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Trends in Neurosciences

Opinion

Going beyond primary motor cortex to improve brain–computer interfaces

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Brain–computer interfaces (BCIs) for movement restoration typically decode the user's intent from neural activity in their primary motor cortex (M1) and use this information to enable 'mental control' of an external device. Here, we argue that activity in M1 has both too little and too much information for optimal decoding: too little, in that many regions beyond it contribute unique motor outputs and have movement-related information that is absent or otherwise difficult to resolve from M1 activity; and too much, in that motor commands are tangled up with nonmotor processes such as attention and feedback processing, potentially hindering decoding. Both challenges might be circumvented, we argue, by integrating additional information from multiple brain regions to develop BCIs that will better interpret the user's intent.

The promise and challenges of brain–computer interfaces

Invasive BCIs for movement restoration translate the activity of neurons recorded with implanted electrodes into commands to either move external objects, such as a computer cursor or a robot arm, or to reanimate the user's paralyzed limbs through electrical stimulation of muscles or nerves [1–3] (Figure 1A). Most current BCIs function by recording from neurons in motor cortex, predominantly from primary motor cortex (M1), but occasionally also from premotor cortex. The reason for targeting motor cortex is clear: M1 is the primary cortical output for directly driving movement [4,5]. Thus, this region's activity can be reasonably expected to have the most integrated picture of the user's movement 'intent.' Yet despite the impressive advances in BCI technology over the past several years [2,6,7], even seemingly simple tasks such as controlling a computer cursor with a BCI turn out to be challenging, often more so than performing analogous tasks with a limb [8]. Why is this the case?

We suggest that an overly narrow focus on reading out ('decoding') motor cortical output might be one constraint on the effectiveness of current and future BCIs to restore movement, for two reasons. First, M1 activity likely has too little information about the motor intent: many other brain regions besides M1 contribute unique outputs to the periphery [5] or are involved in action execution through higher-order processes crucial for behavior, such as planning and sequencing movements and facilitating decision-making [9] (Figure 1B). Second – and perhaps paradoxically – M1 activity also arguably has too much information. Contrary to long-held views, M1 has not only 'motor signals' but also both top-down cognitive signals [10,11] and bottom-up feedback signals [12,13]. These two challenges, which we discuss in detail later, could be overcome by incorporating additional signals from a broader network of brain regions outside of M1. Doing so would allow for both a more complete picture of the user's motor intent and could refine M1 decoding by isolating motor signals directly related to ongoing motor commands.

Why primary motor cortex?

There are various historical and physiological reasons for the emergence of M1 as a primary target of BCIs for movement restoration. Since the emergence of foundational stimulation studies in the

Highlights

Primary motor cortex (M1) is the typical target of brain–computer interfaces (BCIs), though many other brain regions are also critical for motor behavior. These brain regions could represent useful additional recording sites for improving BCI control.

M1 activity is modulated by nonmotor variables, including attention, sensory input, and reward. Accordingly, M1's motor command signals may be better isolated by incorporating recordings from additional brain regions involved in these processes.

Cognitive neuroscience research could be leveraged to further specify other useful BCI targets and to optimize training protocols.

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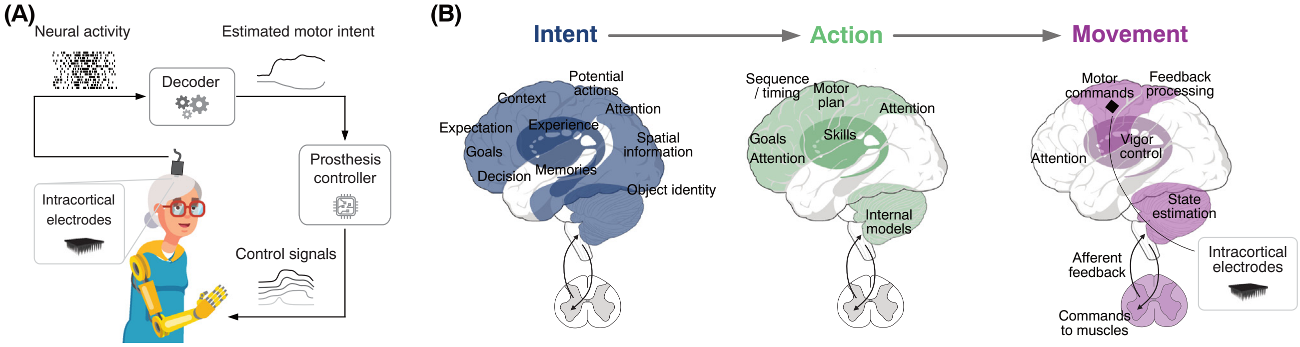


