



Towards neural co-processors for the brain: combining decoding and encoding in brain–computer interfaces

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The field of brain–computer interfaces is poised to advance from the traditional goal of controlling prosthetic devices using brain signals to combining neural decoding and encoding within a single neuroprosthetic device. Such a device acts as a ‘co-processor’ for the brain, with applications ranging from inducing Hebbian plasticity for rehabilitation after brain injury to reanimating paralyzed limbs and enhancing memory. We review recent progress in simultaneous decoding and encoding for closed-loop control and plasticity induction. To address the challenge of multi-channel decoding and encoding, we introduce a unifying framework for developing brain co-processors based on artificial neural networks and deep learning. These ‘neural co-processors’ can be used to jointly optimize cost functions with the nervous system to achieve desired behaviors ranging from targeted neuro-rehabilitation to augmentation of brain function.

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Introduction

A brain–computer interface (BCI) [1–4] is a device that can (a) allow signals from the brain to be used to control devices such as prosthetics, cursors or robots, and (b) allow external signals to be delivered to the brain through neural stimulation. The field of BCIs has made enormous strides in the past two decades. The genesis of the field can be traced to early efforts in the 1960s by neuroscientists such as Fetz [5[•]] who studied operant conditioning in monkeys by training them to control the movement of a needle in an analog meter by modulating the firing rate of a neuron in their motor cortex. Others such as Delgado and Vidal explored techniques for neural decoding and

stimulation in early versions of neural interfaces [6[•],7]. After a promising start, there was a surprising lull in the field until the 1990s when, spurred by the advent of multi-electrode recordings as well as fast and cheap computers, the field saw a resurgence under the banner of brain–computer interfaces (BCIs; also known as brain–machine interfaces and neural interfaces) [1,2].

A major factor in the rise of BCIs has been the application of increasingly sophisticated machine learning techniques for decoding neural activity for controlling prosthetic arms [8,9,10[•]], cursors [11,12,13[•],14,15,16^{••}], spellers [17,18] and robots [19–22]. Simultaneously, researchers have explored how information can be biomimetically or artificially encoded and delivered via stimulation to neuronal networks in the brain and other regions of the nervous system for auditory [23], visual [24], proprioceptive [25], and tactile [26,27,28[•],29,30] perception.

Building on these advances in neural decoding and encoding, researchers have begun to explore bi-directional BCIs (BBCIs) which integrate decoding and encoding in a single system. In this article, we review how BBCIs can be used for closed-loop control of prosthetic devices, reanimation of paralyzed limbs, restoration of sensorimotor and cognitive function, neuro-rehabilitation, enhancement of memory, and brain augmentation.

Motivated by this recent progress, we propose a new unifying framework for combining decoding and encoding based on ‘neural co-processors’ which rely on artificial neural networks and deep learning. We show that these ‘neural co-processors’ can be used to jointly optimize cost functions with the nervous system to achieve goals such as targeted rehabilitation and augmentation of brain function, besides providing a new tool for testing computational models and understanding brain function [31].

Simultaneous decoding and encoding in BBCIs

Closed-loop prosthetic control

Consider the problem of controlling a prosthetic hand using brain signals. This involves (1) using recorded neural responses to control the hand, (2) stimulating somatosensory neurons to provide tactile and proprioceptive feedback, and (3) ensuring that stimulation artifacts do not corrupt the recorded signals being used to control the hand. Several artifact reduction methods have been

proposed for (3) – we refer the reader to Refs. [32–34]. We focus here on combining (1) decoding with (2) encoding.

Most state-of-the-art decoding algorithms for intracortical BCIs are based on a linear decoder such as the Kalman filter. Typically, the state vector \mathbf{x} for the Kalman filter is chosen to be a vector of kinematic quantities to be estimated, such as hand position, velocity, and acceleration. The likelihood (or measurement) model for the Kalman filter specifies how the kinematic vector \mathbf{x}_t at time t relates linearly (via a matrix B) to the measured neural activity vector \mathbf{y}_t :

$$\mathbf{y}_t = B\mathbf{x}_t + \mathbf{m}_t$$

while a dynamics model specifies how \mathbf{x}_t linearly changes (via matrix A) over time:

$$\mathbf{x}_t = A\mathbf{x}_{t-1} + \mathbf{n}_t$$

\mathbf{n}_t and \mathbf{m}_t are zero-mean Gaussian noise processes. The Kalman filter computes the optimal estimates for kinematics \mathbf{x}_t (both mean and covariance) given current and all past neural measurements.

