

# Mood and Motor Brain Machine Interfaces Based Advance Controller for analyzing and remedial of Physiological diseases

Gaurav Pathak  
Computer Science Engineering Department  
Bhagwant University, Ajmer  
Ajmer, India

Virendra Kumar Sharma  
Electrical Engineering Department  
Bhagwant University, Ajmer  
Ajmer, India

**Abstract-** Brain-machine interfaces (BMIs) create closed-loop control systems that interact with the brain by recording and modulating neural activity and aim to restore lost function, most commonly motor function in paralyzed patients. Moreover, by precisely manipulating the elements within the control loop, motor BMIs have emerged as new scientific tools for investigating the neural mechanisms underlying control and learning. Beyond motor BMIs, recent work highlights the opportunity to develop closed-loop mood BMIs for restoring lost emotional function in neuropsychiatric disorders and for probing the neural mechanisms of emotion regulation. Here we review significant advances toward functional restoration and scientific discovery in motor BMIs that have been guided by a closed-loop control view. The work done in this paper focusing on this unifying view of BMIs and reviewing recent work, we then provide a perspective on how BMIs could extend to the neuropsychiatric domain. BMIs have a wide array of potential clinical applications, ranging from restoring communication to people unable to speak due to amyotrophic lateral sclerosis or a stroke, to restoring movement to people with paralysis from spinal cord injury or motor neuron disease, to restoring memory to people with cognitive impairment. Because BMIs are controlled directly by the activity of pre specified neurons or cortical areas, they also provide a powerful paradigm with which to investigate fundamental questions about brain physiology, including neuronal behavior, learning, and the role of oscillations. This article reviews the clinical and neuro scientific applications of BMIs, with a primary focus on motor BMIs.

**Keywords-**Brain Machine Interface, Digital Signal Processing, Intelligent Controller, Mental Disorder, Neurological Disease, Signal Simulation

## INTRODUCTION

Brain-machine interfaces (BMIs) aim to restore lost function in patients with neurological and neuropsychiatric disorders by creating a direct control

pathway to the brain to read out neural activity, interact with an external device, and in some cases write in neural information by stimulating the brain in Fig.1. A motor BMI uses a mathematical algorithm termed a 'decoder' (Box 1) to estimate the user's intended movement state from neural activity, uses the decoded movement to control an external actuator (prosthetic device), and provides [1] [2] sensory and reward feedback to the user as in Fig. 1a. Thus, the Given this closed-loop control nature, BMIs likely

engage innate control and learning mechanisms employed by the brain in natural sensorimotor control. This closed loop control view has led to significant advances in two synergistic directions.

Understanding of control and learning mechanisms has explicitly guided the design of BMI technologies to improve performance toward functional restoration. Second, motor BMIs have served as novel tools for scientific discovery in understanding the neural mechanisms of control and learning because they provide a simplified closed-loop control system that is experimenter defined and can be readily manipulated.

The potential of BMIs for functional restoration and scientific discovery, however, could go well beyond the motor system. Indeed, in many neurological and neuropsychiatric disorders, the goal is to control i.e., regulate an internal brain state rather than the movement of an external actuator. In neuropsychiatric disorders, which are a leading cause of disability worldwide, with depressive disorders being the most disabling among them, the goal could be to restore lost emotional function by controlling a relevant mood state. Many

patients with major depression are not responsive to current treatments, making direct electrical brain stimulation a promising alternative therapy to explore. Open-loop stimulation Box 2 applying a fixed pattern of stimulation regardless of symptom levels has shown promising response and remission rates in treatment resistant depression in seminal open-label studies. However, it has had variable efficacy in randomized controlled trials. Personalized, alternative, or multiple stimulation target sites may help with such outcomes. Additionally, given the variability in neuropsychiatric symptoms both between patients and within an individual patient over time, one way to improve efficacy could be a closed-loop BMI approach that changes the stimulation based on symptom variations decoded from neural activity. We can envision a 'mood' BMI that decodes a mood symptom state (instead of a movement state) as feedback to decide when and how electrical brain stimulation is delivered to control mood toward a therapeutic target within its multidimensional space Fig.

1b. In contrast with open-loop stimulation, mood BMIs would again constitute a closed-loop control system, in which the plant is now the brain and control commands in the form of external electrical stimulation are dictated by feedback of neural activity and by desired therapy goals Fig. 1b. In addition to electrical stimulation, mood [3] [4] BMIs may also optionally provide users with feedback of the decoded mood to engage them actively in control, though likely at a different time-scale Fig. 1b. Further, mood BMIs may provide the opportunity to study the neural mechanisms of emotion regulation, as they could again be experimenter defined, though ethical considerations are critical.

While not tested for neuropsychiatric disorders, closed-loop stimulation has been applied to neurological disorders such as Parkinson's disease (PD) and epilepsy with promising improvements in Box 2. In these cases, low- or one-dimensional neural signal provide a biomarker, based on which stimulation is turned on and off, for example. The challenge for mood BMIs, however, is the involvement of a distributed brain network, the complex and dynamically changing nature of mood symptoms, and the difficulty of their measurement and inter-individual variability. Also, controlling mood-relevant neural dynamics could require principled closed-loop controllers that go beyond turning stimulation on and off. These aspects would likely necessitate a personalized mood decoding approach from network activity rather than a single low-dimensional biomarker approach to tailor the stimulation to the patient's needs in Box 2. This decoding approach is in line with motor BMIs.

Compared with the rich body of work on motor BMIs, mood BMIs are just beginning to be realized and will entail distinct

challenges Table 1. Unlike movements, mood is difficult to measure and involves distributed, multisite corticolimbic networks [5] whose functional organization is not as well understood. Additionally, mood BMIs would need to characterize the effect of stimulation on distributed brain network activity and the Stimulation induced plasticity over months and years. However, there are also striking similarities that may guide mood BMIs based on the insights learned from motor BMIs. First, both these BMI types need to decode an internal brain state from neural recordings. Further, just as users can learn to control a neuro prosthetic [6] based on feedback of neurally decoded movement, they may learn to modulate emotional states based on neuro based

feedback. This suggests that some of the same learning things based a mechanisms may be exploited, in combination with stimulation, for effective mood control. Indeed, similar computational mechanisms may underlie sensori motor learning and control and emotion regulation. These similarities, together with the extensive neuro imaging literature on mood and emotional processing and recent demonstrations of mood decoding, suggest that BMIs have the potential to extend as powerful tools for functional restoration and scientific discovery in the emotion domain. In this Perspective, by focusing on a unifying closed-loop control view Fig.1, we discuss the potential of invasive BMIs for functional restoration and scientific discovery in the motor and emotion domains. We first review the recent work on motor BMIs that is informed by this view and has advanced their design and our understanding of the neural mechanisms underlying BMI control and learning. Guided by insights from motor BMIs, the rich body of work in neuroimaging and psychology, and closed-loop control principles [7] [8], we then lay out a path toward developing mood BMIs, review the literature that suggests their feasibility, and describe recent progress toward their realization.

