Title

Volitional Control of Brain Motor Activity and its Therapeutic Potential

Running Title

Volitional Control of Brain Activity

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ABSTRACT

Background: Neurofeedback training is a closed loop neuromodulatory technique in which real-time feedback of brain activity and connectivity is provided to the participant for the purpose of volitional neural control. Through practice and reinforcement, such learning has been shown to facilitate measurable changes in brain function and behaviour. **Objectives:** In this review, we examine how neurofeedback coupled with motor imagery training has the potential to improve or normalise motor function in neurological diseases such as Parkinson's disease and chronic stroke. We will also explore neurofeedback in the context of brain machine interfaces (BMI), discussing both nonivasive and invasive methods which have been used to power external devices (e.g., robot hand orthosis or exoskeleton) in the context of motor neurorehabilitation. **Conclusions:** The published literature provides mounting high-quality evidence that neurofeedback and BMI control may lead to clinically relevant changes in brain function and behaviour.

Keywords

Neurofeedback; volitional control; brain machine interface; plasticity; neurological diseases.

TITLE

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INTRODUCTION

The execution of goal-directed or reflex movements is directed by a seamless interplay between complex neural circuitry and musculoskeletal structures. Disruption to these networks can impact on everyday life activities and may occur abruptly from trauma or stroke, or progressively as seen in movement disorders. Irrespective of the underlying cause(s), there has been a longstanding interest in the therapeutic potential of neuromodulatory techniques which may enhance volitional neural control in a wide range of clinical settings. Neurofeedback training is one such approach, with the purpose of teaching users how to modulate the activity of an intrinsically (e.g., brain region) or extrinsically (e.g., neuroprosthetic) determined target. It has been associated with improvements in both brain function and behaviour, which have been attributed to direct plasticity changes and/or indirect compensatory processes [1], but these data need careful critique. The mechanisms of neural plasticity underlying the therapeutic potential of neurofeedback may be variably intact according to whether damage is part of a neurodegenerative process or an acute insult.

In this article, we examine the evidence to assess whether neurofeedback using real-time measures of brain activity has the potential to improve motor function in neurological diseases. Furthermore, we will explore neurofeedback in the form of brain machine interfaces (BMI), discussing both nonivasive and invasive techniques which have been used to power external devices to assist recovery from motor disabilities. We critique the strength of the published evidence and highlight areas where additional data are needed to confirm preliminary findings.

WHAT IS NEUROFEEDBACK?

Neurofeedback implements a closed loop system whereby real-time measurements of brain activity are directly fed back to the participant in a visual, auditory, or tactile manner [1-3]. Through practice and reinforcement, the participant learns how to volitionally control this online and dynamic representation of brain activity. This is most often achieved with motor-related mental imagery, although contingent feedback or rewards have also been employed [4]. Defined as the cognitive rehearsal of physical movement, motor imagery activates similar neural substrates to those activated during motor

planning, initiation, and execution [5-7]. Perhaps of most relevance to clinical applications, it has a documented role in motor learning and may precipitate motor recovery by inducing a restitution of normal or compensatory neural activity within the motor system [8]. Following neurofeedback training, behavioural changes can often be observed in the post-training interval, and so causal inferences regarding brain structure and function can be made. Early studies indeed showed that monkeys could selectively increase and decrease the firing rate of precentral neurons when given contingent rewards, in association with specific limb movements [9, 10].

NEUROFEEDBACK TRAINING AND MOTOR FUNCTION

The motor system is a mosaic of distinct but highly interactive areas, with each component contributing to the planning, initiation, and execution of goal-directed behaviours. Surrogate markers of brain function can be via the measurement of blood volume, flow or oxygenation changes, in addition to electrophysiological signals. Accordingly, neurofeedback training can be combined with many different neuroimaging or neurophysiological methods. While a detailed comparison of these techniques goes beyond the scope of this review, the following section explores their usefulness in modulating different aspects of neural activity in neurological diseases.

Real-time Functional Magnetic Resonance Imaging (rt-fMRI)

Real-time fMRI neurofeedback allows a participant to be shown their own ‘online’ activity from a target brain region. Although protocols vary between real-time fMRI studies, representations of brain activity typically occur approximately 5 seconds or more after such changes transpire on a neuronal level (i.e., it is “near real-time”). This includes the time taken for data processing whereby one TR (repetition time i.e., the interval between two consecutive functional scans) introduces a delay of ~1-3 s, but also a ~4-6 s delay due to the detected blood oxygenation level dependent (BOLD) signal being an indirect measurement of neuronal activity (please see [11] for a detailed review regarding rt-fMRI methodology). Neurofeedback presentations can also be updated intermittently (e.g., at the end of a regulation block), although it is thought that continuous feedback after each acquired volume may provide the participants with information at the highest possible temporal resolution [12].