One of the first studies to combine decoding and encoding was by O’Doherty *et al.* [35] who showed that stimulation of somatosensory cortex could be used to instruct a rhesus monkey which of two targets to move a cursor to; the cursor was subsequently controlled using a BCI based on linear decoding to predict the X-coordinate and Y-coordinate of the cursor. A later study by the same group [36**] demonstrated true closed-loop control. Monkeys used a BCI based on primary motor cortex (M1) recordings and Kalman-filter-based decoding to actively explore virtual objects on a screen with artificial tactile properties. The monkeys were rewarded if they found the object with particular artificial tactile properties. During brain-controlled exploration of an object, the associated tactile information was delivered to somatosensory cortex (S1) via intracortical stimulation. Tactile information was encoded as a high-frequency biphasic pulse train (200 Hz for rewarded object, 400 Hz for others) presented in packets at a lower frequency (10 Hz for rewarded, 5 Hz for unrewarded objects). Because stimulation artifacts masked neural activity for 5–10 ms after each pulse, an interleaved scheme of alternating 50 ms recording and 50 ms stimulation was used. The monkeys were able to select the desired target object within a second or less based only on its tactile properties as conveyed through stimulation.

Klaes *et al.* [37] have also demonstrated that a monkey can utilize intracortical stimulation in S1 to perform a match-to-sample task where the goal is to move a virtual arm and

find a target object that delivers stimulation similar to a control object. In their experiment, the monkey controlled a virtual arm using intracortical recordings from posterior parietal cortex and a Kalman-filter-based decoding scheme where the Kalman filter’s state was defined as the virtual hand’s position, velocity and acceleration in three dimensions. The encoding algorithm involved stimulating S1 via three closely located electrodes using a 300 Hz biphasic pulse train for up to one second while the virtual hand held the object. After training, the monkey was able to move the virtual hand to the correct target with success rates ranging from approximately 70% to more than 90% over the course of eight days (chance level was 50%).

Finally, Flesher *et al.* [38**] have recently shown that a paralyzed patient can use a bidirectional BCI for closed-loop control of a prosthetic hand in a continuous force matching task. Control signals were decoded from multi-electrode recordings in M1 using a linear decoder that mapped M1 firing rates to movement velocities of the robotic arm. Initial training data for the linear decoder was obtained by asking the subject to observe the robotic hand performing hand shaping tasks such as ‘pinch’ (thumb/index/middle flexion–extension), ‘scoop’ (ring/pinky flexion/extension) or grasp (all finger flexion) and recording M1 firing rates, followed by a second training phase involving computer-assisted control to fine tune the decoder weights. The subject then performed a 2D force matching task with the robotic hand using the trained decoder to pinch, scoop or grasp a foam object either gently or firmly while using stimulation of S1 to get feedback on the force applied. The encoding algorithm linearly mapped torque sensor data from the robotic hand’s finger motors to pulse train amplitude of those stimulating electrodes that previously elicited percepts on the corresponding fingers of the subject. The researchers showed that the subject was able to continuously control the flexion/extension of the pinch and scoop dimensions while evaluating the applied torque based on force feedback from S1 stimulation. The success rate for pinch, scoop, or grasp with gentle or firm forces was significantly higher with stimulation feedback compared to feedback from vision alone.