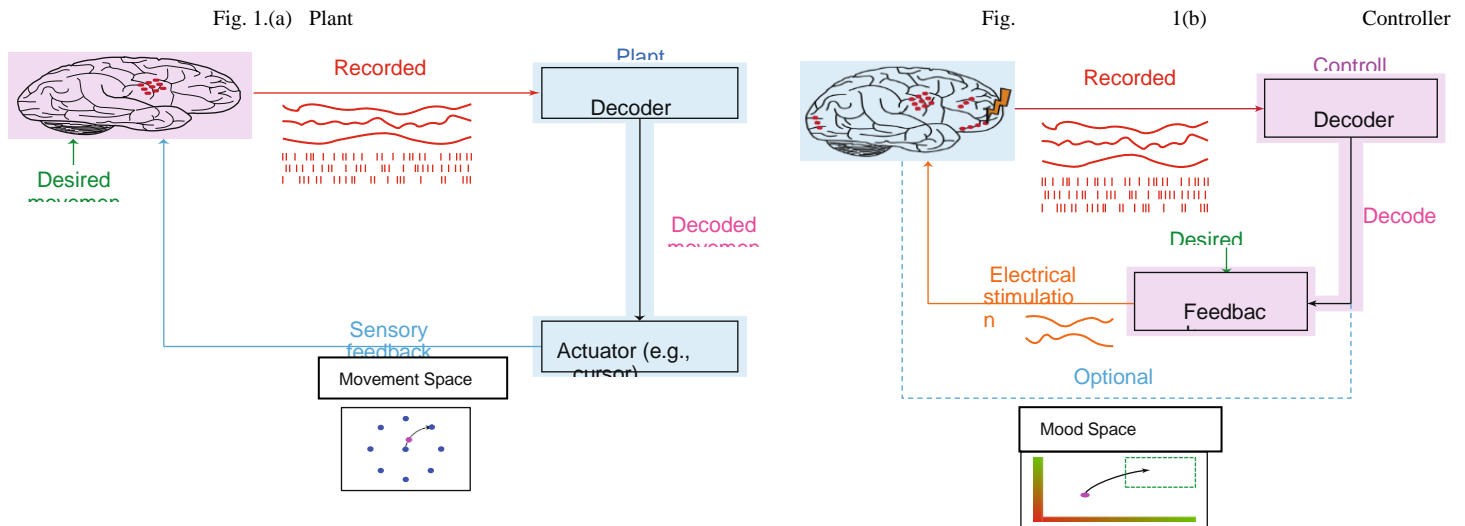
#### BMIS FOR RESTORATION OF LOST MOTOR FUNCTION

The closed-loop control view has advanced BMI decoders by changing how they are constructed and trained and by guiding the properties of the new sensorimotor BMI pathway Fig.2 Further, users learn to control a BMI by changing neural representations a process termed neural adaptation similarly to how we learn new natural abilities. The closed-loop control view has also guided how BMIs engage neural adaptation separately and together with decoder design. While various scales of activity can be recorded in invasive motor BMIs in Box1, we focus on those that use spiking activity.

#### DECODER DESIGNS INFORMED BY CLOSED-LOOP CONTROL PRINCIPLE

The first critical step in BMI design is to train the decoder Fig.2a Once a model structure for the decoder is selected in Box1, its parameters need to be estimated by regressing neural activity to movement intentions within a training session. One approach to training [9] [10] the decoder is to instruct users to move their arm or imagine movements while recording activity. This approach is open-loop in that during training, users do not control the BMI or receive feedback.

Fig.1 a,b BMIs create closed-loop control systems. BMIs aim to restore lost function by creating a direct control pathway to the brain to read out neural activity, interact with an external device (machine), and in some cases write in neural information by stimulating the brain.



Box 1/Neural decoders and dynamical latent state-space models in invasive BMIs

A BMI decoder estimates a brain state from the recorded neural activity, thus creating a brain-behavior mapping. Neural activity at single or multiple spatiotemporal scales—spikes, local field potentials (LFP), and electrocorticogram (ECoG)—can be used in invasive BMIs. Spikes measure the activity of single or multiple neurons, while field potentials such as LFP and ECoG measure the activity of larger-scale neuronal populations and could provide a more stable recording modality over time. Spiking activity has a fast millisecond time-scale while field potential features such as spectral powers may have slower time-scales in their variations.

The decoder structure is typically dictated by the encoding model that relates neural activity to movement. For example, spike counts or LFP power features can be modeled as linear functions of kinematics. Binary spike events—i.e., the 0–1 time-series that represents the absence or presence of spikes in time, respectively can be modeled with point processes that describe instantaneous firing rates as log-linear functions of kinematics.

Various decoders have been developed for spiking activity, which is the scale used in most invasive motor BMIs and enables high performance. Most of these decoders operate on spike counts: they count the number of spikes within time-bins of varying lengths as input. Early decoders consisted of Wiener filters and the related population vector and optimal linear estimators that decode the kinematics [11] as a linear function of spike counts. Later work used Kalman filters to incorporate a model of movement kinematics in decoding. In addition to these decoders that process spike-counts, point-process and optimal-

closed-loop point-process BMIs that instead directly decode the spikes. These point-process BMIs adapt and control the neuroprosthetic with every spike event, and thus at the millisecond time-scale of spikes, and model their binary nature. Point-process decoders also incorporate a model of movement kinematics.

In addition to spikes, LFP recordings can be added in the decoder. One motor BMI counted the spikes in the same time-bins in which LFP power features were computed, thus allowing a single Kalman filter to decode movement from both signals at the same time-scale. To enable fast control and feedback rates and model the different time-scales and statistical profiles of spikes and field potentials, recent studies have developed multiscale decoders; these decoders extract information directly from binary spike events at their millisecond time-scale while also adding information from continuous field potentials at their slower time-scales.

Finally, one approach to describing spatiotemporal neural activity patterns is to develop dynamic latent state-space models. These models describe the dynamics (i.e., variations over time) of high-dimensional network activity (over space) in terms of the dynamics of a latent low-dimensional neural state [12]. Dynamic latent state-space models have for example been used to develop motor BMIs using spikes, decoders of spike-field activity<sup>48</sup> and mood decoders from ECoG. These latent state-space models have also been proposed for modeling the effect of stimulation on neural activity in computer simulations.

Open-loop training builds on the assumption that neural representations of natural and BMI movements are similar. However, compared with controlling a biological arm, in BMIs users control an actuator with different dynamics, typically without tactile or pro-prospective feedback and only with visual feedback, and the activity of only a limited population of neurons directly drives movement. Given these differences, the closed-loop control view predicts that neural representations need not be the same in the two cases<sup>3</sup>. This motivated efforts at training (i.e., adapting) the decoder during closed-loop BMI operation, an approach often termed closed-loop decoder adaptation. In this approach, as the user controls the actuator toward instructed visual targets Fig.1a, decoder parameters are adapted using the generated neural activity and movement intentions typically velocity intentions [13] either intermittently or continuously in time Fig. 2a. This approach has significantly improved BMI performance. Recent studies have also shown that faster decoder adaptation time-scales can result in faster convergence to proficient control, for example by using a point-process adaptive decoder to enable parameter updates with every spike event (Box 1).

One major question in decoder adaptation is how to estimate the movement intention during training, as the decoder is untrained and cannot estimate it. The closed loop control [14] view has also guided the design of intention for

estimation methods Box 3. To estimate the direction of velocity intention, or to also provide assistance during training, some studies have posited that users intend to go straight toward a movement target. This approach has improved the performance of Kalman filter BMIs Box 1. More recent studies estimated intention by building explicit optimal feedback control models of BMIs that estimate both the direction and the speed of velocity intention Box 3, leading to improvements in the performance of point-process BMIs Box 1.