The clinical appeal of rt-fMRI neurofeedback is that it may facilitate the normalisation of aberrant neuronal function and evoke symptom improvements in several conditions

(information regarding neurofeedback training protocols can be found in Table 1). In a double-blind and randomised cross-over trial, 21 adolescents with Tourette Syndrome were first asked to imitate their most common and troublesome tics to identify the region of the supplementary motor area (SMA) responsible for these behaviours. Participants were then cued by an arrow at the top of a screen to increase or decrease SMA activity using cognitive strategies, and a colour-coded line graph provided feedback. After two sessions spaced half a week part, a significant and clinically meaningful 5.3-point reduction in the Yale Global Tic Severity Scale was observed [13]. Improvements were not seen when participants were presented with a 'yoked sham' signal from another person's brain, highlighting that real contingent feedback was needed to drive such effects. The low-risk and drug-free nature of this intervention may therefore be appealing to many families. The time commitment is also relatively minimal, especially in comparison to behavioural therapy. To maximise clinical translation, however, the temporal pattern of clinical changes needs to be further documented as there are data to suggest that the long-term effects may be substantially larger than those seen in the immediate post-training period [13, 14]. Multiple assessment time-points post-intervention would be helpful in answering this question.

In neurodegenerative disorders such as Parkinson's disease (PD) and Huntington's disease (HD), the SMA has been similarly chosen as a target due to its critical involvement in both higher-order motor control and the pathogenesis of motor impairments [15-17]. In a proof-of-concept study, five early-stage PD patients (who were receiving concurrent pharmacological treatment) were first asked to continually squeeze and release their fingers to localise SMA activity. This BOLD signal was then used for neurofeedback training whereby the participants were shown a thermometer bar and asked to increase its height (i.e., upregulate the SMA) by engaging in motor imagery. The data indicated that these participants learned to significantly activate the SMA across two sessions separated by 2-6 months [18]. An improvement in motor speed (finger tapping) and clinical ratings of motor symptoms was seen 2-weeks post-training. These findings, however, were not observed for control patients who did not receive feedback about their SMA activity [18]. These findings were later replicated in a cohort of 30 participants with PD who were randomly allocated to receive neurofeedback with motor training or motor training (MOT) alone with a virtual reality gaming device. Similar to the original study, participants were instructed to upregulate the SMA using motor imagery across three sessions within a 10-week period. Increasing SMA activity corresponded

with a 4.5-point improvement in PD motor ratings in the off-medication state, whereas the MOT group improved by only 1.9-points [19]. The subthalamic nucleus (STN) and putamen were also coactivated during neurofeedback, suggesting that volitional control of higher-order motor regions can in turn modulate subcortical loops, even among people with established neurodegeneration [19].

This concept has been further replicated within the HD literature. Ten patients attended three neurofeedback training visits on separate days and were asked to volitionally upregulate the SMA using motor imagery. Continuous visual feedback was in the form of a dynamic thermometer bar, which represented the level of activation within the target region. After training, participants were able to successfully increase the BOLD signal from the SMA, as well as enhance the functional connectivity between the left presupplementary motor area (preSMA) and left putamen [20]. An increase in preSMA grey matter volume was further associated with these results, indicating that continuous neurofeedback training may induce plasticity. However, it remains unclear whether neurofeedback could be used to improve cognitive or psychomotor function in HD patients to a significant degree [21]. This study utilised behavioural composite scores which were designed to be sensitive to disease progression but may have obscured effects in more specific measures [21]. Evidence regarding the subsequent transfer of learning (i.e., the ability to continue to upregulate regional brain activity without real-time feedback) was also not robust, calling into question how well this technique would translate into everyday clinical practise.