Reanimating paralyzed limbs

Rather than controlling a prosthetic limb, BBCIs can also be used to control electrical stimulation of muscles to restore movement in a paralyzed limb. Moritz *et al.* [39**] demonstrated this approach in two monkeys by translating the activity of single motor cortical neurons into electrical stimulation of wrist muscles to move a cursor on a computer screen. The decoding scheme involved operant conditioning to volitionally control activity of a motor cortical neuron to initially move a cursor into a target. After training, the activity from the motor cortical neuron was converted into electrical stimuli which was delivered to the monkey’s temporarily paralyzed wrist muscles (this type of stimulation is called functional electrical stimulation, or FES). Flexor FES current

was set to be proportional to the rate above a threshold ($0.8 \times [\text{firing rate} - 24]$ with a maximum of 10 mA), and extensor FES was inversely proportional to the rate below a second threshold ($0.6 \times [12 - \text{firing rate}]$ with a maximum of 10 mA). Both monkeys were able to modulate the activity of cortical neurons to control their paralyzed wrist muscles and move a manipulandum to acquire five targets. Ethier *et al.* [40] extended these results to grasping and moving objects using a linear decoder with a static nonlinearity applied to about 100 neural signals from M1.

Extending the approach to humans, Bouton *et al.* [41**] showed that a quadriplegic man with a 96-electrode array implanted in the hand area of the motor cortex could use cortical signals to electrically stimulate muscles in his paralyzed forearm and produce six different wrist and hand motions. For decoding, six separate support vector machines were applied to mean wavelet power features extracted from multiunit activity to select one out of these six motions. The encoding scheme involved activating the movement associated with the highest decoder output using an electrode stimulation pattern previously calibrated to evoke that movement. Surface electrical stimulation was delivered as monophasic rectangular pulses at 50 Hz pulse rate and 500 μ s pulse width, with stimulation intensity set to a piecewise linear function of decoder output. These results were extended to multi-joint reaching and grasping movements by Ajiboye *et al.* [42**]: a linear decoder similar to a Kalman filter was used to map neuronal firing rates and high frequency power at electrodes in the hand area of the motor cortex to percent activation of stimulation patterns associated with elbow, wrist or hand movements. The researchers showed that a tetraplegic subject could perform multi-joint arm movements for point-to-point target acquisitions with 80–100% accuracy and volitionally reach and drink a mug of coffee.

One shortcoming of the above approaches is that continued electrical stimulation of muscles results in muscle fatigue, rendering the technique impractical for day-long use. An alternate approach to reanimation is to use brain signals to stimulate the spinal cord. Spinal stimulation may simplify encoding and control because it activates functional synergies, reflex circuits, and endogenous pattern generators. Capogrosso *et al.* [43] demonstrated the efficacy of brain-controlled spinal stimulation for hind limb reanimation for locomotion in paralyzed monkeys. They used a decoder based on linear discriminant analysis to predict foot-strike and foot-off events during locomotion. The encoder used this prediction to activate extensor and flexor ‘hotspots’ in the lumbar spinal cord via epidural electrical stimulation to correctly produce the extension and flexion of the impaired leg.

Restoring motor and cognitive function

One of the early pioneers exploring bidirectional BCIs for the restoration of brain function was Delgado [6*] who

designed an implantable BBCI called the stimoceiver that could communicate with a computer via radio. Delgado was the first to combine decoding with encoding to shape behavior: his decoding algorithm detected spindles in the amygdala of a monkey and for each detection, triggered stimulation in the reticular formation, which is associated with negative reinforcement. After six days, spindle activity was reduced to one percent of normal levels, making the monkey quiet and withdrawn. Unfortunately, efforts to extend this approach to humans to treat depression and other disorders yielded inconsistent results.

Delgado’s work did eventually inspire commercial brain implants such as Neuropace’s RNS system that detects onset of seizures using time-based and frequency-based methods from brain surface recordings (ECoG) and stimulates the region where the seizure originates. Also inspired by Delgado’s work is the technique of deep brain stimulation (DBS), a widely prescribed form of neurostimulation for reducing tremors and restoring motor function in Parkinson’s patients. Current DBS systems are open-loop but Herron *et al.* have recently demonstrated closed-loop DBS [44] by triggering DBS based on movement intention, which was decoded as reduction in ECoG power in the low frequency (‘mu’) band over motor cortex.

