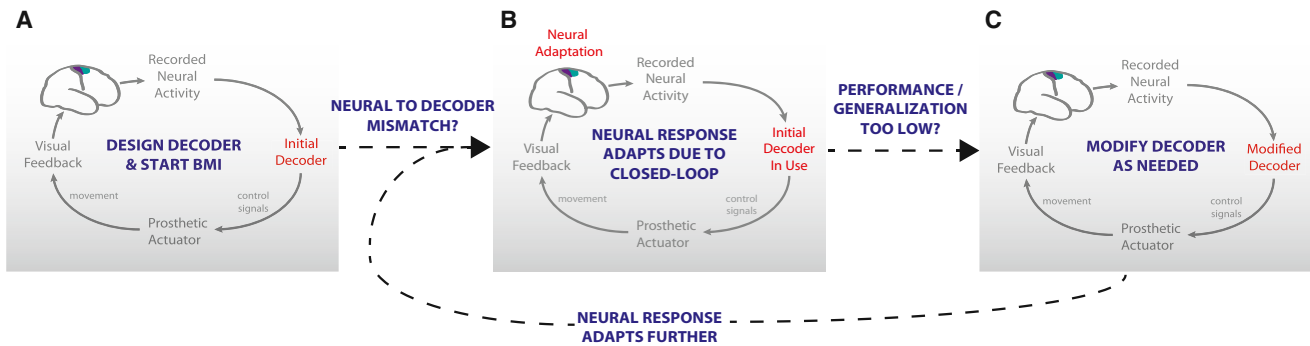
Figure 1. Block Diagram of a BMI System Including Various Design Considerations
(A) BMIs begin with a decoder that mathematically converts recorded neural activity into signals for guiding the prosthetic actuator. If the recorded neural activity is not well modeled by the decoder then (B) the recorded neural activity will likely change (adapt). This is because the subject will attempt to improve performance. After some time if BMI performance or generalization to other tasks is still too low, then it becomes necessary to (C) modify (adapt) the decoder in an attempt to further increase performance and robustness. With this modified decoder in place, the neural response is likely to adapt further. Figure modified from Orsborn and Carmena (2013).

adaptation by building a decoder whose control strategy is similar to that of native arm movement, and thus has strong BMI performance straightaway. One approach to decoder design is a so-called biomimetic decoder, which aims to mimic the neural-to-movement (kinematic) biological mapping as closely as possible (e.g., Fagg et al., 2007; Fan et al., 2014). Biomimetic decoders seek to maximize immediately achieved BMI performance. A central enabling assumption is that neural activity should not change substantially from decoder training to BMI testing period, if the decoder has high predictive power and is controlled similarly to the native limb. While this assumption works well with able-bodied subjects, it could be challenging in clinical scenarios where the native limb is unable to move due to paralysis or amputation, thereby requiring a different decoder training approach. We note, however, that motor imagery-based training paradigms may enable building biomimetic decoders for such clinical trial participants (e.g., Simeral et al., 2011; Pandarinath et al., 2014, Soc. Neurosci., abstract; Nuyujukian et al., 2014, Soc. Neurosci., abstract), as they have in preclinical research (e.g., Gilja et al., 2012).

Our operational definition of neural adaptation is changes in neural activity due to neuroprosthetic learning (i.e., learning to control a prosthetic device through a decoder and/or recovery from internal [coactivation of other networks] and external [environmental] changes). Neural adaptation may arise from a number of potential biophysical and cognitive mechanisms, many of which remain to be isolated and studied individually, including synaptic plasticity, new circuits, new patterns of activity, new intentions, and strategy changes.

The importance of decoder design in BMIs (e.g., Carmena et al., 2003; Dangi et al., 2013; Gilja et al., 2012; Hauschild et al., 2012; Mulliken et al., 2008; Musallam et al., 2004; Orsborn et al., 2012; Santhanam et al., 2006; Shenoy et al., 2003; Serruya et al., 2002; Taylor et al., 2002; Wessberg et al., 2000) has been recognized for many years, as has neural adaptation (e.g., Carmena, 2013; Carmena et al., 2003; Fetz, 1969, 2007; Ganguly and Carmena, 2009; Heliot et al., 2010b; Jackson et al., 2006; Jackson and Fetz, 2011; Legenstein et al., 2010; Orsborn and Carmena, 2013; Taylor et al., 2002; Wang et al., 2010). In contrast,

investigations directly exploring the potential importance of bringing these two concepts together are relatively recent (e.g., Carmena, 2013; Orsborn et al., 2014; Taylor et al., 2002).

We anticipate that the optimal codesign of decoders and concomitant engagement of neural adaptation will be important for the next generation of high-performance, highly robust, and highly generalizable BMIs. This may be especially relevant when controlling complex actuators such as prosthetic arms or the functional electrical stimulation of paralyzed arm muscles, which have many degrees of freedom (DOFs). Questions that arise include whether or not biomimetic decoders, which have shown high performance without the need for extended training or neural adaptation (e.g., Baranauskas, 2014; Bensmaia and Miller, 2014; Gilja et al., 2012; Fan et al., 2014, Nuyujukian et al., 2014b), should be used in combination with neural adaptation. Another question is whether a more arbitrary decode mapping that engages neural adaptation has advantages on its own, such as the creation of a motor map per effector or greater robustness in the face of environmental changes (e.g., Ganguly and Carmena, 2009). Ultimately, the success of this combined decoder design and neural adaptation approach, or any other approach, will be assessed in clinical trials based on how natural the BMI feels to the person when using it to perform tasks of daily living in real-world environments.

Decoder Design and Neural Adaptation: What They Might Enable Together
A critical part of a BMI system is the initial training of the decoder, which we will refer to as the open-loop phase. The decoder can be initiated in a variety of different ways, which will have important implications for whether neural adaptation occurs. These include regressing the recorded neural activity to real or imagined movements of the limb (biomimetic decoders, e.g., Gilja et al., 2012) or using arbitrary parameters, which is often done to engage neural adaptation (e.g., Ganguly and Carmena, 2009). During this training period the user is not aware of the decoder's performance since no feedback is being given, hence the term "open loop." This is followed by the BMI test period in which the user controls the decoder to drive a BMI plant and
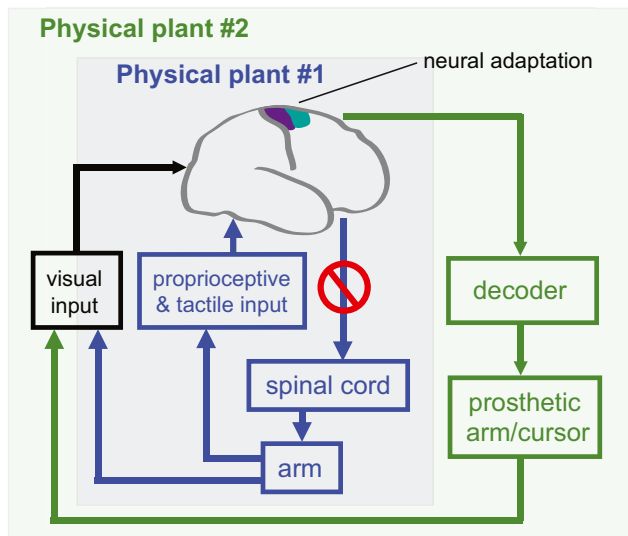
Figure 2. Differences in Physical Plant Properties between the Native Arm and a BMI System
Block diagram of the native arm system (physical plant #1, blue) and a BMI system (physical plant #2, green), emphasizing the potential roles for both neural adaptation and decoder adaptation when controlling a new (prosthetic) physical plant. Numerous cortical areas in the brain, including primary (M1, purple) and premotor (PMd, cyan) cortex, as well as subcortical brain areas, brain stem, and the spinal cord, cooperate to control the native arm. Visual, proprioceptive, and somatosensory inputs complete the feedback loop, allowing the native arm to move and respond with considerable speed and accuracy. When a paralyzing neurological disease or injury, such as an upper spinal cord transection (red circle with slash), disconnects this control loop it is no longer possible to use the native arm. Instead, a BMI system can be used to control a prosthetic arm to interact with physical objects or a prosthetic cursor to interact with a computer.

receives feedback reflecting the decoder's prediction of the plant state (e.g., the position of a computer cursor or prosthetic arm). As shown in Figure 1A, this closed-loop feedback system consists of decoding recorded neural activity into control signals for moving the prosthetic actuator, seeing the movement of the actuator, and controlling neural activity so as to achieve the desired goal with the actuator (e.g., move computer cursor to a visual target). If the decoder captures the relationship between neural activity and desired actuator movement well, resulting in high performance, robustness, and utility, then BMI training could be considered complete. However, as shown in Figure 1B, if the decoded neural activity results in kinematics that mismatch the desired kinematics one would expect neural adaptation to be engaged in an attempt to increase BMI functionality. Again, BMI training could be considered complete if this leads to sufficiently good BMI functionality. If not, then one could retrain the decoder so as to take into account the newly adapted neural activity. See "modified decoder" in Figure 1C. Finally, this process of iterating between decoder design and neural adaptation could be repeated until BMI functionality converges to its maximum level (see arrow beneath Figures 1B and 1C).