The closed-loop control view also predicts that the properties of the sensorimotor pathway created by the BMI affect the user's control Fig. 2b. Shorter BMI sensorimotor delays can improve control, as shown by decoding future movements or reducing the bin-width used in counting spikes within a Kalman filter. Also, faster BMI control rates and feedback rates (how often control commands are sent to the actuator [15] and how often feedback is received), combined with a point-process spike decoder, can enhance BMI control. To add field potentials to spikes while still providing fast control and feedback rates, multiscale decoders were recently developed that add information from continuous field potentials at their slower time-scale while simultaneously decoding the binary spike events at their millisecond time-scale Box 1.

### Engaging learning and neural adaptation in BMIs

The closed-loop control view has also highlighted the potential to combine learning-induced neural adaptation with decoder adaptation to improve BMI performance Fig. 2a. Learning to control the BMI involves neural adaptation, which is driven by sensory and reward feedback and can improve performance. Early studies observed this improvement despite daily decoder retraining. Later studies had animals practice instead with a fixed decoder that

mapped the activity of the same neurons to movement across multiple days. This led to consolidation of skilled BMI control and formation of a highly stable neural representation of movement that was resistant

to interference [16] from learning other decoders and was rapidly recalled, similar to the properties in natural motor skill acquisition. However, it may be difficult to maintain a stable set of neurons across time, and fixed decoders could take a long time (days) to learn. A main question is whether we can incorporate decoder adaptation to rapidly enable high performance while also engaging neural adaptation, possibly at slower time-scales, to enable skill acquisition. A recent study found that even when most of the performance improvement over the initial decoder was achieved by decoder adaptation in the presence of a changing neural population, neural adaptation could still occur and enable improved and skilled.

#### Box 2 | Closed-loop stimulation in epilepsy and Parkinson's disease

Open-loop electrical stimulation systems apply a constant pattern of stimulation (for example, pulse trains with fixed amplitude and frequency) continuously in time regardless of the disease symptoms. The stimulation parameters in these systems are changed infrequently at clinician visits. In contrast, closed-loop electrical stimulation systems would change the stimulation pattern based on changes in disease symptom levels, which may be inferred from the recorded neural activity. While closed-loop stimulation has largely not been tested for neuropsychiatric disorders, it has shown promise for neurological disorders such as epilepsy and PD. However, developing a closed-loop mood BMI will likely involve distinct challenges both in obtaining the feedback signal and in devising the control strategy by which stimulation is adjusted. For epilepsy, the Neuropace responsive neurostimulation system has been approved by the US Food and Drug Administration (FDA) for clinical treatment. This system has one or two leads, which could be cortical or depth strips with four electrode contacts each. Only when abnormal ECoG [17] [18] activity is detected, the system briefly turns on a fixed, predetermined pattern of stimulation. Since abnormal activity patterns can be explicitly observed at the onset of electrographic seizures, a biomarker can be constructed with clinician guidance to serve as the feedback signal for detection. This situation is different from mood, which likely has more complex and subtle representation in distributed brain network activity and further, is hard to measure even behaviorally. Also, on-off control with brief on-periods is likely well-suited in epilepsy because the seizure events are uncommon and intermittent and the disease has long asymptomatic periods<sup>7</sup>. For PD, the current clinical stimulation systems are essentially open-loop. However, in research studies, closed-loop deep brain stimulation has improved efficiency and efficacy. As the feedback signal, these closed-loop control systems typically use a one-dimensional biomarker of PD symptoms recorded from an electrode tip. Most commonly, the amplitude of subthalamic nucleus beta LFP activity (12–30 Hz) is used, which is linked to bradykinesia severity. The stimulation is on a fixed, predetermined level when the biomarker level crosses a threshold. Beyond this on-off control, other simple closed-loop strategies in which the stimulation amplitude is changed proportionally to the biomarker level have also been used.

In terms of the feedback signal, the case for mood BMIs is different from that for epilepsy and PD. Mood symptoms likely involve high-dimensional distributed neural representations and can additionally be heterogeneous across individuals. Thus a single universal one- or low-dimensional neural activity biomarker may not be optimal in this case. Also, mood symptoms can be highly dynamic and change rapidly even over minutes or within a day. Thus, in line with motor BMIs, a real-time personalized decoding approach could be needed to aggregate information across multidimensional recordings from relevant brain networks. This personalized decoding would account for heterogeneities across individuals and continuously track mood symptoms over time to tailor the stimulation to an individual patient's clinical needs.

In terms of the controllers [19] [20], closed-loop systems for epilepsy and PD have been based on simple on-off or proportional control. Moreover, the parameters of the controllers, such as the threshold used in on-off control, the gain for proportional control, or the stimulation frequency and amplitude levels, have been largely determined heuristically. To further optimize efficacy and efficiency, these parameters should be automatically adjusted based on an understanding of how stimulation changes the dynamics of neural activity that is causally related to disease symptoms. This understanding is especially important for mood, which could have complex symptom dynamics that change rapidly. Such understanding could be advanced by building data-driven input-output models that describe the effect of stimulation parameters (input) on neural activity (output) and then controllers that use these models for optimal real-time adjustment of stimulation parameters. The development and validation of such input-output models is a critical research direction, with implications thereafter.

This study hypothesized that a gradual rather than an abrupt change in the decoder and the recorded neurons was the reason that skill formed in face of decoder adaptation and that this may be one way to engage both adaptive processes.

Motor BMIs for studying the neural mechanisms of control and learning

BMIs create a simplified sensorimotor [21] [22] loop by specifying which neurons directly control movement, designing the map from neural activity to movement, dictating the actuator dynamics through the decoder, and dissociating different sensory feedback modalities, such as vision and proprioception. Thus, BMIs can precisely manipulate each element within the loop to study the mechanisms of control and learning.

Decoder manipulations reveal mechanisms of BMI learning BMIs allow us to study how the activity of output neurons those that directly drive movement in the decoder and their interactions with other sensorimotor regions are changed to learn a perturbed or a completely new decoder in

Fig. 2b. Decoder manipulations have revealed two potential neural mechanisms for BMI learning. First, learning can directly change the activity at the level of individual output neurons based on feedback of decoded movement (i.e., neuro feedback) to achieve behavioral goals. Second, learning can involve exploring an existing repertoire of neural activity patterns related to natural movements and then re-associating them with new movement intents. The major difference is that the former can generate novel neural representations while the latter cannot.

Several studies are consistent with the first mechanism. Subjects can learn completely arbitrary mappings between the activity of output neurons and behavior. BMI learning can lead to different activity changes in output neurons compared with nearby neurons. Finally, BMI learning involves changes in corticostriatal interactions that are specific to the output cortical neurons.

Several studies also support the second mechanism. When perturbing the directional tuning of motor cortical neurons within a decoder and creating an overall visuomotor [23] rotation, the majority of changes in neural representation were explained by a re-aiming strategy: an existing activity pattern now corresponded to moving toward a different rotated target location. Also, in the parietal reach region, changes in the activities of the output neuron and a nearby neuron during learning were correlated, as explained fully by re-aiming. Recent studies examined learning at the population level in M1 by using dimensionality reduction to find an intrinsic low-dimensional manifold within which high-dimensional population activity (with each dimension corresponding to one neuron) evolves. Learning to control a perturbed decoder was easier when the required perturbed activity pattern resided within compared to outside the original intrinsic manifold, suggesting that learning is shaped by existing neural repertoires. Further, within this manifold, subjects learned by re-associating an existing activity pattern with a different movement intent. Changes leading to re-association may occur upstream of M1, for example by changing its inputs. While the two learning mechanisms may seem inconsistent, there is evidence that they can co-occur, though likely with different time-scales.