Enhancing memory and augmenting brain function

Besides restoration of lost function, BBCIs can also be used for augmenting brain function. Berger *et al.* [45**,46] have demonstrated that BBCIs implanted in the hippocampus of monkeys and rats can be used to enhance memory in delayed match-to-sample (DMS) and non-match-to-sample tasks. They first fit a multi-input/multi-output (MIMO) nonlinear filtering model to simultaneously recorded spiking data from hippocampal CA3 and CA1 during successful trials, with CA3 as input to the model and CA1 as output. The trained MIMO model was later used to decode CA3 activity and predict CA1 activity encoded as patterns of biphasic electrical pulses. Deadwyler *et al.* [46] showed that in the four monkeys tested, performance in the DMS task was enhanced in the difficult trials, which had more distractor objects or required information to be held in memory for longer durations. However, it is unclear how the approach could be used when the brain is not healthy such as in Alzheimer’s patients [47] where simultaneous recordings from areas such as CA3 and CA1 for training the model in successful trials will not be available.

Nicolelis suggested several brain augmentation schemes based on BBCIs in his book [48], including direct brain-to-brain communication. Pais-Vieira *et al.* subsequently showed how rats can use brain-to-brain interfaces (BBIs) to solve sensorimotor tasks [49*]: an ‘encoder’ rat identified a stimulus and pressed one of two levers while its M1 cortex activity was transmitted to the M1 cortex of a ‘decoder’ rat. The

stimulation pattern was based on a *Z* score computed from the difference in the number of spikes between the current trial and a template trial. If the decoder rat made the same choice as the encoder rat, both rats were rewarded for the successful transfer of information between their two brains. Rao *et al.* utilized noninvasive technologies to demonstrate the first human brain-to-brain interface [50*,51,52]. The intention of a ‘Sender’ who could perceive but not act was decoded from motor or visual cortex using EEG; this information was delivered via transcranial magnetic stimulation (TMS) to the motor or visual cortex of a ‘Receiver’ who could act but not perceive. The researchers showed that tasks such as a video game [50*] or ‘20 questions’ [52] could be completed successfully through direct brain-to-brain collaboration (see Refs. [53,54] for other examples). More recently, brain-to-brain interfaces have been used to create a network of brains or a ‘BrainNet’ allowing groups of humans [55*] or rats [56*] to solve tasks collaboratively.

Inducing plasticity and rewiring the brain

Hebb’s principle for plasticity states that connections from a group A of neurons to a group B are strengthened if A consistently fires before B, thereby strengthening the causal relationship from A to B. Jackson *et al.* [57**] demonstrated that such plasticity can be artificially induced in the motor cortex of freely behaving primates by triggering stimulation at a site B a few milliseconds after a spike was detected at site A. After two days of continuous spike-triggered stimulation, the output generated by site A shifted to resemble the output from B, consistent with a strengthening of any weak synaptic connections that may have existed from neurons in A to neurons in B. Such an approach could be potentially quite useful for neurorehabilitation by rewiring the brain for the restoration of motor function after traumatic brain injury, stroke or neuropsychiatric disorders such as depression and PTSD. Along these lines, Guggenmos *et al.* [58*] have shown that the approach can be used to improve reaching and grasping functions in a rat after traumatic brain injury to the rat’s primary motor cortex (caudal forelimb area). Their approach involves creating an artificial connection between the rat’s premotor cortex (rostral forelimb area or RFA) and somatosensory cortex S1 and for each spike detected by an electrode in RFA, delivering an electric pulse to S1 after 7.5 ms. All of these prior approaches have relied on 1-to-1 spike-to-stimulation-pulse protocols, leaving open the question of how the approach can be generalized to the induction of goal-directed multi-electrode plasticity, a question we address with the concept of ‘neural co-processors’ below.