The closed-loop BMI system is substantially different from the natural central and peripheral nervous system controlling the native arm (see Figure 2). But how exactly are the BMI and native systems different? Let us first focus on the motor system used

to control the native arm. This is a complex, hierarchical system comprising large neural networks across multiple cortical and subcortical structures, brain stem, and spinal cord, projecting to a highly redundant, multiple-DOF musculoskeletal plant. On the other hand, in the BMI system a small number (tens to hundreds) of neurons are selected by the experimenter and connected to the decoder that outputs motor commands to control a prosthetic plant (e.g., a computer cursor or a robotic arm) that is substantially different than the native arm. Moreover, while visual feedback is present in both systems, the BMI user lacks the tactile and proprioceptive sensory afferents (at least with current BMI systems) available in the native motor system. The fundamental differences between these systems may result in inferior performance using a BMI compared to the native arm (Gowda et al., 2014; Orsborn and Carmena, 2013). Several groups have further noted that an open-loop decoder's predictive power (i.e., how well the decoder predicts real or imagined movements with open-loop training data) does not necessarily correspond well with closed-loop BMI performance; sometimes open-loop predicted performance is higher than closed-loop measured performance, and sometimes the opposite is true (e.g., Cunningham et al., 2011; Ganguly and Carmena, 2009, 2010; Gilja et al., 2012; Kim et al., 2008; Koyama et al., 2010). While some of the differences between the native and BMI systems might be reduced in the future through more advanced BMI actuators and surrogate sensory feedback (e.g., Bensmaia and Miller, 2014; Gilja et al., 2011; O'Doherty et al., 2011; Venkatraman and Carmena, 2011), it is not clear whether attempting to mimic the natural motor system through decoder design, engaging neural adaptation to help accommodate differences, or both will ultimately lead to naturalistic levels of performance and robustness. This is especially so in high-DOF prosthetic actuators such as arms and hands (e.g., Collinger et al., 2013; Hochberg et al., 2012).

At the heart of this question would seem to be a decoding-versus-learning debate (e.g., Fetz, 2007; Jackson and Fetz, 2011), but such a dichotomy may well not exist. In broad terms, (biomimetic) decoder design begins by (1) training a decoder to predict natural or intended movement from previously recorded (and therefore open-loop) neural data, and then (2) assumes (at least initially) that the statistics of the neural activity remain the same when controlling the BMI during the closed-loop phase (e.g., Gilja et al., 2012). As depicted in Figure 2, this corresponds to training the decoder using neural activity that controls the native arm (physical plant #1), and then using the decoder to control a BMI such as a computer cursor or a prosthetic arm (physical plant #2). Also in broad terms, the neural adaptation approach begins by (1) starting with a decoder that is not trained to predict natural or intended movement, and instead has minimal structure within its decoder parameters, and (2) takes the view that there is a de novo, closed-loop system that has to be learned by the brain (i.e., physical plant #2) in order to achieve proficient BMI control (e.g., akin to a surrogate spinal cord; Carmena, 2013). Despite initial appearances, these two approaches are not mutually exclusive and, in fact, have important relationships and likely synergies. As described below, if the (biomimetic) decoder design leads to high BMI performance, then there is little incentive for the subject to adapt neural activity

since there is little BMI performance to be gained. As a result, little neural adaptation may be engaged or observed (e.g., Gilja et al., 2012; Fan et al., 2014). However, if a decoder with largely arbitrary parameters is used and leads to relatively low initial BMI performance, then there is considerable incentive for the subject to adapt neural activity and thereby increase BMI performance. As a result, considerable neural adaptation may be engaged and observed (e.g., Ganguly and Carmena, 2009; Moritz et al., 2008). But there is no reason that these two approaches—(biomimetic) decoder design and neural adaptation—cannot coexist, synergize, and result in even higher performance, better robustness, and greater generalization and utility. We believe that this is an important area for future research, and that these two approaches should be pursued together in order to discover new conjoint decoder design and neural adaptation approaches, discern what functionality is possible, and thereby potentially better help people with paralysis and advance basic neuroscience understanding.

How BMI Experiments Are Conducted Impacts Decoder Design and Neural Adaptation

The exact way in which BMI experiments are conducted matters a great deal with respect to how much decoder and neural adaptation are necessary for high performance. Thus, before describing how decoder design and neural adaptation may be brought together, we must first describe various ways that decoders are trained (open-loop phase) and how BMIs are operated (closed-loop phase). As described below, better matching the training and operating contexts so as to minimize mismatch has shown considerable benefits.

Except for two FDA pilot clinical trials with people with paralysis (e.g., Collinger et al., 2013; Gilja et al., 2013, Soc. Neurosci., abstract; Hochberg et al., 2012, 2006; Kim et al., 2008, 2011; Pandarinath et al., 2014, American Society for Stereotactic and Functional Neurosurgery, abstract; Pandarinath et al., 2014, Soc. Neurosci., abstract; Simeral et al., 2011) and some studies in animal models of spinal cord injury that transiently mimic paralysis (Ethier et al., 2012; Moritz et al., 2008; Pohlmeyer et al., 2009), the majority of intracortical BMI research relevant to the upper limb is currently carried out in able-bodied rhesus monkeys. Within this general animal model there are at least three specific animal models that are prevalent and are quite distinct (reviewed in Nuyujukian et al., 2011). Their distinctness becomes apparent when considering decoder design and neural adaptation approaches.

The first animal model can be thought of as "hand-controlled training, and hand-free BMI control." In this model the subject first performs a native arm movement task (e.g., center-out reaches to visual targets), from which a (open-loop) decoding algorithm is trained. The experiment setup is arranged such that the visual feedback for both the native arm movement task and BMI task come from the same source (e.g., a computer cursor visible to the user) instead of the former from their limb and the latter from a BMI-specific effector. Thus, upon switching to BMI control, the lack of explicit contextual change in the task (i.e., changing from native arm reaching to BMI control) suggests to the subject that the native arm should continue to be moved. The resulting closed-loop BMI system is very similar to the native

closed-loop system. Namely the native arm physical plant and sensory feedback during BMI operation remain essentially the same as during training. This approach can lead to relatively high BMI performance, and is often used as part of biomimetic decoder design (e.g., Gilja et al., 2012; Sussillo et al., 2012; Fan et al., 2014; Nuyujukian et al., 2014, Soc. Neurosci., abstract). This animal model can also be used with different decoders such as those that start with minimal parameter training and aim to investigate neural adaptation-driven performance increase (Carmena, 2013). It is also important to note that in this animal model, monkeys often reduce the range of their native (contralateral) arm movement during BMI control, or stop moving their arm altogether. In this animal model, BMI performance is often largely retained (e.g., Carmena et al., 2003; Gilja et al., 2012; Fan et al., 2014; Serruya et al., 2002; Taylor et al., 2002).

The second animal model can be thought of as "hand-controlled training, and hand-independent BMI control with context change." This model is like the first model described above, except a contextual change is made such as removing a manipulandum used during hand-controlled cursor training. This requires the user to now explore and find a way to generate useful neural activity patterns after the switch from hand-controlled training to closed-loop BMI use (e.g., Carmena et al., 2003; Ganguly and Carmena, 2009; Taylor et al., 2002). This neural exploration process to control the prosthetic cursor does not depend directly on hand/arm movement, since the cursor is neurally controlled. The user may explore either by varying native arm movements, or through biofeedback-based volitional neural control without native arm movement, in order to appropriately move the prosthetic device and obtain a reward. Critically, the same movements that were used to train the open-loop decoder cannot be readily made during BMI use because of the context change. This learning process predicts that there will be meaningful neural adaptation changes, since the neural responses must be modified in order to control the BMI.

The final animal model can be thought of as "hand-constrained training, and hand-constrained BMI control without context change." In this model the subject's arm/hand is typically constrained in a variety of ways such that there is little, if any, EMG activity or native arm movement. The user then observes a movie showing a cursor moving in various directions and at various speeds, which elicits cortical neural activity similar to that used to produce native arm movements (e.g., Gilja et al., 2012; Tkach et al., 2008; Suminski et al., 2010; Orsborn et al., 2012, 2014). Why passive observation of movement evokes responses similar to those generated during actual reaches is not well understood, but is an active area of research. Nonetheless, this observation paradigm allows an open-loop decoding algorithm to be trained. Since the BMI physical plant (Figure 2, physical plant #2), in addition to lack of overt movement and its resulting proprioceptive and somatosensory feedback, remains essentially the same as during training, in this animal model there is less mismatch between (closed-loop) BMI operation and (open-loop) decoder training. This approach can lead to relatively high BMI performance with biomimetic decoders (e.g., Gilja et al., 2012). This BMI approach would predict less neural adaptation since the same effector and context is used both during training and during BMI operation.