Trends in Neurosciences

Figure 1. Intracortical brain–computer interfaces (BCIs). (A) Schematic highlighting the standard architecture of an intracortical BCI. A decoder is used to estimate the user's motor intent from the spiking activity of neural populations. The decoded motor intent is mapped onto control signals, in this case to move a bionic limb. (B) The complex pathway from intentions to movements. Left: motor intent is shaped by a complex set of variables, including the context of movement (e.g., is this bottle of beer empty or full), motivational state (e.g., do I want to drink from the bottle), experience (e.g., the weight of the bottle as felt when trying to lift it), and expectations (e.g., I should be able to lift this bottle with X amount of force). The desired action, which one attempts to capture with BCIs, will be influenced by all these factors, as well as other online processes happening during movement execution, such as sensory feedback (e.g., my fingers are sweaty etc.). Middle: for a BCI to enable flexible control of an external device or a stimulator that reanimates the user's limbs, it should encapsulate the rich context of action. In our view, here, action is not synonymous with movement, in that it encapsulates high-level considerations relating to motor planning, goals, generalization of movements across contexts, and rapid adaptation and movement correction commands. Action in this sense is, thus, mediated by processes that are not necessarily readily available in M1 activity, such as the hierarchical planning of motor sequences. Right: M1 decoders are designed to extract information about the motor commands needed to carry out a desired action. In effect, they may also pick up multiple signals available in M1, not all of which are directly relevant to motor commands, for example, relating to attentional state, somatosensory feedback, arousal, and even reward. While these signals might be ultimately valuable for improving the decoding of the motor intent, they might be tangled with movement information worsening the performance of the BCI.

late 19th century [14], motor cortex has proven to be a relatively easily accessible and responsive target for neurophysiologists. In primates, M1 is the primary source of motor output: many neurons in this region project disynaptically or even monosynaptically to the spinal motoneurons that, in turn, project to muscles to produce movement [5]. The activity of many M1 neurons correlates with movement parameters such as hand velocity [15] and muscle activation [16], and M1 populations can show impressive stability in their correlations with motor behavior [17–19]. It has also been known for over 50 years that monkeys can learn to modulate the firing rate of M1 neurons when trained using operant conditioning techniques [20]. These observations make M1 a logical target for decoding intended movements, as confirmed by an offline comparison of decoding performance across several sensorimotor areas and associative areas [21].

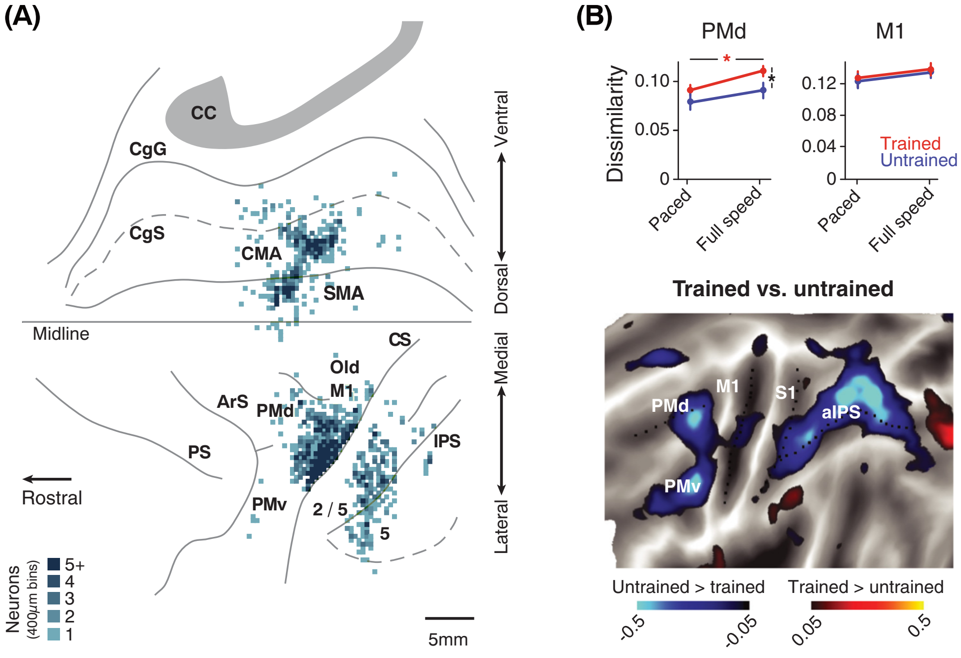
There are also clear clinical justifications for M1-based BCIs: in clinical BCI applications where patients have lost the ability to move, it is prudent to target M1 to reduce the risk of damage to (and potential interference from) cortical areas involved in the patient's spared behaviors and abilities. Moreover, due to its location near the dorsal surface of the brain, M1 is easier to access surgically. For these reasons, M1 is perhaps the best default target of BCIs aimed at restoring an individual's lost motor abilities.