Transfer of learning has however been reported in chronic stroke patients with mild to severe hemiparesis [22]. At the end of a second 2-hour neurofeedback training session, four patients were asked to imagine movement in the affected limb without visual feedback [23]. Not only were they still able to upregulate the BOLD activity of target ventral premotor cortex, they also could increase the cortico-subcortical connectivity between perilesional primary motor cortex (M1) and ipsilesional thalamus [23]. Interestingly, patients with greater motor impairments at inclusion seemed to appreciate the largest increases in both learning and cortico-thalamic connectivity [23]. While these data indicate that specific sub-groups may benefit the most from this paradigm, the mechanistic explanation for the differential extent of response remains unclear. It is also important to highlight that the transfer task was performed directly after the second neurofeedback

session, meaning this result could potentially reflect short term rather than long term effects.

Further evaluation with larger sample sizes and dedicated clinical outcome measures is obviously required prior to widespread clinical acceptance of rt-fMRI neurofeedback and routine therapeutic employment. More work is also needed to understand whether the effects are retained over long periods and how often would patients need to re-train to sustain those effects.

Real-time Functional Near Infrared Spectroscopy (fNIRS)

A growing number of studies have utilised optical imaging as a way of delivering neurofeedback. Similar to fMRI, fNIRS measures changes in oxy-and-deoxygenated haemoglobin from the cortical surface [24]. Not only is this method inexpensive and portable, but it also offers a relatively high temporal resolution (sampling rate of 0.01 s versus 1 s for fMRI) and is robust against head motion artefacts [25]. The latter point may be of high relevance to populations with movement disorders, as tics or dyskinesias could cause excessive head or body movements which may influence data quality.

In healthy populations, fNIRS-mediated neurofeedback has been shown to reliably detect oxygenated haemoglobin signal changes in real-time [26]. Its utility was further supported by several reports which showed strong engagement of motor substrates, including the premotor and motor cortices, during mental imagery [27, 28]. As with rt-fMRI neurofeedback, manipulation of motor cortical activity appeared to be very much dependent on the presence of visual or auditory feedback, suggesting that information about the haemodynamic response was a prerequisite for successful self-regulation [28]. However, successful self-regulation was not dependent on the presence of a specific task (e.g., motor imagery), potentially suggesting that fNIRS neurofeedback itself has a neuromodulatory effect [29]. This has clear practical implications, as it may lessen the need for continuous or strenuous cognitive input which can be compromised in the population of interest.

While fNIRS neurofeedback has been utilised broadly in psychiatric conditions (e.g. ADHD, schizophrenia, anxiety disorders) [30], there are not many investigations exploring its utility in neurological diseases. Twenty hemiplegic patients due to sub-cortical infarcts received six sessions of mental practice with motor imagery of the distal upper limb

across two weeks, in addition to standard rehabilitation. Participants were randomly allocated to receive neurofeedback with a real or sham signal, which was presented visually using a red bar. Those in the real group were able to significantly upregulate the ipsilesional premotor area using kinaesthetic motor imagery and fNIRS-mediated neurofeedback [31]. These effects were correlated with a significant 3.0-point improvement in the hand/finger subscale of the Fugl-Meyer Motor Assessment (compared to 0.8-points in the sham group), demonstrating that excitability of the premotor area and its related networks had the potential to augment functional recovery. Using a similar experimental method, the authors of this study have recently extended their findings to post-stroke gait and balance recovery in a larger cohort of participants (n = 54). Six sessions of SMA neurofeedback training during motor imagery led to significant improvements in the Timed Up and Go Test in participants who were trained with a true signal compared with the control group exposed to sham neurofeedback [32].

While promising, further studies are needed with longer follow-up to confirm the clinical efficacy of fNIRS-mediated neurofeedback. It would also be helpful to replicate these results in broader post-stroke cohorts, although these preliminary findings have shown that hand function and gait disturbances can be improved in both mildly and severely impaired patients.

Electroencephalography (EEG)

Noninvasive Surface Recordings

Oscillating at a frequency of 8-13 Hz, sensorimotor rhythms (SMR) reflect synchronous activity occurring across neuronal populations within the sensorimotor area. Decreases in SMR power transpire during motor execution and motor imagery tasks, making this oscillation suitable for neurofeedback training with clinical populations [33].