Considering these three major able-bodied animal models for BMI research helps highlight how the model selected can substantially impact the amount of neural adaptation expected. Less neural adaptation is expected in the first and third animal models, in which there are reasonably matched experimental conditions between the training mode and the BMI mode. In the second animal model, where there is mismatch between experimental conditions between training and BMI modes, significantly more neural adaptation is expected. These expectations are based on a combination of simple reasoning as well as recent experimental support, as described more below.

Recent Investigations of Decoder Design, Neural Adaptation, and Engaging Both

We anticipate that engaging both decoder design and neural adaptation will be increasingly important in order to achieve higher levels of performance, robustness, and utility. This combined approach is likely to be especially important for dexterous control of high-DOF prosthetic actuators such as prosthetic arms. To better understand this emerging opportunity, we review here recent studies that investigate decoder design, including open-loop decoders (Figure 1A) and decoders that have been modified after operating in closed loop (Figure 1C). Next we review recent studies that investigate neural adaptation (Figure 1B). Finally we review recent studies that begin to investigate the principled combination of these approaches (Figures 1A–1C).

Studies Focused on Decoder Design

The first closed-loop BMI studies used an open-loop approach to train the decoder, and in most cases the decoder was kept fixed and unchanged throughout the subsequent BMI session. This resulted in compelling levels of performance (see Figure 3B; e.g., a velocity Kalman filter [V-KF]). Several studies over the past decade have employed this general approach for continuous control of a computer cursor or robotic arm (e.g., Serruya et al., 2002; Carmena et al., 2003; Wu et al., 2004; Velliste et al., 2008; Mulliken et al., 2008) as well as discrete selection of targets (e.g., Musallam et al., 2004; Santhanam et al., 2006; Achtman et al., 2007). In a few studies the decoder was adapted during closed-loop BMI operation as described more below (e.g., Gilja et al., 2012; Gage et al., 2005; Taylor et al., 2002).

Most clinical trial studies to date have also adopted this approach. One important difference is that in people with severe paralysis, movement of the arm or fingers is not possible. Decoders are therefore trained by asking people to observe or imagine moving an automated computer cursor in different directions and at different speeds (similarly to the third animal model described earlier). The decoder is then trained to convert the neural data recorded into the automated computer-cursor kinematics (Chadwick et al., 2011; Kennedy and Bakay, 1998; Kennedy et al., 2000, 2004; Kim et al., 2008, 2011; Hochberg et al., 2006, 2012; Simeral et al., 2011; Wahnoun et al., 2006).

While early BMIs primarily operated with an open-loop decoder and did not employ a closed-loop decoder design perspective, it has been recognized for some time that a closed-loop decoder design perspective would likely be important (e.g., Taylor et al., 2002; Gage et al., 2005; Shpigelman et al., 2009; DiGiovanna et al., 2009; Santhanam et al., 2009; Koyama et al., 2010; Heliot et al., 2010a; Li et al., 2011; Mahmoudi and Sanchez, 2011; Orsborn et al., 2012; Gilja et al., 2012; Dangi et al., 2013; Fan et al., 2014; Bishop et al., 2014; Dangi et al., 2014). More specifically, it is important not only to estimate desired movements from neural activity, which has traditionally been the decoder design approach, but also to appreciate and incorporate into the decoder design the knowledge that this is a control problem with the BMI a part of a closed-loop feedback system (e.g., Gilja et al., 2012). We now describe the closed-loop decoder design perspective and recent investigations.

These recent experiments begin the same way as described above, but ultimately add at least one additional element to the decoder design. As described earlier, the animals initially perform a set of movements, during which time kinematics and neural activity are measured; an initial decoder is trained from these data. This initial (open-loop) training data is not collected while the animal controls the BMI, but the eventual goal is to collect additional (closed-loop) training data while the animal is controlling the BMI so that the decoder design and/or parameters can be changed to more accurately capture the relationship between neural activity and intended movement during BMI use.

This is accomplished with a second decoder training step, as illustrated in Figure 3A, panel 3. While simply retraining the decoder using the newly collected closed-loop kinematics and neural data in this way may increase performance, there are cases where this is not sufficient. Indeed, this can potentially even reduce performance because errors during the decoder's use are perpetuated in the new decoder (Fan et al., 2014). Rather, to overcome the noisiness and inaccuracy of the open-loop-trained decoder, other closed-loop-inspired modifications should be done to further increase performance. For example, the open-loop-trained decoder may not move the prosthetic cursor as the animal truly intended (Figure 3A, panel 4, red arrows). However, we (the experimenters) can take an educated guess that the animal actually intended for the cursor to move straight toward the target at all points in time; this would take the prosthetic cursor most directly to the target where a reward is received. This assumption is termed "intention estimation" (Gilja et al., 2012; Jarosiewicz et al., 2013) and suggests altering the kinematic training data by rotating the movement vectors such that they point directly toward the target (Figure 3A, panel 4, cyan arrows). The neural data are not altered, as it is assumed that this neural data ought to have produced the intention-estimated cyan movement vectors if a more ideal decoder had been in use. The decoder is then retrained using these data from the closed-loop phase so as to produce a better decoder (i.e., closed-loop decoder adaptation). In this example the new decoder design is termed "Recalibrated Feedback Intention-Trained" Kalman filter (ReFIT-KF) as shown in Figure 3A, panel 5. Importantly, these kinematics modifications are done to the training data only; during closed-loop use the ReFIT-KF has no supervised knowledge of the task and allows the user to move the prosthetic cursor anywhere in 2D space.

ReFIT-KF incorporates a second closed-loop decoder design element: the uncertainty in prosthetic cursor position that would
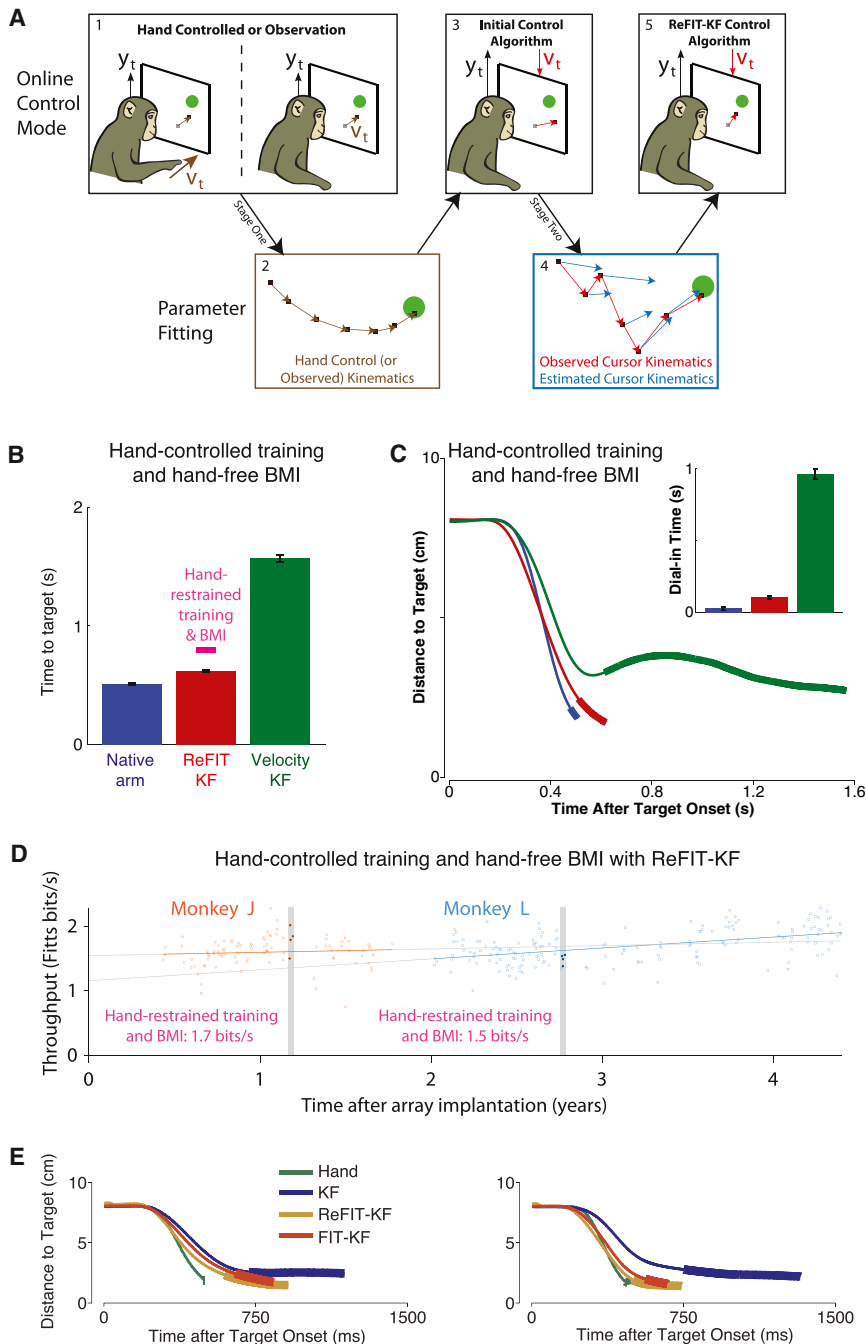
Figure 3. Performance and Robustness of Cursor Control with Native Arm, ReFIT-KF Decode Algorithm, and Velocity-KF Decode Algorithm

(A) ReFIT-KF is trained in two stages. Initially, cursor kinematics and neural activity are collected during arm control or during an observation phase in which cursor movement is automated (panel 1). These arm movement kinematics or observed cursor kinematics are regressed against neural activity to generate an initial (open-loop) decode algorithm (panel 2). Then, a new set of cursor kinematics and neural activity is collected using the initial decode algorithm in a closed loop (panel 3). The kinematics collected during neural control (red vectors) are used to estimate intention by rotating the velocities toward the goal (blue vectors). This estimate of intended kinematics is regressed against neural activity to generate and run a CLDA termed ReFIT-KF (panel 4). A ReFIT-based BMI experiment is then conducted. (panel 5).