Existing neural repertoire re-association has been observed when learning happens within 1–2 hours consistent with mechanisms underlying motor adaptation. In comparison, differential changes to the activity of individual output neurons could involve learning over longer time-scales of days, consistent with mechanisms underlying skill acquisition. Prior studies suggest that natural motor learning in adaptation and skill tasks is dominated by model-based and model-free computational mechanisms, respectively. In model-based mechanisms [24], improvement in motor performance is guided by an internal model of the environment; the internal model is learned based on the experience of error between the model-predicted and the actual sensory consequences of

motor commands. In contrast, model-free mechanisms directly guide the selection of control commands by learning which commands lead to successful outcomes through trial and error, and thus are slower. Model-based mechanisms are computationally complex but flexible, unlike model-free mechanisms. It is important to investigate whether similar computational mechanisms also underlie BMI learning. For example, perhaps existing neural repertoire re-association is more consistent with model-based mechanisms, and thus faster and individual neuron learning is more in line with model-free mechanisms involved in skill tasks.

### FEEDBACK AND CONTROL PATHWAY MANIPULATIONS

BMIs can help study the role of sensory feedback in control and learning by manipulating it Fig. 2b. A recent BMI study used a rate independent point-process decoder to independently manipulate the rates of control and feedback without changing the decoder Fig. 2b and Box 1. Increasing the control rate even when the feedback rate was unchanged significantly improved control, and increasing the feedback rate further facilitated control, suggesting a hybrid of internal-model-based feed forward and feedback control strategies in BMIs, as has been suggested for natural motor control. Another study found evidence of an internal model in BMI control within neural activity, which could compensate for sensory feedback delays. BMIs can also dissociate the role of visual and proprioceptive feedback. One study showed that when the arm is passively moved congruently with the BMI movement, performance is improved by this addition of proprioceptive to visual

feedback. Prior studies have also developed bidirectional BMIs in which intracortical microstimulation of the somatosensory [25] cortex provides artificial tactile feedback to guide BMI control in Table 1. Finally, recent work demonstrates BMI control of the native limbs with muscular or spinal stimulation, which may also enable manipulating the control pathway.

### BMIS FOR RESTORATION OF LOST EMOTIONAL FUNCTION

In its general form, we can envision a mood BMI for electrical stimulation to consist of two main components Fig. 3a a neural decoder of a relevant mood state Fig. 3b and a feedback controller Fig. 3c that takes the decoded mood as feedback to adjust the stimulation parameters. This vision bears similarities to motor BMIs that need to control a cursor toward a desired target position within physical space Fig. 1. Instead of decoding movement, mood BMIs would decode a mood state and control it toward a desired therapeutic target within the abstract multidimensional space of mood Fig. 1 and Fig. 3. However, developing mood BMIs involves distinct

decoding challenges in Fig. 3b and Table 1 and requires solving a new modeling problem: how stimulation changes the activity of distributed multisite brain networks related to mood Fig. 3c; also see Table 1 and Fig

### MOOD DECODERS

Mood representation involves multiple distributed brain sites whose functional organization is not as well understood. Moreover, unlike movements that can be measured continuously in time, mood cannot be behaviorally measured frequently, resulting in sparse measurements at discrete times for example, filling a questionnaire a few times per day). Together, these aspects create a challenging machine learning problem in training the decoder within high-dimensional neural recordings but with only sparse mood measurements. Given these challenges, noninvasive neuroimaging modalities [26] [27] with high spatial re

important in guiding the sites for read-out and write-in in mood BMIs. These studies have shown regional changes induced by emotional stimuli in healthy participants identified altered resting-state activity that may be related to neural circuit dysfunction or treatment effects in mood disorders, and guided the open-loop stimulation sites. In terms of decoding, while neuro imaging can detect average differences between groups, a BMI would need to track mood symptom variations and stimulation responses in an individual, which can change rapidly. Thus mood decoding will benefit from electrophysiological modalities. Intracranial EEG—often in the form of electrocorticography provides an opportunity to access multiple mood-relevant brain sites at high temporal resolution and with potential for implantable devices.

Despite machine learning challenges, a recent study achieved decoding of mood variations in individuals by developing a novel methodology. In this study, multisite intracranial EEG [28] was continuously recorded from people with epilepsy over multiple days, thus creating a high-dimensional continuous neural feature space. Simultaneously, sparse aggregate mood scores were obtained on average twice per day using a validated. The study designed a new region-selection method that identified a small subset of distributed mood-relevant regions that were sufficient for decoding. Within these smaller networks and unsupervised with respect to mood, the method further reduced dimension by training a dynamic model [29] Box 1 to describe network activity in terms of a low-dimensional latent state, which was then regressed to mood scores in Fig. 3b. The decoder first estimated the low-dimensional state and then used this to successfully predict mood variations in each individual participant.



Published by :

<http://www.ijert.org>

A key observation in the mood decoding study was that personalization is needed because there were variabilities between participants in the selected networks and decoder parameters. Two additional recent studies are also consistent with this observation. First, one study aimed to find a common neural marker across individuals that correlated with mood within the same datasets [30]. This study found that the variance of amygdala hippocampus beta-frequency coherence was correlated with mood in about 62% of participants; the participants who displayed this correlation exhibited higher anxiety levels. Second, another study found that stimulating the orbitofrontal cortex produces mood improvements that are specific to people with moderate-to-severe depression symptoms (a trait-dependent response). These studies suggest that personalized decoders that aggregate information across space and time are needed for reliable mood decoding that goes beyond a single biomarker correlations and works in every individual despite the inter-individual variability's in mood disorders Box 2.

Another question is which brain sites are needed for mood decoding. In the decoding study, despite personalized

decoder training, there were commonalities across individuals. The decoders consistently recruited the limbic regions and largely failed without them. Moreover, in about 60% of the participants, the method selected the orbitofrontal cortex for decoding despite the many available regions to choose from. Interestingly, an independent study showed that orbitofrontal open-loop stimulation can acutely improve mood. These studies confirm the importance of limbic regions for decoding consistent with neuro imaging studies and suggest an important role for orbitofrontal cortex [31] [32]. Future chronic studies will be essential in further investigating the decoding sites.

Recent electrophysiological studies used a momentary mood measure to track acute mood-state changes that can happen rapidly in response to stimulation for symptom control. The BMI design provided here can be generalized to other mood measures to study the feasibility of their decoding and control. Future studies should investigate whether a mood BMI aimed at symptom control can change the baseline level of mood or whether BMIs should be trained on different or more sustained measures of mood. Finally, it is important to study whether the recent results obtained within epilepsy populations generalize to other populations.