Sources of motor output and movement-related information beyond M1

While M1 is the most reasonable first target for BCIs, it is certainly not the only brain region that plays an important role in motor control. To begin with, subcortical regions including the basal ganglia, the cerebellum, and the brainstem, all of which project to descending pathways [22], are critical for motor control. These regions have been implicated not just in movement execution, but also in other aspects of motor behavior and learning, including in BCI applications [23,24]. The basal ganglia appear to be key for modulating movement vigor [25] and are critical for the execution of well-practiced skills [26]. Recent studies also highlight the nuanced contributions of spinal circuits to motor control, challenging the prevalent view of their roles as simply routing sensory and motor signals upstream and downstream. For example, despite the crucial role of corticomotoneuronal connections in the control of dexterous movements, blocking neurotransmission in propriospinal circuits drastically impairs grasping [27]. Even the 'simple' stretch reflex is much more complex than the common leg extension example suggests – these short latency responses can be modulated via extensive training and are altered by body configuration and task context [28], indicating that reflex responses contribute to the generation of motor output in a much more sophisticated manner than traditionally thought.

Within cortex, many areas outside M1 also play a direct role in motor control. Anatomical, lesion, and neural recording studies have identified key cortical motor regions including the premotor, cingulate, and parietal cortices [5]. All these regions have their own (disynaptic) connections to motoneurons, in addition to contributing inputs to M1 (Figure 2A). In fact, only around one-third of the corticospinal system originates from M1 [5].

Importantly, brain areas within the motor system beyond M1 also appear to provide contextual and high-order information about movement. Motor output is often thought to be specified following a hierarchical process, with the most abstract aspects of the upcoming action (e.g., when a particular movement should occur in an extended sequence) being integrated to



Trends in Neurosciences

Figure 2. Cortical control of movement extends beyond M1. (A) Map of the density of Layer V neurons with disynaptic connections to forearm motoneurons (innervating the extensor digitorum communis muscle). The key indicates the number of motoneurons in 400 μm bins. Many neurons with disynaptic projections to motoneurons are located in the premotor areas (SMA and CMA). Adapted from [68]. (B) Learning to produce a speeded motor sequence, over the course of 5 weeks, is associated with shifts of action 'representations' in dorsal premotor cortex (PMd) but not in M1. Top: greater dissimilarity (y-axis) indicates greater information content for the different actions, as measured using representational similarity analysis. Dissimilarities are significantly larger for trained versus untrained sequences in PMd but not in M1. Bottom: differences in activation elicited from trained relative to untrained sequences. Significant differences are found in PMd but not in M1. Adapted from [34]. Abbreviations: aIPS, anterior intraparietal sulcus; ArS, arcuate sulcus; CC, corpus callosum; CgG, cingulate gyrus; CgS, cingulate sulcus; CMA, cingulate motor area; CS, central sulcus; IPS, intraparietal sulcus; M1, primary motor cortex; PMv, ventral premotor cortex; PS, principal sulcus; SMA, supplementary motor area.

produce the appropriate motor commands that are eventually sent to the muscles [29]. In cortex, this process seems to flow from more ‘cognitive’ regions (in premotor and parietal cortex) to M1 [29,30]. For example, the supplementary motor area (SMA) has prominent signals related to higher-level task parameters such as when a movement should be initiated [31] and the progress of an action being performed [32]. The premotor cortex is known to be important for reflecting high-order variables in motor control, especially those related to motor sequences [29,33–35] (Figure 2B), and has, crucially, been used in BCIs [36]. Finally, human neuroimaging studies suggest a key role for the anterior midcingulate cortex in the voluntary initiation of movements [37] and integration of environmental cues during learning, potentially providing top-down control signals to other regions [38]. These alternative sources of information are crucial for fluent motor control and may perform computations that are not necessarily straightforward to decode from M1 activity alone.