(B) Time to target for successful trials for Monkey J (mean ± SEM). The decode algorithms were trained with the native arm controlling the cursor, and the arm was free to move during BMI operation. Magenta line indicates mean performance during hands-restrained decode algorithm training and hands-restrained BMI operation. Mean calculated from data in Table 1 in Gilja et al. (2012).

(C) Mean distance to the target as a function of time. Inset, mean ± SEM of the dial-in time, which is the time required to finally settle on the demand box, after first acquired, to successfully hold for 500 ms. Hold time is not included in the dial-in time. Thickened portions of line graphs also indicate dial-in time, beginning at the mean time of first target acquisition and ending at mean trial duration minus 500 ms. The decode algorithms were trained with the native arm controlling the cursor, and the arm was free to move during BMI operation.

(D) Performance of ReFIT-KF decode algorithm across 4 years. Performance was measured by the Fitts' law throughput metric (see Gilja et al., 2012). Data from Monkey J and Monkey L are shown as 98 orange circles and 182 cyan squares, respectively. Each point plots the performance of the ReFIT-KF decode algorithm trained on that experimental day. The average performance across all data sets for Monkey J and Monkey L is 1.60 ± 0.22 bits/s and 1.69 ± 0.26 bits/s, respectively, and the average success rate across all data sets is 95.7% ± 4.4% and 96.6% ± 4.3%, respectively. ReFIT-KF was trained with the native arm controlling the cursor, and the arm was free to move during BMI operation. The eight filled data points (four for each monkey) within the time period indicated in gray are calculated from the same data sets used to generate (B) and (C) above. Linear regression lines for data for Monkey J (orange) and Monkey L (cyan) are shown. Regression slopes for Monkey J and Monkey L are positive (0.052 and 0.17) with p values (> 0.43 and < 0.001), respectively. Magenta numbers are the mean performance when using hands-restrained decode algorithm training and hands-restrained BMI operation (see Table 1 in Gilja et al., 2012). Figure modified from Gilja et al. (2012).

(E) Comparison of the online performance of one- and two-stage decoders with intention estimation. The average distance to target is plotted for center-out reaches using hand control (green), KF (blue), ReFIT-KF (yellow), and FIT-KF (red). Data from Monkey L (left) aggregated across 6 experimental days; data from Monkey J (right) aggregated across 7 experimental days. Figure modified from Fan et al. (2014).

need to be propagated in the Kalman filter if this were strictly an estimation problem is instead set to zero (i.e., a causal intervention in graphical model parlance). This is because in this closed-loop feedback control system the user can accurately see the position of the prosthetic cursor. While this innovation contrib-

utes to ReFIT-KF's performance increase, intention estimation contributes more (Gilja et al., 2012).

The resulting ReFIT-KF decoder enabled prosthetic cursor movements (Figure 3A, panel 5) that were faster and straighter than with the standard V-KF. This speed and accuracy results

in a shorter time needed to arrive at and stay on a target (Figure 3B). A hallmark of good feedback control is not just being able to go fast toward a target, but also being able to stop and hold over the target. A metric that captures this is the so-called "dial-in time," which refers to the time between first contacting the target and the time when the cursor is stable enough that it can then complete a substantial hold time on the target (0.5 s). The thickened lines and inset bar graph of Figure 3C illustrate this substantial reduction in dial-in time for ReFIT-KF compared with V-KF.

Taken together, the two closed-loop design perspective innovations in the ReFIT-KF algorithm enabled improvements in speed, straightness, dial-in time, and accuracy (percent of targets that can be hit within a given time limit, typically > 95%, thus data not shown). One measure of performance is the Fitts' law metric, which can also be thought of as throughput, in units of bits per second (Card et al., 1978). This metric averages about 1.5 Fitts' bits/s in each of two monkeys (Figure 3D). This is quite high compared with other recent BMI systems (Gilja et al., 2012 [supplemental materials]; Fan et al., 2014; Kao et al., 2014; but also see Sussillo et al., 2012, which used a different approach). This level of performance suggests that it should be possible to achieve high "typing rates" when monkeys move BMI cursors to targets arrayed on the screen in the form of a keyboard, hold on a target/key to select it (or use a related discrete neural state to make the selection), and then move on to the next selection (Nuyujukian et al., 2014a). High typing rates of around 5–6 bits/s (achieved information bits, not Fitts' bits) using ReFIT-KF and a hidden Markov model for discrete selection have been reported recently (Nuyujukian et al., 2012, Soc. Neurosci., abstract).

In addition to increased performance, increased robustness is also a potential benefit of decoder adaptation and the closed-loop decoder design perspective. Figure 3D shows the performance from hundreds of days of ReFIT-KF BMI experiments, spanning over four years and across two monkeys. Robustness, defined here as the ability to train a decoder in a few minutes at the beginning of each experimental session and then produce performance on par with the day before, is stable as quantified by the slope of the regression lines in Figure 3D. Of relevance to neural adaptation, we note that performance is fairly high (including > 95% success rate), and thus there may not be strong behavioral pressure on the animal to actively engage neural adaptation to further increase performance. This is evident in the largely flat regression lines in Figure 3D. It is also worth noting that ReFIT-KF, which operated on threshold crossings as opposed to isolated single neurons (Chestek et al., 2011; Gilja et al., 2012), is capable of maintaining performance (3–4 information bits/s) for more than a month without retraining, which is a stricter definition of robustness than when daily retraining is allowed (Nuyujukian et al., 2014b).

Considering the discussion above regarding the three specific animal models, a question is whether the results presented are a consequence of using the first model ("hand-controlled training, and hand-free BMI control"). One reason this is not the case is that the ReFIT-KF BMI performs substantially better than the V-KF BMI using the same animal model. A second reason is that the ReFIT-KF BMI performance results were quite similar when using the third specific animal model ("hand-restrained

training, hand-restrained BMI control, without context change") (Gilja et al., 2012). This training is indicated in Figure 3A, panel 1. Note that for this specific animal model the hand is also constrained (and no hand movements were observed) in the steps shown in panels 3 and 5. The similar levels of performance are shown in Figures 3B and 3D in magenta. Therefore, at least in this experiment, performance was maintained across two different specific animal models. Encouragingly for the goal of translating BMIs to people with paralysis, the ReFIT-KF and V-KF performance results, including ReFIT outperforming V-KF, have been translated to a person with paralysis (ALS) as part of an FDA pilot clinical trial (Gilja et al., 2013, Soc. Neurosci., abstract; Nuyujukian et al., 2014, Soc. Neurosci., abstract; Pandarinath et al., 2014, American Society for Stereotactic and Functional Neurosurgery, abstract; Pandarinath et al., 2014, Soc. Neurosci., abstract). Another study has also reported that the intention estimation decoder adaptation innovation, incorporating a variant of the kinematic vector rotation retraining described above, also performs well in two people with paralysis (pontine stroke and ALS) as part of the same clinical trial (Jarosiewicz et al., 2013).

A final question regarding ReFIT-KF is particularly germane to this discussion of decoder design. The intention estimation innovation used in ReFIT-KF was applied to closed-loop data (i.e., closed-loop decoder adaptation), but would this same benefit have been achieved if this intention estimation was applied to the original open-loop (arm-reaching) data? This was recently tested, and it was found that a variant of intention estimation resulted in performance nearly as good as ReFIT-KF as shown in Figure 3E ("Feedback Intention-Trained" Kalman filter [FIT-KF]; Fan et al., 2014). In FIT-KF, neural and native arm movement training data were collected, and then a largely biomimetic decoder was trained from these data, with the modification that the native arm movement vectors were rotated so as to always point directly toward the target. This is different than a standard biomimetic decoder, which attempts to reproduce the native arm's kinematics from the neural data; here the largely biomimetic decoder attempts to generate target-directed movements from the neural data. Though FIT-KF was motivated by the intention estimation employed in ReFIT-KF, again it is different as native arm kinematics are rotated during training in FIT-KF, instead of prosthetic cursor kinematics being rotated during retraining in ReFIT-KF. As such, FIT-KF is a decoder design, but it does not reflect decoder adaptation. It is also important to note that little neural adaptation was observed with FIT-KF, as indicated by observing little change in the preferred directions (PDs) of neurons (Fan et al., 2014).