<b>Table 1. Differences between Motor and Mood BMI</b>		
<b>Challenge</b>	<b>Motor BMI</b>	<b>Mood BMI</b>
<b>Neural Measurement</b>	Motor Cortical networks(including premotor, primary motor, and posterior parietal cortex)	Distributed multisite corticolimbic networks, whose functional organization is not as well characterized
<b>Behavioral Measurements</b>	Continuous in time(movements)	Infrequent and discrete in time(for example, self reports)
<b>Time Scale of Behavioral Dynamics</b>	Millisecond(Movements Dynamics)	Minutes to days and longer(mood Dynamics)
<b>Behavioral Assessment</b>	Relatively easy and accurate	Difficult and less accurate, with self-reports being common measurement instruments
<b>Modeling the effects of direct brain stimulation</b>	In general not needed, unless artificial sensory feedback is provided in bidirectional BMIs	Needed, and should be modeled across distributed multisite corticolimbic networks



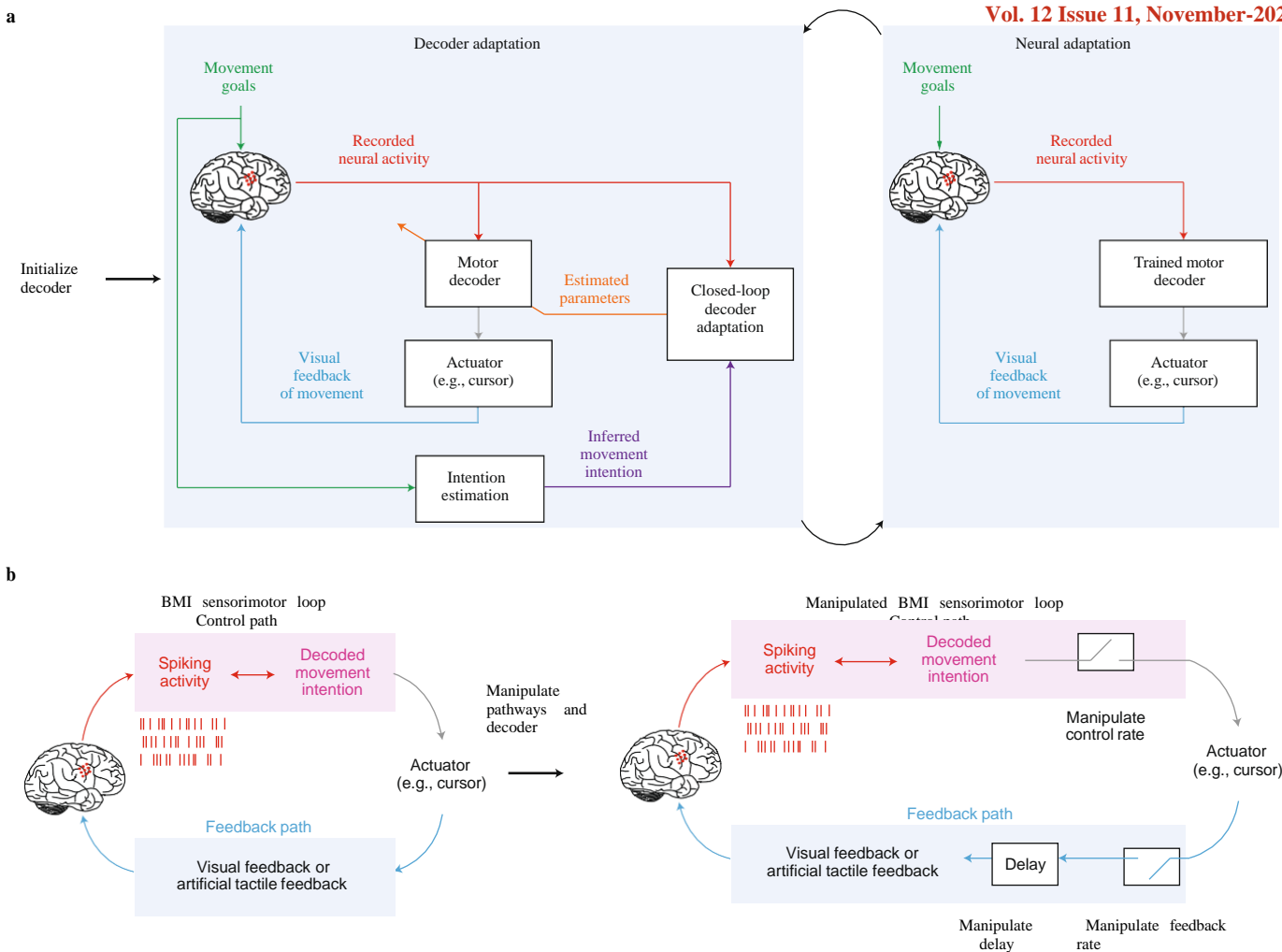


Fig. 2 a,b,c Motor BMIs for functional restoration and scientific discovery.

**Box 3 | Closed-loop adaptation in motor BMIs and the optimal feedback control model**

To adapt the decoder parameters in real-time BMI control, the intended movement of the user should be estimated. Various intention estimation methods have been devised guided by the closed-loop control view. Since the user receives visual feedback of the decoded position at each time, one method posits that the optimal strategy is to intend to go straight toward the instructed target from this position and stop there. The velocity intention at each time is estimated by rotating [33] the cursor’s decoded velocity vector toward the target while keeping its magnitude (i.e., speed) unchanged and by equating it to zero at the target. This method has improved the performance of Kalman filter BMI decoders. Another method based on the assumption of straight reaches is to assist the user toward the target either by adding to the decoded velocity vector an assistive vector that directs toward the target or by subtracting from the decoded vector a vector perpendicular to the straight line to the target.

An alternative approach to intention estimation is to build explicit optimal feedback control (OFC) [34] models of BMIs, inspired by the OFC models of the natural sensorimotor system. OFC estimates intention by positing that the brain (controller) selects the next control command based on visual feedback of the current movement state and an internal model of movement and by minimizing a cost function that quantifies the movement goals (for example, reaching a target position and stopping there). Given its model-based nature, OFC can incorporate different actuator dynamics and estimate both the direction of velocity intention and its speed, a capability that has improved the performance of point process BMI decoders. In addition to intention estimation, OFC models have also been used to enable goal-directed decoding by predicting the movement targets and combining them with neural activity during movement execution.

## DEVELOPING FEEDBACK-CONTROLLER

Unlike motor BMIs in which the controller is the brain mood BMIs need an external controller Figs. 1b and Fig. 3 with Table 1. This controller needs to change the stimulation pattern to modulate neural activity that is casually related to mood [37] [38]. Thus building a controller requires learning an input–output model that describes how changes in stimulation parameters (input) modulate neural activity output Fig.3c, a problem termed system identification.

One system identification approach to explore is to develop bio-physical models for neuropsychiatric disorders to gain a mechanistic understanding, just as these models have been built to explain disease- specific population-level effects in PD and epilepsy. Biophysical models, however, are often for disease-specific brain regions and require some knowledge of their functional organization (for example, cortex–basal ganglia networks in PD). Thus, generalizing them to and across neuropsychiatric disorders may be difficult, at least initially, given the involvement of different multi region brain networks whose functional organization is not well characterized and do not aim to predict the neural response observed in an individual, which is needed for personalized mood BMIs. This is because their large number of nonlinear parameters may make it difficult to fit to data for each individual patient and to design controllers. Given these challenges, an alternative system identification approach to explore is to train simplified input–output models using data obtained from each patient to facilitate BMI control. Input– output training data can be collected by stimulating the brain and recording the neural response. Within computer simulations, simplified linear transfer function and autoregressive models have been used to design controllers [5]. Recent computer simulation work has described the network response to stimulation in terms of a low-dimensional latent state with dynamic latent state-space models Box 1. A critical step in a data-driven approach is to collect informative input–output datasets by designing stimulation waveforms that both sufficiently excite the network activity and are clinically safe. To do so, a theoretical study proposed a new waveform in the form of pulse trains whose amplitude and frequency were changed stochastically between two levels. Developing and validating data driven input–output models of brain network response to stimulation [36] needs to be achieved and is a critical future direction. Such models may also guide mechanistic biophysical modeling. Once personalized input–output models are built, future model-based feedback controllers can be developed. Computer simulations have explored proportional-integral controllers, adaptive minimum