In theory, it is possible that some information related to these more abstract processes is simply ‘funnelled’ down the hierarchy to shape motor commands in M1. However, given the anatomical fact that M1 is not the only cortical area involved in descending motor output [5], we believe that the premise that M1 would contain all the necessary information to capture the end products of higher-level computations is questionable. We suggest that attempts to operate a BCI using exclusively M1 signals, without integrating additional higher-order information, should undershoot the brain’s ability to translate intention into action. This is at heart a conceptual problem, rather than necessarily a technical one; that is, we argue that even if one were to record M1 activity during a vast range of behaviors across a rich set of contexts and used it to train powerful decoders using machine learning techniques such an approach would likely hit a performance ceiling. Recording additional information from one or more of the regions discussed earlier could provide a composite view of the user’s intended action across a wider variety of behaviors and environments. We think this could circumvent the challenge of M1 having ‘too little information’ about the full motor intent.

Empirically, direct evidence of the feasibility of BCIs targeting nonmotor cortical areas has been most clearly demonstrated in posterior parietal cortex (PPC) [39]. The motivation for targeting this region is predominantly functional [39–41], although there is some anatomical justification too: neurons in area 5 of PPC appear to have direct control over complex hand movements, since intracortical stimulation there evokes complex finger and wrist movements in monkeys [42]. Functionally, mentalized movement variables, including mental imagery of specific movement trajectories and intended task goals, can be decoded from both human PPC [43] and the anterior intraparietal area [44]. In the latter case, participants can even directly control a BCI by aiming imagined movements to different locations. Indeed, mental imagery of an intended reach trajectory has also been recently decoded in human somatosensory cortex [45]. Importantly, although these other regions have been shown to be effective for decoding high-level movement intentions, we do not claim that M1 completely eschews this information. For example, ‘re-aiming’ processes also appear to be decodable in M1 [46]. Thus, M1 activity likely reflects, to some degree, multiple upstream learning processes [47–49,70]. Our main contention is that the bar for BCI performance might be raised if one looks to other areas. In other words, to achieve a richer behavioral repertoire sufficient to enable the acquisition and maintenance of multiple novel skills [50], an exclusive reliance on a single cortical area may be insufficient.

Nonmotor signals in M1

Current BCIs face key challenges when it comes to perhaps the most crucial test of motor intent – generalization across a set of potential movements with a similar action goal. Studies quantifying the stability of single neuron correlates of behavior hint at how daunting this challenge is; for example, in monkeys, the relationship between the activity of M1 neurons and both hand movement and muscle activity changes drastically when subjects perform the same reaching task with the hand centered at two different locations [51]. Similarly, standard decoders trained on a one-dimensional wrist task fail to generalize across tasks in which subjects need to generate different combinations of movements and forces to acquire targets arranged in a similar configuration [52] – although complex neural network decoders do show some promising results in this narrow case of generalization [52].

We believe that this lack of generalization across task demands – a crucial challenge to make BCIs useful in real-world scenarios – is driven in part by a simplified interpretation of the complex barrage of nonmotor processes that are likely entangled with motor command signals in M1. That is, in some situations, there is ‘too much’ information in M1 to achieve robust generalization. This argument is based on the simple assertion that activity in M1 related to executing a motor intent will be inherently intermixed with nonmotor signals reflecting other aspects of the user’s state. This excess information will make M1 decoders susceptible to slight changes in context [53], such as the user’s internal attentional state [10], and can thus contribute to generalization failures.

Context-related signals modulate M1 activity, along with other related signals reflecting additional processes that are not primarily ‘motor’ in nature. These include afferent inputs arriving to M1 via the primary somatosensory cortex [12], signals specifically related to the subject’s attentional state or level of arousal [10], and reward [11,54,55]. Interestingly, studies in other brain regions, including the visual and prefrontal cortices (PFC), indicate that various internal state signals may be present simultaneously across multiple cortical regions, perhaps due to the neuromodulatory origin of these signals [56]. In M1, it may be the case that the nonmotor signals are so entangled (i.e., correlated) with motor signals that no BCI training methods may be able to tease them apart within reasonable practical constraints.