In one study, 30 stroke patients with paralysis were randomly assigned to three intervention cohorts: occupational therapy, occupational therapy plus EMG biofeedback of the abductor pollicis brevis muscles, or occupational therapy plus neurofeedback training. Across 10 sessions, the participants in the neurofeedback group were first asked to imagine performing a task with their paretic hand. Signals from the sensorimotor area were then presented on the screen, and the participant was instructed to play a boat race game. This entailed moving a target boat to a greater

extent by volitionally enhancing SMR power, while slowing down two other boats presenting theta and beta waves (i.e., decreasing their spectral power). Not only did the participants learn to control these EEG signals, but the training led to significant clinical improvements in hand function assessed using the Jebsen Hand Function Test [34]. However, training gains from occupational therapy plus neurofeedback were similar to those seen with occupational therapy alone. Without a superior clinical outcome, it is difficult to justify the need for neurofeedback in this context. On the other hand, the fact that stroke patients were able to self-regulate EEG signals may have important implications for future BMI protocols which involve prosthetic devices.

Home-based EEG neurofeedback of SMR has also been investigated as a means of minimising frequent hospital or laboratory visits [36]. This lessens the physical burden that may be placed on disabled patients and could in turn increase their motivation to engage fully with the training. Using a portable system, three stroke survivors were thus trained at home for four weeks to overcome maladaptive changes in cortical lateralization patterns. Participants were instructed to imagine the kinaesthetic sensation of a power grip from the first-person perspective. During neurofeedback blocks, a ball moved along the horizontal and vertical axes according to the classification of contralateral event-related desynchronization (ERD) or the difference between contralateral and ipsilateral ERD, respectively. While promising, the data showed that a significant increase in EEG lateralization during motor imagery of the affected hand was only observed in one patient. This was accompanied by an increased lateralization of fMRI activity, a rebalance in corticospinal tract integrity (revealed by diffusion tensor imaging), and a 7.0 improvement in a modified Fugl-Meyer Motor Assessment [36]. The obvious limiting factor of this study was the small sample size, and further data will be needed to assess whether these findings are reproducible given the potential feasibility of utilising home-based neurofeedback systems in neurorehabilitation settings.

Voluntary control of SMR via neurofeedback has also been employed in monkey models of PD, with the aim of enhancing compensatory mechanisms that may occur in response to striatal degeneration. In a controlled study, the impact of SMR neurofeedback training on MPTP induced parkinsonian symptoms was explored [37]. Marmoset monkeys underwent 9-12 sessions to positively reinforce SMR spindles by food rewards. Control monkeys followed the same procedure, but the rewards were not contingent on brain activity. Representative power spectra during SMR neurofeedback training showed

pronounced SMR peaks, whereas controls showed random EEG spectra. Less severe parkinsonian symptoms were seen in the neurofeedback trained monkeys, both in the presence and absence of dopaminergic treatment [37]. These findings have been more recently replicated in a human case report. Across two consecutive days of training, a PD participant learned to volitionally increase SMR power over the motor cortex with visual feedback and positive rewards. The rate of SMR bursts increased with each subsequence training session, while relative power in the beta band decreased in the later session [38]. These results correlated with improvements in both rigidity and gait on the second day of training.

The intact thalamo-rubro-cerebellar pathway, common in the presymptomatic stages of PD, is thought to possibly underlie these clinical improvements [39]. There is evidence that SMR activation by neurofeedback training increases the size of the red nucleus in marmoset monkey models of PD, indicating that morphological plasticity occurs to maintain regular functioning [39]. These changes are not thought to reflect neuroprotective processes as cell loss is still evident, nor that the compensation mechanism is dopamine mediated [40]. Despite this, biofeedback based on respiration rate and neurofeedback training of SMR has been associated with a lower daily dose of levodopa post-intervention [41]. These findings are, however, based on case reports and need to be replicated with larger cohorts. A randomised control trial would also be needed to account for placebo-induced expectation of clinical improvement as this is known to activate endogenous dopamine in the striatum [42].

Invasive Recordings using DBS Electrodes

Deep brain stimulation (DBS) is a well-established therapy for movement disorders [43]. It involves the surgical implantation of electrodes in deep brain structures, most commonly the STN, to deliver high frequency stimulation. DBS patients thus present a unique opportunity for neurofeedback training as precise information about the selective engagement of neuronal populations can be demonstrated at a millimetric scale, while the temporal dynamics of their engagement can also be monitored at the millisecond scale [44].