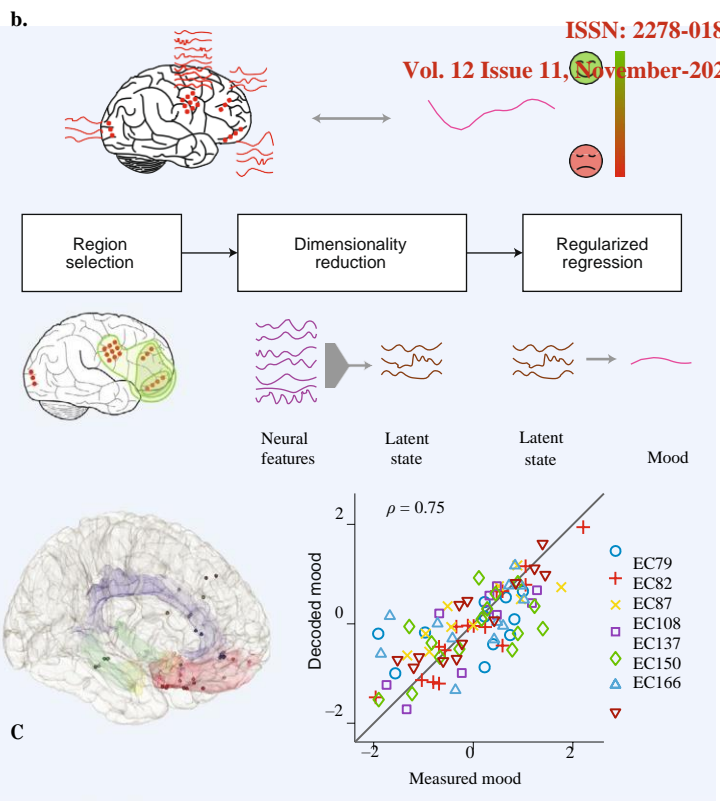
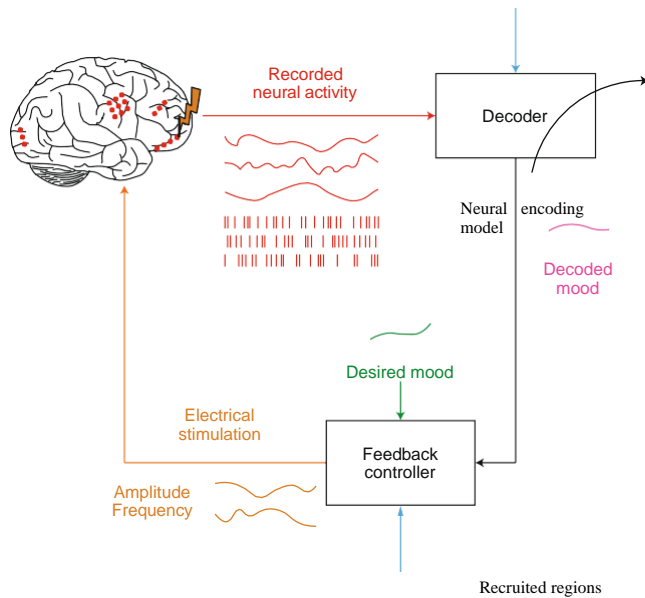
variance controllers, and model-predictive optimal feedback controllers. Also, insights from implementing model-based controllers [37] in other domains, for example in modulating brain activity with anesthetics, may guide their development in mood BMIs.

Incorporating neural adaptation and learning The success of motor BMIs builds on the ability to learn to control them through neural adaptation of the system section.

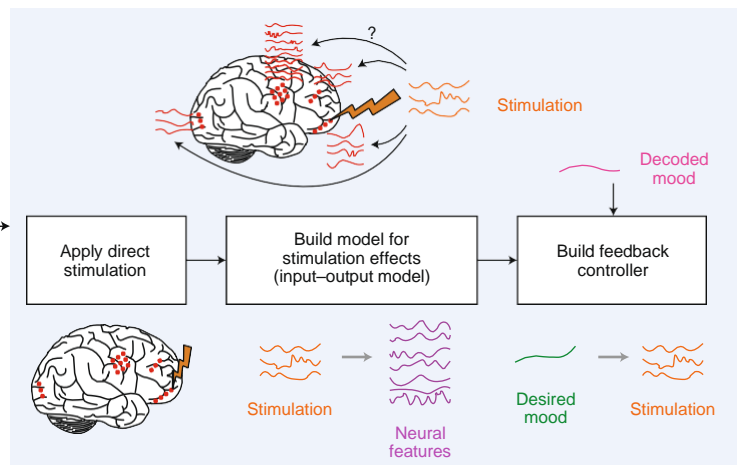
It is driven by sensory feedback of the decoded movement state. In what we have described so far for mood BMIs, explicit feedback of the decoded mood state is provided to the external stimulation controller rather than the user. Arguably, by also providing this feedback to users Fig. 1b similarly to providing feed- back of decoded movement they can become active participants in the mood BMI loop rather than a subconscious plant; they may learn to skillfully contribute to controlling their own mood state. This process would be a special instance of neuro feedback training and may provide an optional separate or simultaneous mode of therapy within mood BMIs.

In neuro feedback training, feedback of neural activity in the form of visual or auditory cues is provided to participants so that they can self-regulate the activity. Without electrical stimulation, successful self-regulation of activity in emotion-related brain regions such as anterior insula, amygdala, or orbitofrontal cortex with neurofeed- back of functional MRI or (functional MRI guided) EEG has led to improved control [39] of negative emotions, improved mood in patients with depression, and reduced stress. However, there is inter-individual variability in outcomes, with some individuals failing to learn to self-regulate, which highlights the benefit for personalization and combination with other therapies such as stimulation. Instead of localized regional activity, asking participants to modulate an intuitive mood state that is ‘decoded’ from network activity has been suggested to benefit training. This is precisely how neurofeedback works in motor BMIs, which decode a global movement intention state as feedback to guide neural adaptation Figs. 2a and 2b.

Mood BMIs may thus also provide neuro feedback training as an optional complementary mode of therapy [40] [41]. Electrical stimulation based on a decoded mood could provide a continuous mode of therapy aimed at symptom control. Neurofeedback training can then be provided intermittently to improve efficacy by driving neural adaptation and learning at longer time scales, though an important question is how to combine it with electrical stimulation. Some motor BMI findings in combining decoder and neural adaptations may guide the way. For example, perhaps adaptive controllers [42] are needed to track neural adaptation driven by neurofeedback and stimulation-induced plasticity and to guide stimulation [43]. Also, the time-scale and extent of controller adaptation may need to be carefully adjusted to enable some acute symptom alleviation with electrical stimulation yet still engage neural adaptation with neurofeedback training to learn skilled mood control at slower time-scales.



Input-output model



**Fig. 3 a,b,c** Steps toward realizing mood BMIs for functional restoration and scientific discovery. **a**, Mood BMIs for electrical stimulation would require developing two key elements: a mood decoder and a stimulation feedback-controller

#### Box 4 | Animal models and ethical considerations

Despite their inherent limitations, developing animal models<sup>90</sup> will provide a valuable test bed to prototype decoding and control technologies for mood BMIs by offering the ability to simultaneously record and manipulate using electrical and optogenetic techniques [44] [45]. Further, developing animal models that meet the criteria of validity will be important for studying the neural basis of emotions, especially to gain a mechanistic circuit-level understanding. Rodent models have shown promise in studying the limbic system, such as the neural circuits of anxiety, with findings that have paralleled those in humans. It is important for future work to develop animal models that reproduce the depression-like phenotype observed in humans.