We have focused above on one recent line of decoder design investigation in order to walk through the essential steps and design considerations using one cohesive example, as well as because it translates to people with paralysis. But several other experiments have been performed along these lines. Another type of decoder adaptation experiment starts with the user controlling the prosthetic cursor with a mixture of open-loop decoder output and knowledge about how the cursor ought to move toward a target, a process referred to as "assistive training." By progressively weaning the prosthetic cursor off of this external assistance, all the while retraining the decoder

based on ongoing closed-loop cursor kinematic and neural data, a decoder adaption design emerges. This general approach has been investigated in several recent studies (e.g., Velliste et al., 2008; Chase et al., 2009), including in a person with paralysis (spinocerebellar degeneration; Collinger et al., 2013).

Another type of decoder adaptation experiment investigates decoder adaptation on intermediate timescales, with the goal of facilitating rapid BMI performance improvements independent of decoder initialization conditions (e.g., Orsborn et al., 2012; Dangi et al., 2013). This approach may be particularly important in clinical applications where people with paralysis have limited movement and/or sensory abilities due to various disabilities. Given the user-to-decoder interactions inherent in closed-loop BMIs, the decoder adaptation timescale may be of particular importance when initial performance is limited. An example of this approach is "SmoothBatch," a decoder adaptation algorithm that updates decoder parameters on a one- to two-minute timescale using an exponentially weighted sliding average (Orsborn et al., 2012). Here a monkey first performed a center-out reaching BMI task. SmoothBatch parameters were initialized four different ways with varying offline decoding performance: (1) visual observation of a cursor, (2) ipsilateral arm movements, (3) baseline neural activity, and (4) arbitrary weights. The SmoothBatch algorithm rapidly improved performance regardless of the method of initialization, with performance improving from very low performance with the initial decoder (0.018 ± 0.133 successes/min) to proficient performance (a threshold of 8 successes/min) within just 13.1 ± 5.5 min of operation. After decoder adaptation ceased, the subject maintained the adaptation-mediated performance. Moreover, performance improvements were paralleled by SmoothBatch convergence, suggesting that decoder adaptation converges toward accurately decoding user intent. Ongoing decoder design developments include the continuous update of the decoder's parameters using a recursive maximum likelihood algorithm (Dangi et al., 2014) and the use of a point-process filter that allows users to issue neural commands and receive feedback of the consequence of such commands at a faster rate (Shanechi et al., 2013).

Central to the design of decoder adaptation algorithms is choosing the timescale of adaptation, selecting which decoder parameters to adapt, and crafting the corresponding update rules. These design choices directly affect the algorithm's ability to make decoder parameters converge to values that optimize performance. A general framework for the design and analysis of decoder adaptation algorithms is now becoming possible, and has recently been validated with experimental results from two monkeys performing a BMI task (Dangi et al., 2013). First, existing decoder adaptation algorithms were analyzed and compared in order to highlight the importance of four critical design elements: the adaptation timescale, selective parameter adaptation, smooth decoder update rules, and which decoder parameters should adapt. Second, mathematical convergence analysis using measures such as mean-squared error and "KL divergence" were investigated for evaluating the convergence properties of a prototype decoder adaptation algorithm. It was found that these measures led to effective and quick closed-loop decoder adaptation. These advances may be important for combining decoder adaptation with neural adaptation.

Studies Focused on Neural Adaptation

Several studies have investigated neural adaptation and its possible underlying mechanisms. One line of investigation employs the "hand-controlled training, and hand-independent BMI control with context change" animal model described above. This experimental paradigm requires the user to explore in order to find a way to generate neural activity patterns capable of guiding a prosthesis via a decoder. This exploration process, in part, drives neural adaptation. Some early studies following this paradigm reported observing neural adaptation, including adaptation potentially due to plasticity (e.g., Taylor et al., 2002; Carmena et al., 2003; Musallam et al., 2004; Lebedev et al., 2005). Neural adaptation is presumably due to the animal altering neural activity so as to control the prosthetic actuator better and thereby receive reward more quickly. Some of these studies also reported significant frontoparietal cortical reorganization (Carmena et al., 2003; Lebedev et al., 2005).

These studies employed various decoder designs and, importantly, trained the decoder parameters anew at the beginning of every session. Thus, the animal had to effectively learn at least a slightly different decoder each day (i.e., intrasession learning) before being able to perform the task proficiently. However, as BMI task complexity increases (e.g., trying to control a high-DOF prosthetic arm and hand at near-native performance), the design of decoders capable of achieving good performance will become more difficult. It will therefore also become more difficult for the user to learn to control a decoder trained afresh each day. This can result in variable performance from day to day that prevents consolidation and retention of the neuroprosthetic skill (Ganguly and Carmena, 2010; Carmena, 2013). Hence, intrasession neural adaptation combined with daily-trained decoders may become impractical for learning skillful neuroprosthetic control of complex prosthetic actuators in demanding tasks.

How then might it be possible to engage neural adaptation to achieve consolidation of what is being learned every day through intrasession learning? Previous work hypothesized that pairing stable neural recordings (i.e., not changing which neurons contribute to BMI control) with a fixed, static decoder (i.e., a decoder design that is not retrained daily, and does not have decoder adaptation) would lead to retention of the learned task across time and therefore facilitate the consolidation of a prosthetic motor memory (Ganguly and Carmena, 2009). The key element here is the stability of the BMI circuit; the neural input to the decoder, as well as the decoder itself, remains unchanged throughout the length of the study and thereby consolidates skilled control of a prosthetic actuator in a way that resembles that of natural motor learning. Colloquially speaking, the brain should "own" the BMI (e.g., DiGiovanna et al., 2009). Ownership presumably confers desirable properties for action in real-world scenarios, such as skill formation, motor memory (e.g., rapid recall, formation of a motor map), and specialization of a BMI circuit that is resistant to interference from other native motor networks (e.g., residual movement in the person with paralysis). Figure 4 highlights the importance of brain ownership of the BMI facilitated through neural adaptation. Consider a monkey

learning to control a BMI reaching task in "hand-controlled training, and hand-independent neuroprosthetic control with context change" mode. In this case the change in context consists of removing the 2D exoskeleton used to perform the task manually during training. Figure 4A depicts a cartoon of a monkey during the neuroprosthetic control phase independent of natural movement. In this setting, when a fixed decoder algorithm was applied to stable recordings from an ensemble of 15 primary motor cortex (M1) neurons across days, there was substantial long-term consolidation of prosthetic motor skill (Ganguly and Carmena, 2009). This is first characterized in Figure 4B where the daily performance is shown for two monkeys. For both subjects there was a monotonic increase in task accuracy, as well as a decrease in the mean time to reach targets. Detailed examination of the accuracy during each daily session revealed that, with practice, the monkeys could attain accurate performance at the very start of a session. This suggests that neuroprosthetic skill could be transferred from one day to the next (Figure 4C). Moreover, a highly stable neuron-behavior relationship emerged as a result of BMI learning, resulting in proficient BMI performance. This is illustrated in the color maps of Figure 4D (left panel), in which the daily directional tuning relationship for all units within the 15-neuron ensemble was estimated during neuroprosthetic control. The similarity among daily ensemble maps initially increased and then stabilized (middle panel). Interestingly, as shown in the right panel, changes in map similarity (red traces) closely tracked improvements in task performance (black trace); the temporal course of skill acquisition accompanied that of map stabilization.

Thus, it appears that the neural adaptation process created a motor map for prosthetic function that was readily recalled and highly stable across days. Surprisingly, the same set of neurons could learn and consolidate a second motor map without interference with the first map (Figure 4E), highlighting another attribute of neural adaptation that is similar to natural motor learning: that of being able to learn new motor memories without interfering with previously acquired ones. Hence, neural adaptation leads to the formation of a stable BMI map that has the putative attributes of a memory trace. Namely it is stable across time, is readily recalled, and is resistant to interference from learning other maps (Ganguly and Carmena, 2009).