From proof-of-concept to real-world applications

Most of the BBIs reviewed above (see Table 1) involved proof-of-concept demonstrations. An important question is: how close are we to real-world applications of BCIs? While a small number of BCIs such as deep brain stimulators and Neuropace’s RNS epilepsy control system are

already being used for medical applications, the vast majority of BCIs are still in their ‘laboratory testing’ phase. Consider, for example, the most commonly cited BCI application of communication using brain signals alone. The maximum bit rate achieved by a human using an invasive BCI is currently about 3.7 bits/s and 39.2 correct characters per minute [16**]. This is an order of magnitude lower than average human typing speeds of about 150–200 characters per minute. In noninvasive EEG-based BCIs, the highest bit rate has been achieved using steady state visually evoked potentials (SSVEP): each choice on a menu is associated with a flickering visual stimulus (e.g. an LED) flashing at a specific known frequency. SSVEP BCIs have achieved bit rates as high as 5.3 bits/s or 60 characters per minute [59], which is again an order of magnitude less than manual typing speeds, with the added drawback of visual fatigue. BBIs are even more in their infancy. For example, the noninvasive brain-to-brain interfaces in humans cited above have bit rates of less than 1 bit/s, partly due to safety considerations of transcranial magnetic stimulation.

Towards a unifying framework: neural co-processors based on deep learning

A major limitation of current BBIs is that they treat decoding and encoding as separate processes, and they do not co-adapt and jointly optimize a cost function with the nervous system. We propose that these limitations may be addressed using a ‘neural co-processor’ as shown in Figure 1. A neural co-processor uses two artificial neural networks, a co-processor network (CPN) and an emulator network (EN), combined with a new type of deep learning that approximates *backpropagation through both biological and artificial networks*.

Suppose the goal is to restore movement in a stroke or spinal cord injury (SCI) patient, for example, to enable the hand to reach a target object (see Figure 1). The CPN is a multi-layered recurrent neural network that maps neural activity patterns from a large number of electrodes in areas A1, A2, and so on (e.g. movement intention areas spared by the stroke) to appropriate stimulation patterns in areas B1, B2, and so on (e.g. intact movement execution areas in the cortex or spinal cord). When the subject forms the intention to move the hand to a target (e.g. during a rehabilitation session), the CPN maps the resulting neural activity pattern to a stimulation pattern. Unfortunately, to train the CPN, we do not have a set of ‘target stimulation patterns’ that produce the intended movements. However, for any stimulation pattern, we can compute the error between the resulting hand movement and the target. How can this behavioral error be translated and backpropagated through the CPN to generate better stimulation patterns?

We propose the use of an emulator network (EN) that emulates the biological transformation between