The ethical considerations for human mood BMIs are also extraordinary and should be closely guided by neuroethicists. Mood BMI studies in humans should be performed with strict selection criteria similar to open-loop stimulation [46] studies, or within epilepsy populations with implantations already in place. Any studies toward scientific discovery should be further guided by the task designs and perturbations used in previous neuroimaging and neurofeedback training studies. More broadly, establishing the criteria for the use and application of such BMIs requires much future work and education [47]. BMIs must respect and preserve people's privacy, identity, agency and equality.

## CONCLUSIONS

BMIs produce closed-loop control systems that are instruments for scientific research and functional restoration. The enormous amount of research conducted over the past 20 years in animal models and early clinical studies has shown that motor BMIs have the potential to help paralyzed people regain function while also expanding our knowledge of the brain underpinnings of control and learning. We outlined a way toward expanding BMIs to the emerging field of neuropsychiatric illnesses using the lessons learned from motor BMIs, the extensive body of work in psychology and neuro imaging that explores emotional processing, closed-loop control principles, and recent advancements.

## REFERENCES

### MOOD BMIS FOR STUDYING THE NEURAL MECHANISMS OF EMOTION REGULATION

By choosing the proper emotion-regulatory activities, one can start, change, and stop the trajectory of an emotion within its multidimensional space. Developing mood BMIs may benefit from understanding the brain mechanisms underpinning emotion regulation. The use of mood BMIs as scientific instruments that can record from dispersed corticolimbic networks, disrupt neuro feedback, and change the amount and location of electrical stimulation is another crucial future direction for advancing this understanding. The creation of animal models and ethical guidelines is also essential for this and mood BMIs to occur (Box 4). Our knowledge of emotion regulation and its brain underpinnings has considerably increased as a result of prior psychological and neuroimaging research, and many implicit and explicit control mechanisms have been proposed. By learning to reinterpret the meaning of a stimulus, people can lessen negative emotion. For instance, they might perceive a distant scream as signifying exhilaration rather than panic [48].

Given the aforementioned parallels between computational pathways in motor learning it is possible that some observations in motor learning could yield testable ideas for upcoming mood BMI investigations of emotion regulation. For instance, it's possible that the brain mechanisms driving model-based reappraisal are comparable to the neuronal re-association seen in the previously stated motor BMI learning. A distinct movement intent is linked with an existing pattern of neural activity in the latter situation to modify the motor reaction, whereas in the former, a different meaning is connected with the same stimulus to change the emotional response [49]. Additionally, prefrontal areas have been linked to both suggesting that the cognitive control processes in reappraisal may be comparable to those in motor learning. Lastly, several areas connected to mood, such as the orbitofrontal cortex associated with reward-driven learning, which is also important for motor BMIs. As a result, BMIs have the potential to shed light on brain processes underlying learning and control in motivated behavior that go much beyond the motor and well into the emotional domains.