Having reviewed some of the attributes of engaging neural adaptation in BMIs, it is now relevant to ask about the neural dynamics of switching between manual (native arm movement) and BMI modes of operation. Since the monkeys performed manual control (MC) blocks both before and after the BMI block (BC), comparison of modulation depth (MD) during MC_1 and MC_2 could assess lasting effects of the modifications during neural adaptation. Examination of the directional modulation relationship across sessions revealed rapid changes in PD and MD for BMI (hereafter "direct") neurons (Figure 4F, top). Similar dynamics were evident for non-BMI ("indirect") neurons, albeit with a reduction of modulation (Figure 4F, bottom). Moreover, the properties of both direct and indirect neurons remained relatively stable during each state. Thus, the observed large-scale network modifications through neural adaptation were rapidly reversible between BMI operation and normal arm use in a state-dependent manner (Ganguly et al., 2011).

A prediction from this adaptive BMI network is that the characteristics of direct neurons will differ from indirect neurons because the direct neurons are causally linked to behavioral output. In other words, as the direct neurons become the output layer of the network, examination of the neural population in late learning should reveal changes in the contribution of direct neurons for neuroprosthetic control with respect to the indirect neurons. As predicted, analysis of the differences in the ratio of MD between brain control and MC (BC:MC MD_{ratio}) revealed a consistent difference between the relative mean MDs of the direct and indirect neuronal populations (Figure 4G, BC:MC$_1$ Late, ten sessions from six experiments in Monkey P and Monkey R). Surprisingly, even the population of near (indirect) neurons, which are those recorded from the same electrode as a direct neuron, but not used for neuroprosthetic control, behaved similarly to a more distant set of indirect "far" neurons. Far neurons are defined as being from at least one electrode away from a direct neuron (interelectrode distance 500 μm). These differences appeared to only emerge in late learning upon stabilization of task performance. Similarly, a recent study using a calcium imaging BMI paradigm revealed a progressive spatial refinement of activity in local networks comprising direct (output-relevant) neurons within a 160 × 160 μm field of view (Clancy et al., 2014). Together, these results indicate that neural adaptation is associated with differential modulation of neuronal populations based on their causal link to neuroprosthetic control. Moreover, proficient neuroprosthetic control is linked to the formation of a stable large-scale set of neural activations that coexists with native networks for arm movement control (Ganguly et al., 2011). Neural adaptation studies have also demonstrated that primates and rodents can learn nearly arbitrary, nonbiomimetic decoders (e.g., Fetz, 1969; Radhakrishnan et al., 2008; Ganguly and Carmena, 2009; Ganguly et al., 2009; Koralek et al., 2012; Moritz et al., 2008), highlighting the capacity of the brain to create de novo circuits to perform novel (neuroprosthetic) actions (Orsborn and Carmena, 2013). Finally, these recent studies indicate that proficient neuroprosthetic control through neural adaptation is associated with the formation of specific neuroprosthetic activations that readily coexists with the long-standing network for natural motor control. When switching between control states, the cortical network appears to switch rapidly, without interference, based on task requirements.

These results generate important questions regarding neural adaptation and the underlying mechanisms. For example, where do these error-driven changes take place? How do they change? Are the same brain structures required for natural motor learning, such as the basal ganglia, also necessary for learning neuroprosthetic actions? To address these questions, a recent study developed a BMI paradigm where rodents learned to control an "auditory cursor" (i.e., the level of auditory pitch across a frequency range, to reach one of two target frequencies by differentially modulating the activity of two ensembles of M1 neurons). Through neural adaptation, the animals learned to perform these neuroprosthetic actions in a goal-directed manner and in the absence of physical movement (Koralek et al., 2012). Examination of recorded neural activity from dorsolateral striatum (DS), a basal ganglia structure that is involved in motor skill learning
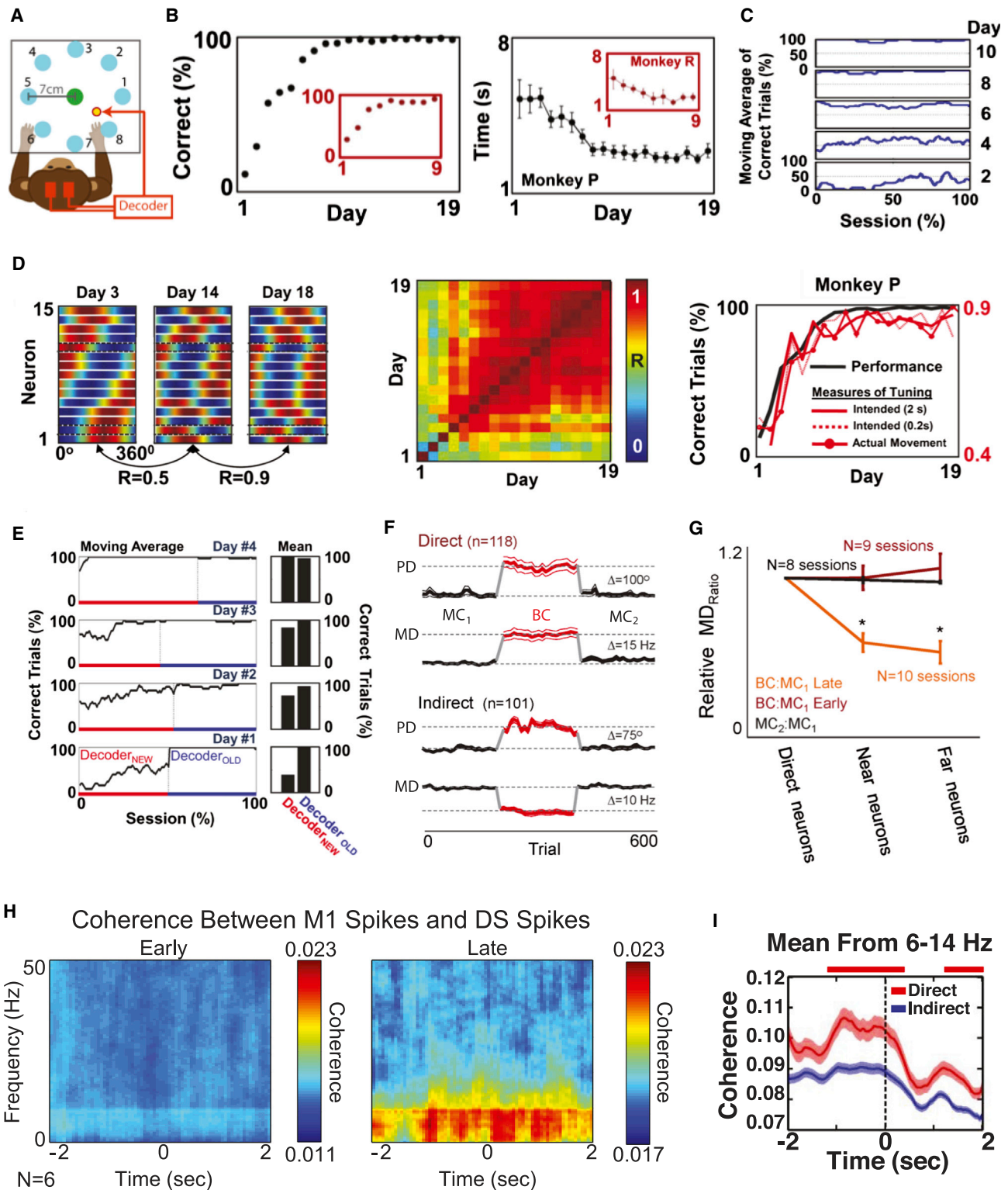
Figure 4. Neural Adaptation Facilitates Neuroprosthetic Learning

(A) Schematic of a monkey performing a 2D center-out task using a computer cursor under direct neural control, irrespective of physical movement. In this case, the animal model is "hand-controlled training, and hand-irrespective BMI with context change."

(B) Closed-loop BMI performance improves with practice. Changes in performance for consecutive days when keeping the BMI loop stable (i.e., fixed decoder and a fixed set of units) in two monkeys. Left panel shows the mean accuracy per day, and right panel shows the mean time to reach each target with training. Error bars represent ± 2 SEM.

(legend continued on next page)

(Yin et al., 2009), revealed that striatal neurons were highly modulated during neuroprosthetic control, and that M1 increased its coherence with the DS as learning progressed (Figure 4H). These changes in corticostriatal coherence between early and late learning epochs were found to be temporally precise (data not shown) and significantly more pronounced in direct M1 neurons than in those not controlling the BMI (Figure 4I). This is consistent with the formation of a BMI-specific network as discussed above (Koralek et al., 2013). Moreover, knockout mice lacking NMDA receptors in the striatum (which are critical for long-term potentiation at corticostriatal synapses) were not able to learn the same task, supporting the notion that corticostriatal plasticity is necessary for neuroprosthetic learning (Koralek et al., 2012). Together, these results suggest that corticobasal ganglia circuits are involved in BMI learning, even when they do not require physical movement. Moreover, these results show that neural adaptation not only elicits changes in motor cortical networks, but also recruits elements of the natural motor system outside of the cortex, such as the basal ganglia. Finally, recent results suggest that slow-wave activity during sleep is involved in the consolidation of neuroprosthetic skills (Gulati et al., 2014).