Table 1

Summary and comparison of some notable BBIs built so far

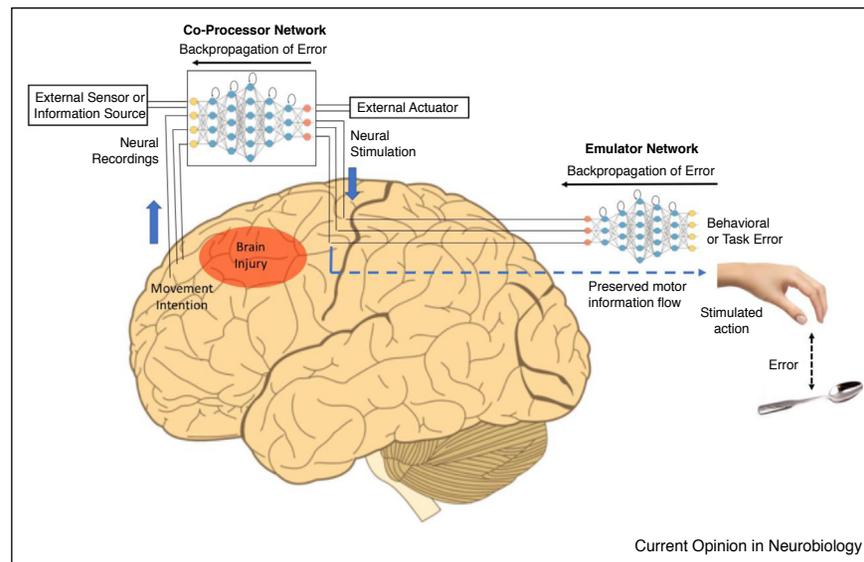
BBCI	Input and output	Decoding and encoding	Achievements	Limitations
O'Doherty <i>et al.</i> [36**]	Spikes from monkey M1 cortex and intracortical microstimulation in S1 cortex	Unscented Kalman filter and biphasic pulse trains of different frequencies	Simultaneous brain-controlled cursor and artificial tactile feedback in monkeys	Artificial tactile feedback limited to reward/no reward information
Flesher <i>et al.</i> [29]	Spikes from human M1 cortex and intracortical microstimulation in S1 cortex	Velocity-based linear decoder and linear encoding of torque to pulse train amplitude	Simultaneous brain-controlled prosthetic hand and force feedback in humans	Simple force matching task with only two levels (gentle or firm)
Moritz <i>et al.</i> [39**]	Spikes from monkey M1 cortex and functional electrical stimulation of muscles	Volitional control of firing rate of single neuron and linear encoder	Direct brain control of paralyzed muscles to restore wrist movement in monkeys	Simple flexion and extension movements of the wrist only, muscle fatigue with prolonged use
Bouton <i>et al.</i> [41**]	Multiunit activity from hand area of human M1 cortex and functional electrical stimulation of paralyzed forearm muscles	Support vector machines for classifying one of six wrist/hand motions and previously calibrated stimulation for each motion	Direct brain control of forearm muscles for hand/wrist control in paralyzed human	Decoder based on classification of six fixed motions, muscle fatigue with prolonged use
Ajiboye <i>et al.</i> [42**]	Spikes and high frequency power in hand area of human M1 cortex and functional electrical stimulation of paralyzed arm muscles	Linear decoder and percent activation of stimulation patterns associated with hand, wrist or elbow movements	Direct brain control of arm muscles for multi-joint movements and point-to-point target acquisitions in paralyzed human	Percent activation of fixed stimulation patterns, muscle fatigue with prolonged use
Capogrosso <i>et al.</i> [43]	Multiunit activity from leg area of monkey M1 cortex and epidural electrical stimulation of the lumbar spinal cord	Linear discriminant analysis to predict foot strike/foot off and activation of spinal hotspots for extension/flexion	Direct brain control of the spinal cord for restoring locomotion in paralyzed monkeys	Simple two-state decoder and encoder models, viability for restoration of bipedal walking in humans yet to be demonstrated
Delgado [6*]	Local field potentials in monkey amygdala and electrical stimulation in the reticular formation	Decoder algorithm for detecting fast 'spindle' waves and an electrical stimulation for each detection	First BBIC to control behavior and induce neuroplasticity in animals	Results not consistent from subject to subject, did not generalize to treating depression in humans
Deadwyler <i>et al.</i> [46]	Spikes from area CA3 in monkey hippocampus and electrical microstimulation in area CA1 in hippocampus	Multi-input/multi-output (MIMO) nonlinear filtering model to decode CA3 activity and encode predicted CA1 activity as biphasic electrical pulses	First demonstration of memory enhancement in a short-term memory task in a monkey	Applicability to memory restoration in Alzheimer's or other patients unclear due to MIMO model training algorithm
Jackson <i>et al.</i> [57**]	Spikes from a region of monkey M1 cortex and intracortical microstimulation of a different region of M1	Single spike detection and biphasic electrical pulse for each spike detection	First demonstration of Hebbian plasticity induction using a BBIC in a freely behaving monkey	Single input/single output protocol, not designed for multi-input/multi-output goal-directed plasticity induction
Guggenmos <i>et al.</i> [58*]	Spikes from rat premotor cortex and intracortical microstimulation of S1 somatosensory cortex	Single spike detection in premotor cortex and electrical pulse stimulation in S1 after 7.5 ms	First demonstration of improved motor function after traumatic brain injury in a rat using a BBIC for plasticity induction	Single input/single output protocol, plasticity induction not geared toward optimizing behavioral or rehabilitation metrics

stimulation patterns and behavioral output. The EN is a deep recurrent neural network whose weights can be learned using standard backpropagation from a dataset consisting of a large variety of stimulation (or neural activity) patterns in areas B1, B2, and so on and the resulting movements or behavior. After training, the EN

acts as a surrogate for the biological networks mediating the transformation between inputs in B1, B2, and so on and output behavior.

With the help of a trained EN, we can train the weights of the CPN to produce the optimal stimulation patterns for

Figure 1



Neural co-processor for the brain for restoring and augmenting function.