- [1] Aggarwal V, Mollazadeh M, Davidson AG, Schieber MH and Thakor NV. 2013. State-based decoding of hand and finger kinematics using neuronal ensemble and LFP activity during dexterous reach-to-grasp movements. *Journal of Neurophysiology* 109 (12): 3067–3081.
- [2] Ajiboye AB, Willett FR, Young DR, Memberg WD, Murphy BA, Miller JP, and others. 2017. Restoration of reaching and grasping movements through brain-controlled muscle stimulation in a person with tetraplegia: a proof-of-concept demonstration. *The Lancet*.
- [3] Ang KK, Chua KSG, Phua KS, Wang C, Chin ZY, Kuah CWK, and others. 2015. A randomized controlled trial of EEG-based motor imagery brain-computer interface robotic rehabilitation for stroke. *Clinical EEG and Neuroscience* 46 (4): 310–320.
- [4] Athalye VR, Ganguly K, Costa RM and Carmena JM. 2017. Emergence of Coordinated Neural Dynamics Underlies Neuroprosthetic Learning and Skillful Control. *Neuron* 93 (4): 955–970.
- [5] Bacher D, Jarosiewicz B, Masse NY, Stavisky SD, Simeral JD, Newell K, and others. 2015. Neural point-and-click communication by a person with incomplete locked-in syndrome. *Neurorehabilitation and Neural Repair* 29 (5): 462–471.
- [6] Balasubramanian K, Vaidya M, Southerland J, Badreldin I, Eleryan A, Takahashi K, and others. 2017. Changes in cortical network connectivity with long-term brain-machine interface exposure after chronic amputation. *Nature Communications* 8 (1): 1796.
- [7] Bansal AK, Vargas-Irwin CE, Truccolo W and Donoghue JP. 2011. Relationships among low-frequency local field potentials, spiking activity, and three-dimensional reach and grasp kinematics in primary motor and ventral premotor cortices. *Journal of Neurophysiology* 105 (4): 1603–1619.
- [8] Bensmaia SJ and Miller LE. 2014a. Restoring sensorimotor function through intracortical interfaces: progress and looming challenges. *Nature Reviews Neuroscience* 15: 313.
- [9] Bensmaia SJ and Miller LE. 2014b. Restoring sensorimotor function through intracortical interfaces: progress and looming challenges. *Nat Rev Neurosci* 15 (5): 313–325.
- [10] Berger TW, Hampson RE, Song D, Goonawardena A, Marmorelis VZ and Deadwyler SA. 2011. A cortical neural prosthesis for restoring and enhancing memory. *Journal of neural engineering* 8 (4): 046017.
- [11] Birbaumer N, Ghanayim N, Hinterberger T, Iversen I, Kotchoubey B, Kubler A, and others. 1999. A spelling device for the paralysed. *Nature* 398 (6725): 297–298.
- [12] Birbaumer N, Hinterberger T, Kubler A, Kaiser J, Kotchoubey B and Wolpaw J. 2000. The thought-translation device: An update. *Psychophysiology* 37: S28–S28.
- [13] Boto E, Holmes N, Leggett J, Roberts G, Shah V, Meyer SS, and others. 2018. Moving magnetoencephalography towards real-world applications with a wearable system. *Nature* 555: 657.
- [14] Bouchard KE, Mesgarani N, Johnson K and Chang EF. 2013. Functional organization of human sensorimotor cortex for speech articulation. *Nature* 495 (7441): 327–332.
- [15] Bouton CE, Shaikhouni A, Annetta NV, Bockbrader MA, Friedenberg DA, Nielson DM, and others. 2016. Restoring cortical control of functional movement in a human with quadriplegia. *Nature* 533 (7602): 247–250.
- [16] Brumberg JS, Wright EJ, Andreasen DS, Guenther FH and Kennedy PR. 2011. Classification of intended phoneme production from chronic intracortical microelectrode recordings in speech-motor cortex. *Frontiers in neuroscience* 5.
- [17] Buch E, Weber C, Cohen LG, Braun C, Dimyan MA, Ard T, and others. 2008. Think to move: A neuromagnetic brain-computer interface (BCI) system for chronic stroke. *Stroke* 39 (3): 910–917.
- [18] Bundy DT, Pahwa M, Szrama N and Leuthardt EC. 2016. Decoding three-dimensional reaching movements using electrocorticographic signals in humans. *Journal of neural engineering* 13 (2): 026021.
- [19] Bundy DT, Zellmer E, Gaona CM, Sharma M, Szrama N, Hacker C, and others. 2014. Characterization of the effects of the human dura on macro- and micro-electrocorticographic recordings. *Journal of neural engineering* 11 (1): 016006.
- [20] Buzsáki G, Anastassiou CA and Koch C. 2012. The origin of extracellular fields and currents—EEG, ECoG, LFP and spikes. *Nature Reviews Neuroscience* 13 (6): 407–420.
- [21] Capogrosso M, Milekovic T, Borton D, Wagner F, Moraud EM, Mignardot J-B, and others. 2016. A brain–spine interface alleviating gait deficits after spinal cord injury in primates. *Nature* 539 (7628): 284.
- [22] Carmena JM, Lebedev MA, Crist RE, O’Doherty JE, Santucci DM, Dimitrov DF, and others. 2003. Learning to control a brain-machine interface for reaching and grasping by primates. *PLoS Biol* 1 (2): E42.
- [23] Carmena JM, Lebedev MA, Henriquez CS and Nicolelis MA. 2005. Stable ensemble performance with single-neuron variability during reaching movements in primates. *The Journal of Neuroscience* 25 (46): 10712–10716.
- [24] Chao ZC, Nagasaka Y and Fujii N. 2010. Long-term asynchronous decoding of arm motion using electrocorticographic signals in monkeys. *Front. Neuroeng* 3 (3).
- [25] Chapin JK, Moxon KA, Markowitz RS and Nicolelis MA. 1999. Real-time control of a robot arm using simultaneously recorded neurons in the motor cortex. *Nature Neuroscience* 2 (7): 664–670.
- [26] Chaudhary U, Xia B, Silvoni S, Cohen LG and Birbaumer N. 2017. Brain–computer interface–based communication in the completely locked-in state. *PLoS Biology* 15 (1): e1002593.
- [27] Chen X, Wang Y, Nakanishi M, Gao X, Jung T-P and Gao S. 2015. High-speed spelling with a noninvasive brain–computer interface. *Proceedings of the National Academy of Sciences* 112 (44): E6058–E6067.
- [28] Cheng M, Gao X, Gao S and Xu D. 2002. Design and implementation of a brain-computer interface with high transfer rates. *IEEE Transactions on Biomedical Engineering* 49 (10): 1181–1186.
- [29] Chestek CA, Batista AP, Santhanam G, Byron MY, Afshar A, Cunningham JP, and others. 2007. Single-neuron stability during repeated reaching in macaque premotor cortex. *The Journal of Neuroscience* 27 (40): 10742–10750.
- [30] Chestek CA, Gilja V, Nuyujukian P, Foster JD, Fan JM, Kaufman MT, and others. 2011. Long-term stability of neural prosthetic control signals from silicon cortical arrays in rhesus macaque motor cortex. *Journal of neural engineering* 8 (4): 045005.
- [31] Clancy KB, Koralek AC, Costa RM, Feldman DE and Carmena JM. 2014. Volitional modulation of optically recorded calcium signals during neuroprosthetic learning. *Nature Neuroscience* 17 (6): 807–809.
- [32] Cohen D and Nicolelis MA. 2004. Reduction of single-neuron firing uncertainty by cortical ensembles during motor skill learning. *Journal of neuroscience* 24 (14): 3574–3582.
- [33] Collinger JL, Wodlinger B, Downey JE, Wang W, Tyler-Kabara EC, Weber DJ, and others. 2012. High-performance neuroprosthetic control by an individual with tetraplegia. *The Lancet*.
- [34] Crone NE, Miglioretti DL, Gordon B, Sieracki JM, Wilson MT, Uematsu S, and others. 1998. Functional mapping of human sensorimotor cortex
- [35] with electrocorticographic spectral analysis. I. Alpha and beta event-related desynchronization. *Brain* 121 ( Pt 12): 2271–2299.
- [36] Daly I, Faller J, Scherer R, Sweeney-Reed CM, Nasuto SJ, Billinger M, and others. 2014. Exploration of the neural correlates of cerebral palsy for sensorimotor BCI control. *Frontiers in Neuroengineering* 7 (20).
- [37] Daly JJ, Cheng R, Rogers J, Litinas K, Hrovat K and Dohring M. 2009. Feasibility of a new application of noninvasive brain computer interface (BCI): A case study of training for recovery of volitional motor control after stroke. *Journal of Neurologic Physical Therapy* 33 (4): 203.
- [38] Daly JJ and Wolpaw JR. 2008. Brain-computer interfaces in neurological rehabilitation. *Lancet Neurol* 7 (11): 1032–1043.
- [39] Deadwyler SA, Hampson RE, Song D, Opris I, Gerhardt GA, Marmorelis VZ, and others. 2017. A cognitive prosthesis for memory facilitation by closed-loop functional ensemble stimulation of hippocampal neurons in primate brain. *Experimental Neurology* 287: 452–460.
- [40] Do AH, Wang PT, King CE, Chun SN and Nenadic Z. 2013. Brain-computer interface controlled robotic gait orthosis. *Journal of NeuroEngineering and Rehabilitation* 10 (1): 111.
- [41] Donati AR, Shokur S, Morya E, Campos DS, Moiola RC, Gitti CM, and others. 2016. Long-term training with a brain-machine interface-based gait protocol induces partial neurological recovery in paraplegic patients. *Sci Rep* 6: 30383.

- [42] Engelhard B, Ozeri N, Israel Z, Bergman H and Vaadia E. 2013. Inducing gamma oscillations and precise spike synchrony by operant conditioning via brain-machine interface. *Neuron* 77 (2): 361–375.
- [43] Ethier C, Oby ER, Bauman MJ and Miller LE. 2012. Restoration of grasp following paralysis through brain-controlled stimulation of muscles. *Nature* 485 (7398): 368–371.
- [44] Evarts EV. 1968. Relation of pyramidal tract activity to force exerted during voluntary movement. *Journal of Neurophysiology* 31 (1): 14–27.
- [45] Ezzyat Y, Wanda PA, Levy DF, Kadel A, Aka A, Pedisich I, and others. 2018. Closed-loop stimulation of temporal cortex rescues functional networks and improves memory. *Nature Communications* 9 (1): 365.
- [46] Fagg AH, Ojakangas GW, Miller LE and Hatsopoulos NG. 2009. Kinetic trajectory decoding using motor cortical ensembles. *IEEE Trans Neural Syst Rehabil Eng* 17 (5): 487–496.
- [47] Farwell LA and Donchin E. 1988. Talking off the top of your head: Toward a mental prosthesis utilizing event-related brain potentials. *Electroencephalography and Clinical Neurophysiology* 70 (6): 510–523.
- [48] Fetz EE. 1969. Operant conditioning of cortical unit activity. *Science* 163 (3870): 955.
- [49] Flesher SN, Collinger JL, Foldes ST, Weiss JM, Downey JE, Tyler-Kabara EC, and others. 2016. Intracortical microstimulation of human somatosensory cortex. *Science Translational Medicine* 8 (361): 361ra141–361ra141.
- [50] Flint RD, Ethier C, Oby ER, Miller LE and Slutzky MW. 2012a. Local field potentials allow accurate decoding of muscle activity. *Journal of Neurophysiology* 108 (1): 18–24.

#### ACKNOWLEDGEMENTS

This research received Laboratory infrastructure, research and design facility from Computer Engineering department, Mahila Engineering College Ajmer and Bhagwant University Ajmer.

#### Competing interests

The author declares no competing financial interests.