For these reasons we believe that neural adaptation will be central to the skillful control of high-DOF BMIs in real-world environments. A goal would be to control BMIs through the potentially effortless recall of motor memory in a manner that mimics natural skill acquisition and motor control.

Studies Focused on Decoder Design and Neural Adaptation

We now turn our attention to the proposition of combining decoder design, which includes decoder adaptation, and neural adaptation. Some early studies engaged both decoder and neural adaptation, which is sometimes referred to as coadaptation (e.g., Taylor et al., 2002; Gage et al., 2005). However, little is known about the mechanisms of distributed learning within BMIs, which are the simultaneous or iterative processes of both decoder and neural adaptation. Studying the characteristics and mechanisms of decoder-neural interactions appears to be a key step toward understanding if and how BMIs might benefit.

Decoder design, including decoder adaptation, enables good BMI performance immediately following training and can maintain performance over days and months when using multineuron threshold crossings, which tend to be fairly stable (Chestek et al., 2011; Fan et al., 2014; Gilja et al., 2012). But it remains to be determined if this approach can provide desirable motor memory properties, as described in Ganguly and Carmena (2009) (but see Nuyujukian et al., 2014b). Conversely, neural adaptation provides motor memory properties (Ganguly and Carmena, 2009, 2010; Ganguly et al., 2011), but it remains to be determined if this approach can increase performance faster than on the order of days or weeks, which is not ideal for use with people with paralysis. It also remains to be determined how this approach works if there is a dearth of stable single-neuron action potential waveforms, which tends to be the case after weeks to months of electrode array implantation (e.g., Chestek et al., 2011). Finally, it remains to be seen if neural adaptation alone can result in decoders exceeding the performance of biomimetic decoders. Can we facilitate the coadaptation between the brain (neural adaptation) and the machine (decoder design and adaptation) so that the brain ownership (neuroprosthetic skill) properties emerging through neural adaptation can be preserved while adapting the decoder? We believe that this will be possible, and that framing it as a two-learner system may be helpful (e.g., DiGiovanna et al., 2009); (1) the decoder can be thought of as a "surrogate spinal cord," which effectively reads out cortical neural activity and is learned by the brain (learner 1) via neural adaptation, and (2) the decoder itself can also learn (learner 2) via decoder design and decoder adaptation. In other words, a system where the brain and decoder collaborate to produce more optimal BMI control.

A recent study tested the feasibility of combining neural and decoder adaptation to achieve and maintain neuroprosthetic skill in two scenarios relevant for real-world BMIs: (1)

(C) Intrasession learning across days for one monkey. For each day, the moving average (i.e., percent of correct trials for a moving window of 20 trials) of performance is shown.
(D) Stable task performance is associated with stabilization of ensemble tuning properties. The three color maps to the left illustrate the directional tuning of a 15-neuron ensemble during brain control (BC) for days 3, 14, and 18 of a 19-day learning experiment in one monkey. The units were sorted on day 3 with respect to PD. The middle panel is a color map of pairwise correlations of ensemble tuning (i.e., map) for each BC session. Warm colors represent a higher level of correlation. The panel to the right depicts the comparison of the learning rate with changes in ensemble tuning across the 19-day experiment. The black solid line reproduces the learning rate from Monkey P in (B). The red solid line represents the average correlation between a daily map and all other ensemble maps (directional tuning was assessed with 2 s of activity relative to intended target). The dotted red line shows the same relationship for directional tuning assessed with a 0.2 s window. The red line with superimposed red dots illustrates the relationship for directional tuning relative to actual cursor movements.
(E) Simultaneous retention of two BMI maps without interference. The left panels depict the BMI performance (moving average with window size of 20 trials) across 4 consecutive days for one monkey learning a new decoder (Decoder$_{NEW}$, red bar), and then switching neuroprosthetic control with an already-learned decoder (Decoder$_{OLD}$, blue bar). The panels on the right represent the mean session performance.
(F) Stability of state-dependent changes in neural properties during a session with MC and brain (i.e., BMI) control (BC) blocks. Traces show the PD and MD for a moving window of trials (window of 16 trials) for an average of multiple direct units (top) and indirect units (bottom) from two monkeys. Each segment is color coded and labeled according to the block type (MC$_1$, BC, MC$_2$). n, number of units included in the average.
(G) Differential modulation of neuronal populations during neuroprosthetic control. The panel depicts the ratio of relative MDs between MC and BC for the three populations (direct, indirect near, and indirect far; see text). Each session was normalized to the mean MD$_{ratio}$ for direct neurons. "Early" and "Late" represent BC sessions, respectively, from days 1–2 and days $\geq$ 3 of training. MC$_1$:MC$_2$ is the ratio of MDs of the MC blocks before and after BC.
(H) Neuroprosthetic learning is accompanied by corticostriatal plasticity in the rodent. Coherence between M1 spikes and DS spikes in early (left) and late (right) learning shows a clear increase in low-frequency coherence in late learning relative to early learning. Rats learned to intentionally control an auditory cursor to reach for food pellets (high-pitch target) or sucrose water (low-pitch target) by differentially modulating two ensembles of M1 neurons.
(I) Corticostriatal plasticity is cell type-specific. Differential corticostriatal plasticity measured as mean spike-field coherence between direct neurons (i.e., task output-relevant) and indirect neurons from 6 to 14 Hz in late learning. Shaded regions denote SEM. Colored bars above plot designate time points with significant differences. (B)–(E) modified from Ganguly and Carmena (2009). (F) and (G) modified from Ganguly et al. (2011). (H) modified from Koralek et al. (2012). (I) modified from Koralek et al. (2013).

nonstationary recorded neural activity and (2) changing control contexts (Orsborn et al., 2014). Two nonhuman primates controlled a 2D cursor using neural activity from motor cortices in the absence of overt arm movements, as in the "hand-con-strained training, and hand-constrained BMI control without context change" animal model described earlier. The stability constraints on neural inputs to the BMI were relaxed by using multiunit and/or channel-level activity, and the population of units contributing to the decoder was intermittently changed over time. Decoder adaptation was used to both improve initial performance of the decoder (and recover performance if it declined) and to maintain performance in the presence of nonstationary recordings; meanwhile, the degree of concurrent neuroprosthetic skill improvement was measured. The findings of this study showed that the combination of decoder and neural adaptation facilitates the formation of a BMI-specific network (Orsborn et al., 2014). That is, the brain identifies neurons critical for BMI performance, and changes their modulation during BMI use while the decoder is also adapted. This is encouraging evidence that leveraging neural and decoder adaptation may be useful for achieving robust, flexible neuroprosthetic control that can be maintained long term.

The study also explored whether the attained neuroprosthetic skill was resistant to interference from native motor networks (Orsborn et al., 2014). While this BMI-specific network was previously reported as a result of neural adaptation (Ganguly et al., 2011), no decoder adaptation was involved in that study. Previous work suggested that, in the setting of a static decoder, neural adaptation facilitated neuroprosthetic learning that is resistant to interference, with subjects being able to learn multiple BMI decoders with the same neural ensemble and retain both in memory (Ganguly and Carmena, 2009). This swapping between two learned decoders took place in the same experimental context (i.e., in BMI mode and irrespective of physical movement). But what would happen if we change the context by instructing the animal to perform, simultaneously with the BMI task, a previously learned natural motor task (e.g., an iso-metric force gripping task) with the native hand contralateral to the motor cortex being used for BMI control? Would the neural circuits facilitated by neural adaptation be resistant to interference from recruitment of these and other neighboring cells by networks controlling the native arm? The findings in (Orsborn et al., 2014) demonstrate that after practicing for several days with a decoder that was initially optimized for BMI control alone via closed-loop decoder adaptation, the BMI-specific network attained through neural adaptation was able to overcome most of the perturbing effects from the simultaneous force-generation task (Orsborn et al., 2014). This experiment mimics the type of real-world, multitasking scenario in which neural adaptation could play a key role in facilitating BMI performance. Moreover, the problem of simultaneous BMI and native motor use is rele-vant to people with strokes operating a BMI with neurons from the unimpaired (ipsilateral) motor cortex (Ganguly et al., 2009).

Discussion
Let us consider a specific BMI example in order to help bring together the various concepts and findings presented above, as well as to help make more explicit why we believe that

combining decoder design and neural adaptation may be fruitful. This then leads to three topics, considered in turn: future ques-tions, motor and neuroprosthetic skills, and learning mecha-nisms underlying neuroprosthetic control.