There are several potential technical solutions for disentangling M1 motor commands from nonmotor signals (e.g., signals relating to reward, arousal, and attention). In addition to further improving M1 decoding algorithms using techniques like decoder adaptation [57,58], a potential avenue for improvement involves better estimation of the nonmotor signals by recording from upstream areas such as PPC and PFC [30,59,60], as well as S1 [12], and ‘subtracting’ those signals from M1 activity to obtain a cleaner estimate of motor commands (Figure 3). This is likely not a simple task – an important caveat is that these signals may also be difficult to isolate in other cortical areas that, like M1, reflect multiple features of the user’s state and the environment. That said, we believe that a multiarea BCI could produce a more accurate estimate of ongoing motor command signals in M1, in addition to extracting higher-order information relevant for decoding actions. This remains to be tested.

Concluding remarks

Flexible learning of motor skills is central to human behavior, and it is perhaps unsurprising that much of the nervous system is involved in the process. Sensorimotor learning and control are largely distributed processes that involve a network of structures across the central nervous system. Yet, for both practical and theoretical reasons, BCIs have almost exclusively targeted a single cortical region – M1. BCIs focused on M1 have led to many important findings and clinical applications and provide a thrilling opportunity to benefit from the rich computational processes in that region. However, while practically appealing, M1 BCIs may not fully realize the promise that they once inspired. We propose that the reason for this is twofold: (i) M1

Outstanding questions

BCIs for movement restoration are designed to decode the user’s motor intent, typically from motor cortex recordings. In order to fully realize their promise, BCIs need to be useful across a variety of contexts. Is it possible to get a full picture of the user’s intent, including the higher-level aspects necessary for generalization, from M1 activity alone?

Would recording from additional areas that contain nonmotor signals related to the user’s state (e.g., attentional vigilance) allow for improved M1 decoding? Could nonmotor signals be ‘subtracted’ from signals specifically related to motor commands?

Current BCI decoders are trained by asking users to attempt specific tasks and building a mapping between ongoing neural activity and behavior. Can advances in cognitive neuroscience be leveraged to develop training curricula that improve this process?