A deep recurrent artificial network is used to map input neural activity patterns in one set of regions to output stimulation patterns in other regions ('co-processor network' or CPN). The CPN's weights are optimized to minimize brain-activity-based error (between stimulation patterns and target neural activity patterns when known), or more generally, to minimize behavioral error or task error using another network, an emulator network. The emulator network is also a deep recurrent network that is pre-trained through backpropagation to learn the biological transformation from stimulation or neural activity patterns at the stimulation site to the resulting output behaviors. During CPN training, errors are backpropagated through the emulator network to the CPN to adapt the CPN's weights but not the emulator network's weights. The trained CPN, thus, produces optimal stimulation patterns that minimize behavioral error, thereby creating a goal-directed artificial information processing pathway between the input and output regions. The CPN also promotes neuroplasticity between weakly connected regions, leading to neural augmentation or targeted rehabilitation. External information from artificial sensors or other information sources can be integrated into the CPN's information processing as additional inputs to the neural network and outputs can be computed for external actuators as well. The example here shows the CPN creating a new information processing pathway between prefrontal cortex and motor cortex, bypassing an intermediate area affected by brain injury or stroke. The CPN is trained to transform movement intentions in the prefrontal cortex to appropriate movement-related stimulation patterns in the motor cortex for the restoration of movement and rehabilitation.

minimizing behavioral error (e.g. error between current hand position and a target location). For each neural input pattern X (e.g. movement intention) that the subject produces in areas A1, A2 and so on, the CPN produces an output stimulation pattern Y in areas B1, B2 and so on, which results in a behavior or movement Z .

The error E between actual movement Z and the intended movement target Z' is first backpropagated through the EN *but without modifying its weights*. We continue to backpropagate the error through the CPN, this time modifying the CPN's weights. In other words, the behavioral error is backpropagated through a concatenated CPN-EN network but only the CPN's weights are changed. This allows the CPN to progressively generate better stimulation patterns that enable the brain to better achieve the target behavior, thereby resulting in a co-adaptive BBCI.

Furthermore, by repeatedly pairing patterns of neural inputs with patterns of output stimulation, the CPN

promotes neuroplasticity between connected brain regions via Hebbian plasticity. Note that unlike previous plasticity induction methods [57*,58*], the plasticity induced spans multiple electrodes and is goal-directed since the CPN is trained to minimize behavioral errors. After a sufficient amount of coupling between regions X and Y , neurons in region X can be expected to automatically recruit neurons in region Y to achieve a desired response (such as a particular hand movement). As a result, in some cases, the neural co-processor system may eventually be no longer required after a period of use and may be removed once function is restored or augmented to a satisfactory level.

To illustrate the generality of the neural co-processor framework beyond restoring motor function, consider a co-processor for emotional well-being (e.g. to combat trauma, depression, or stress). The emulator network could first be trained by stimulating one or more emotion-regulating areas of the brain and noting the effect of stimulation on the subject's emotional state, as captured, for example, by a mood score based on a

questionnaire answered by the subject [60]. The CPN could then be trained to map emotional intentions or other brain states to appropriate stimulation patterns that lead to a desired emotional state (e.g. less traumatic, stressful or depressed state).

Another example is using a neural co-processor to create a sensory prosthesis that converts sensory stimuli from an external sensor (Figure 1), such as a camera, microphone, or even infrared or ultrasonic sensor, into stimulation patterns that take into account the ongoing dynamics of the brain. In this case, the CPN in Figure 1 takes as input both external sensor information and current neural activity to generate an appropriate stimulation pattern in the context of the current state of the brain. The emulator network could be trained based on the subject's reports of perceptual states generated by a variety of stimulation patterns.

More generally, the external input to the CPN could be from any information source, even the internet, allowing the brain to request information via the external actuator component in Figure 1. The resulting information is conveyed via the CPN's input channels and processed in the context of current brain activity. The emulator network in this case would be trained in a manner similar to the sensory prosthesis example above to allow the CPN to convert abstract information (such as text) into appropriate stimulation patterns that the user can understand.