Consider a person who has lost an arm and hand due to injury. An electrode array is implanted surgically in her contralateral primary motor cortex, and a high-DOF prosthetic arm is fitted. A decoder is designed, trained with neural data collected while she imagines moving her missing arm, and the BMI arm and hand are then used. When the BMI is in use, cortex is in a closed-feedback loop with the BMI (i.e., Figure 2, plant #2). When the BMI is not in use, for example, when the prosthetic arm/hand is disconnected or when she is using her other arm/hand alone, cortex is not in a closed-feedback loop with the BMI. But cortex is still active, with spontaneous activity or imag-ined/planned movements. Thus, two motor memories would seem to be required as described above. Returning to envision-ing the BMI in use, it is probable that movement of her intact arm also causes unintended movement of the prosthesis because motor cortex is not strictly lateralized and instead is part of a coordinated bimanual circuit (Ganguly et al., 2009; Ifft et al., 2013). This correlation may not be readily separated by the decoder, especially if neural activity from both contra- and ipsilateral motor cortex occupy the same neural dimensions (Churchland et al., 2012; Shenoy et al., 2013; Kaufman et al., 2014). Thus, the onus would then fall on neural adaptation to create a new motor control circuit, which effectively decorrelates control of the intact arm from the prosthesis, so that the subject can have independent control of both her real and prosthetic limb and hand. Finally, as she becomes more adept at using the BMI in tasks of daily living it is likely that new and different tasks will be attempted, and in an increasingly real-world environment. While a decoder design with adaptation is likely needed, it is also likely that neural adaptation will be engaged to help improve performance on these new and different tasks. An important and humbling reminder of how much we still have to learn about cortical activity and BMI control was provided in the form of an anecdote from a recent study where the person with paralysis was able to close her BMI hand, but not if a red object was also present (Collinger et al., 2013). These are but a few questions that arise from a realistic BMI use case example.

We envision that combining decoder design (including decoder adaptation) with neural adaptation will help facilitate BMI skill that is rapidly learned, has high performance, robust-ness, and utility, is less sensitive to initial decoder training conditions, is resistant to interference from residual native movements, has reduced sensitivity to environmental and task context changes, and is well maintained long term with little calibration needed even with degrading neural signal quality. If so, then this approach may meaningfully increase the neural prosthesis's clinical viability.

Future Questions
One question to address when designing a two-learner BMI system is finding the best way to initialize and train the decoder. In other words, given a BMI system with certain characteristics (number of neurons being recorded and their physiology, characteristics of the prosthetic plant, etc.), which is intended

to be used in certain contexts and for certain tasks, what is the optimal set of parameters to achieve rapid learning and proficient BMI control? In real-world scenarios there will be unforeseen complexities in the environment and in the task, beyond what can be anticipated ahead of time during decoder design, even designs including decoder adaptation. This may be where neural adaptation will play a key role. Moreover, the more we scale up plant and task complexity (e.g., high-DOF prosthetic arms and hands to perform tasks of daily living), the greater the difference may be between the BMI and native plants. If so, then decoder and neural adaptation may be needed all the more.

Another question concerns the optimal sequence and timing for decoder and neural adaptation. One possible schedule would be to start with an early decoder adaptation epoch, in which the decoder is adapted until a certain level of performance is achieved, followed by a prolonged epoch with the resultant decoder held fixed while neural adaptation is engaged (e.g., Orsborn et al., 2014). Another possibility would be to more rapidly toggle between decoder adaptation and neural adaptation epochs, with the rationale that possible interaction between the adaptation types may lead to higher performance and other benefits if neither adaptation type is allowed to too strongly influence BMI system operation at any given time. Along these lines, recent work in simulations has explored optimal strategies to improve coadaptation dynamics (Merel et al., 2013). A closely related, but distinct, third possibility would be to simultaneously engage both decoder and neural adaptation so that both are actively adapting at the same time. This would require special attention to the rates, and the signs of the rates, of changes that are allowed so as to avoid conditions where the two adaptation types wrestle with each other; wrestling could create oscillations, or cases where one type of adaptation inappropriately dominates the other entirely. These are some design questions that deserve future theoretical, computational, and experimental investigation.

Motor and Neuroprosthetic Skills

Recent views on the nature of motor skill suggest that learning to become skilled at a motor task, for example, tennis, depends on two things. The first is motor acuity, defined as increased precision of selected actions. The second is knowledge-based selection of the right actions, with both increasing with practice (Stanley and Krakauer, 2013). Similarly, it was recently argued that skill acquisition involves the synergistic engagement of strategic and adaptive processes, the former being sensitive to goal-based performance error, whereas the latter is sensitive to prediction errors between the desired and actual consequences of a planned movement (Taylor and Ivry, 2012). An interesting aspect of this view of skill acquisition is that the skilled state does not necessarily saturate at a given level of performance, as there is always the possibility to perform new actions based on further knowledge and to then develop acuity at these new actions. An example of this continued increase in performance over an already developed skill is the Fosbury flop, which led to a paradigm shift in high jumping (Stanley and Krakauer, 2013; Taylor and Ivry, 2012).

What would acquiring skill entail in a BMI context? If we define neuroprosthetic skill as the accurate, readily recalled neural control of artificial actuators irrespective of natural physical move-

ment, then an analogy with motor skill theory could be applied. We suggest that the synergy between two learning processes in human motor skill (motor acuity and knowledge-based action selection) may be analogous to the two-learner BMI system case in which decoder and neural adaptation interact. Operant learning (neural adaptation) can provide the neural scaffolding, the representation in the brain, and the motor memory effect described above that can facilitate motor acuity, but neural adaptation probably cannot facilitate all that is needed for skillful performance to occur. Decoder design including decoder adaptation, however, allows for implicit knowledge about the task to be used when updating the decoder parameters based on inferred or known task goals (e.g., intention estimation). Hence, synergies between the two types of adaptation may facilitate the emergence of neuroprosthetic skill. A candidate metric for assessing neuroprosthetic skill that is typically used in motor control is the difference between the speed-accuracy tradeoff functions across different days of practice (e.g., Shmuelof et al., 2012).

Learning Mechanisms Underlying Neuroprosthetic Control

There are many important questions related to the mechanisms and circuitry underlying the neural plasticity hypothesis that warrant further inquiry. One key question is the so-called "credit assignment problem," with so many neurons in the brain, how does the brain figure out which neurons are controlling the prosthetic cursor, such that the brain can change just those neurons and others to a much lesser extent? While this would seem like finding a needle in a haystack, experimental and theoretical studies suggest that it is possible (Fetz, 1969, 2007; Jarosiewicz et al., 2008; Heliot et al., 2010b; Legenstein et al., 2010; Ganguly et al., 2011; Koralek et al., 2012, 2013; Clancy et al., 2014).

As discussed above, neural adaptation is associated with a differential modulation of neuronal populations based on their causal link to neuroprosthetic control (Figure 4G). Hence, what is the role of indirect neurons (i.e., those not connected to the BMI) in the credit assignment problem? The stability of the tuning properties of the indirect population reported in Ganguly et al. (2011) suggests that indirect neurons have an active supportive role in neuroprosthetic control, presumably shaping the activity of the direct neurons. Alternatively, the indirect activity may have a negative role (e.g., adding noise) in which case the observed reduction in MD may allow more efficient neuroprosthetic control by avoiding interference with the direct neurons. Particularly relevant to this question is the work of Jarosiewicz and colleagues that reported functional reorganization of neuronal tuning properties after perturbation of a previously learned decoder. Such reorganization had two main effects: a global change in neuronal tuning that compensated for the error in cursor movement, followed by a larger compensatory change in tuning in the perturbed population of neurons than in the unperturbed population (Jarosiewicz et al., 2008). This reweighting phenomenon after perturbation suggests that error-correcting mechanisms can partially establish a link between neurons and their specific contributions to errors during neuroprosthetic control, presumably facilitating both the initial establishment of proficient control as well as adjustments after perturbations. Recent evidence from the same group suggests that the local

error-correction mechanism depends on the specific perturbation applied to the direct neurons, and that it coexists with a global adaptation strategy similar to a visuomotor transformation (Chase et al., 2012).

Further evidence of the role of indirect neural populations for neuroprosthetic control comes from the work about the role of basal ganglia discussed above (Koralek et al., 2012, 2013; Figures 4H and 4I) as well as a recent human ECoG study reporting that a distributed network of cortical areas were involved in learning a BMI task (Wander et al., 2013).

Summary

To help address unmet intracortical BMI needs, we provide here a perspective on how two complementary lines of investigation (decoder design including decoder adaptation, and neural adaptation) may be brought together. This combination may enable an increased sense of ownership of the BMI, learning acceleration, performance and robustness increases, good generalization to novel contexts, and resistance to interference from internal (coactivation of other networks) and external (changes in the environment) perturbations. Together, these properties may make the control of BMIs more natural. Our hope is that the ideas presented here will help spur new and important research advances that, ultimately, may help improve the quality of life for people with neurological disease and injury. We believe that BMIs are also exciting and promising tools for motor systems neuroscience since they enable new opportunities to directly control the causal relationship between neuronal activity and behavioral output (e.g., Carmena, 2013; Fetz, 2007; Shenoy et al., 2011; So et al., 2012; Kao et al., 2013) and enable the investigation between volitional control of neural activity and the natural motor repertoire (e.g., Hwang et al., 2013; Sadtler et al., 2014).

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