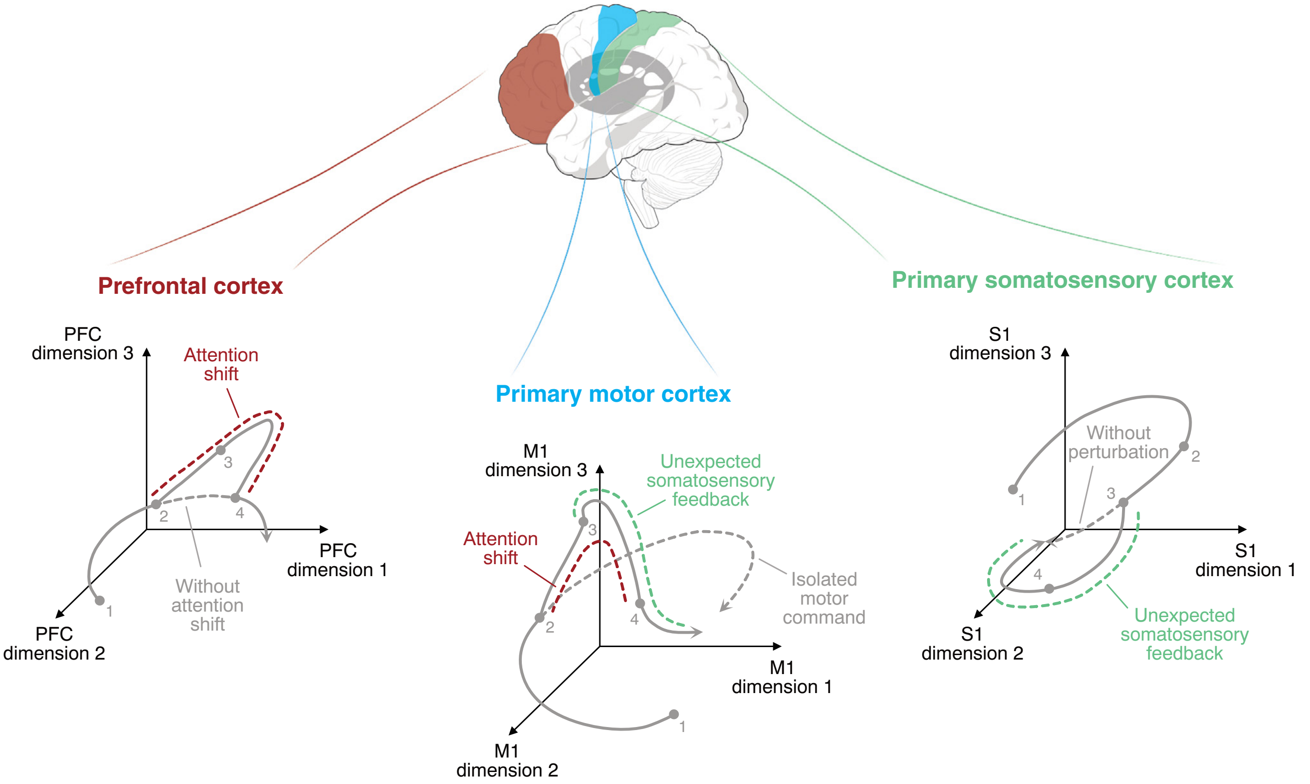


Figure 3. Isolating motor commands within M1 population activity. Neural population activity in three key behavior-related areas of the brain: prefrontal cortex (left), primary motor cortex (middle), and primary somatosensory cortex (right). Neural activity in each of these areas during one movement is represented by a 'neural trajectory' in a space in which each dimension represents a dominant pattern of the neural population activity. In this example, the subject shifted their attention during the movement (red broken line in prefrontal cortex), which caused a slight motor error leading to appropriate (unexpected) feedback signals in primary somatosensory cortex (green broken line in primary somatosensory cortex). These attention and feedback signals influence the primary motor cortex activity in a complex manner, making it difficult to isolate the motor command (gray broken line) after the attention shift and subsequent perturbation. Thus, a BCI reading out this entangled motor cortical signal may be unable to fully isolate the motor command, potentially rendering the user unable to perform the intended action. 'Subtracting' the attention and feedback signals based on recordings from other brain areas (prefrontal and primary somatosensory cortex, in this example) could be used to help isolate motor command signals within M1. Abbreviations: BCI, brain–computer interfaces; M1, primary motor cortex; PFC, prefrontal cortex; S1, primary somatosensory cortex.

activity has too little information about the motor intent, namely regarding higher-order aspects of behavior, and (ii) M1 activity has too much nonmotor information, in the sense that there are many signals related to sensory and internal processes that are intermingled with motor signals and can interfere with the decoding of action intent.

Integrating neural recordings from additional key areas of the sensorimotor network beyond M1 may allow for better learning and generalization by incorporating higher-order action information and by enabling better decoding of ongoing motor commands through a dissociation of motor intent from nonmotor signals. To aid this effort, the development of novel BCI training protocols could also lead to more robust BCI-based skills for users (Box 1). While extremely demanding, both from a practical and theoretical perspective (see Outstanding questions), this more diverse program may be necessary to ease BCI learning, improve generalization, and foster important technological advances in healthcare. Looking beyond M1 by treating the brain as a complex, holistic functional network may prove to be a critical step in the development of next-generation BCIs.

Box 1. Nonneural approaches to improving BCI

Skilled movements in humans reflect refinements that occurred both over evolutionary timescales and during development. These skills range from reaching and grasping, to playing the violin. Perfecting new skills often requires tremendous amounts of deliberate practice. Thus, it should not be surprising that novel (‘*de novo*’) motor skill learning is slow and laborious [69]. Moreover, new patterns of movement can be hard to remember and might be interfered with previously established ones [61,62]. Findings in the BCI literature align with these observations. When subjects are given a BCI decoder that requires activity patterns that can be readily generated by the recorded neural population, the BCI can be mastered within minutes [63]. By contrast, if a BCI decoder requires starkly different patterns of neural activity, learning has to be pursued in incremental steps over several days, possibly because it requires synaptic changes in the brain circuits [64]. This sets potential limits on *de novo* learning with a BCI at the level of neural populations and suggests a rather severe constraint on learning speed. However, ideas from psychology and machine learning can potentially inspire improvements in BCI training to overcome these hurdles. In particular, the training curriculum itself may be an important target for future BCI advances. For speeding up learning and boosting retention, decomposition of a task into simpler subcomponents (‘curriculum learning’) has proven to be highly effective in both animal learning and machine learning applications [65,66]. To improve generalization, multitask learning approaches [67] may prove to be useful as well. Encouraging users to generalize successful BCI motor control policies across different interleaved training contexts may lead to more robust skill learning. Incorporating these psychologically inspired methods to expand the scope of BCI training curricula could be a useful low-cost method for facilitating better performance, perhaps in addition to increasing the number of recording sites.

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Declaration of interests

The authors declare no competing interests in relation to this work.

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