Finally, we note that neural co-processors can be useful tools for testing new computational models of brain and nervous system function [31]. Rather than using traditional artificial neural networks in the CPN in Figure 1, one could use more realistic cortical models such as networks of integrate-and-fire or Hodgkin–Huxley neurons, along with biological learning rules such as spike-timing-dependent plasticity rather than backpropagation. A critical test for putative computational models of the nervous system would then be: can the model successfully interact with its neurobiological counterpart and be eventually integrated within the nervous system's information processing loops?

Challenges

A first challenge in realizing the above vision for neural co-processors is obtaining an error signal for training the two networks. In the simplest case, the error may simply be a neural error signal: the goal is to drive neural activity in areas B1, B2, and so on toward known target neural activity patterns, and we can therefore train the CPN directly to approximate these activity patterns without using an EN. However, we expect such scenarios to be rare. In the more realistic case of restoring motor behavior, such as in stroke rehabilitation where the goal is, for example, to reach towards a target, a computer vision system could be used to quantify the error between the

hand and the target or a sensor worn on the hand may indicate error in the force applied. Similarly, in speech rehabilitation after stroke, a speech analysis system could quantify the error between the generated speech and the target speech pattern.

A bigger challenge is to train an EN to be a sufficiently accurate model of the transformation from stimulation patterns to behavioral output. It may be difficult to obtain a sufficient amount of data containing enough examples of how stimulation affects behavior. One possible solution is to record neural activities in regions that are causally related or correlated with observed behavior and use these data to train the EN, under the assumption that stimulation patterns will approximate the neural activity patterns. Another possible approach is to build the EN in a modular fashion, starting from biological structures closest to the target behavior and going up the hierarchy, for example, learning to emulate the transformation from limb muscles to limb movements, spinal activity to muscle activity, and so on. Finally, one could combine the above ideas with the concept of transfer learning using networks trained across similar neural regions or even across subjects, and incorporate prior knowledge from computational neuroscience models of the biological system being emulated. Regardless of the training method used, we expect that the EN (and CPN) will need to be regularly updated with new neural data as the brain adapts to having the CPN as part of its information processing loops.

Conclusions

Traditionally, much of BCI research has focused on the problem of decoding, specifically, how can movement intention be extracted from noisy brain signals to control prosthetic devices? More recently, there has been growing interest in 'closing the loop' using bidirectional BCIs (BBCIs) which incorporate sensory feedback, for example, from artificial tactile sensors, via stimulation. The ability to simultaneously decode neural activity from one region and encode information to deliver via stimulation to another region confers on BBCIs tremendous versatility. In this article, we have reviewed how BBCIs can be used to not only control prosthetic arms with sensory feedback but also (1) control paralyzed limbs using motor intention signals from the brain, (2) restore and augment cognitive function and memory, and (3) induce neuroplasticity for rehabilitation. Promising proof-of-concept results have been obtained in animal models and in some cases, humans, but mostly under laboratory conditions.

To transition to real-world conditions, BBCIs must adapt with the nervous system and jointly optimize behavioral cost functions. We introduced the concept of a neural co-processor which uses artificial neural networks to jointly optimize behavioral error functions with biological neural networks. A trained emulator network is

used as a surrogate for the biological network producing the behavioral output. Behavioral errors are backpropagated through the emulator network to the co-processor network which adapts its weights to minimize errors and delivers optimal stimulation patterns for specific neural input patterns. We illustrated how a neural co-processor could be used to improve motor function in a stroke or spinal cord injury patient. Such co-processors have not yet been validated in animal models or humans, but if successful, they could potentially be applied to modalities other than movement such as:

- Mapping inputs from one memory-related area to another to facilitate or restore access to particular memories (e.g. in memory loss) or to unlearn traumatic memories (e.g. in PTSD),
- Mapping inputs from novel external sensors or one sensory area to another to restore or augment sensation and perception,
- Connecting areas involved in emotion processing to augment or rehabilitate emotional function, and
- Augmenting the brain's knowledge, skills, information processing, and learning capabilities with deep artificial neural networks.

Conflict of interest statement

Nothing declared.

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References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
 - of outstanding interest
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