Preliminary findings with the dual approach of surface and deep recordings appear promising. Three PD patients who underwent STN DBS (plus recording leads which covered the sensorimotor cortex) were asked to play a neurofeedback game at home

which entailed moving a computer cursor to a cued target using self-regulation of beta power [45]. After playing for 1-2 hours, all patients were able to use the feedback signal to update their endogenous beta power from the sensorimotor cortex regardless of subcortical stimulation levels [45]. In another study, it was shown that three PD patients were able to downregulate pathological beta power after five neurofeedback training sessions. They did this by using motor imagery to control the position of a virtual basketball, which represented beta oscillations recorded from STN local field potentials in real-time Behaviourally, these effects were associated with an improvement in the speed of movement initiation, even when off-dopaminergic medication [46]. Neurofeedback may therefore be a promising tool to work in tandem with DBS and may ultimately help augment current approaches, although larger studies with objective measurements of motor function are needed first. Further, exploiting the opportunity to record from DBS patients may help to objectively confirm the dose and duration of neurofeedback required to successfully manipulate abnormal firing patterns in subcortical structures in non-DBS cases.

Bimodal Approaches to Neurofeedback

There has been a growing interest in bimodal approaches to neurofeedback, offering researchers the opportunity to evaluate the correlation between electrical brain activity and hemodynamic changes. In stroke rehabilitation, the feasibility of EEG-fMRI neurofeedback training has been demonstrated with small cohorts [47-49]. In one pilot study, four patients with mild to severe hemiparesis were asked to self-modulate ipsilesional M1 using kinaesthetic motor imagery of the hemiplegic hand. They received feedback from both modalities simultaneously, which consisted of a yellow ball moving in a one-dimensional gauge proportionally to the average of the EEG and fMRI features. Two participants were able to complete the task successfully and showed upper-limb improvements in the Fugl-Meyer Motor Assessment [47]. These effects were further correlated with the integrity of the ipsilesional corticospinal tract, thus confirming the critical role of preserved neural pathways in functional recovery [50]. Such factors are important as they consider subject variability, which may help to inform future trial design whereby preliminary imaging may form an inclusion criterion to facilitate optimal patient selection.

The integration of EEG and fMRI undoubtedly overcomes the intrinsic limitations of these techniques (i.e. poor spatial or temporal resolution, respectively) [51]. However,

obtaining good quality EEG recordings remains a challenge due to the noisy environment of fMRI. Artefacts or noise may also make it more difficult to obtain a clear EEG signal [52], which in turn could impact the participants ability to achieve successful self-modulation. Moving forward, it may be feasible for future studies to use simultaneous EEG with fMRI to identify the electrophysiological signature of deep subcortical structures. Once identified, EEG could be used in isolation for neurofeedback training which would lower the associated costs and improve accessibility.

NEUROFEEDBACK TRAINING FOR BMI CONTROL

It is increasingly evident that neurofeedback can be used to enhance motor brain activity, giving rise to quantifiable functional improvements in patients with neurological or neurodegenerative conditions. Employing neurofeedback in the form of brain powered BMI may thus offer paralysed individuals the opportunity to move within their environment or communicate with others [53].

BMI is a direct collaboration between an external device and the brain. Using neurofeedback, participants can learn how to induce specific patterns of brain activity related to voluntary movement. These can then be detected and decoded into command signals to power a disembodied actuator such as robotic limb or computer keyboard. Beyond this, BMI may also assist the rehabilitation of natural motor function. The following section will give an overview of current BMI approaches, which most commonly employ electrical signals recorded from the scalp via EEG or intracranially using microelectrode arrays.

Non-invasive BMI

EEG-BMI neurorehabilitation systems have the advantage of being safe and inexpensive. In 10 chronic hemiparetic stroke survivors, signals related to motor imagery (recorded from the unaffected hemisphere) were used to control the affected hand with a powered exoskeleton [55]. Visual and proprioceptive feedback was provided through spectral power changes updating the hand position, which was initially closed and only opened during imagined movement trials. As expected, significant decreases in beta and mu/SMR power could be exploited to control the exoskeleton with motor imagery after 12 weeks of training. These findings also correlated with an increase of 6.2 points in the Action Research Arm Test (ARAT) [55]. A randomised and placebo controlled multicentre study with 74 stroke survivors found comparable data when using a similar

experimental paradigm. Motor imagery-related EEG activity was translated into contingent exoskeleton-driven opening movements of the affected hand, which led to better clinical outcomes as assessed by the ARAT and Fugl-Meyer Motor Assessment [56].

It is thought that such improvements may reflect a functional reorganisation of motor-related regions. Neural plasticity following a stroke is not a novel concept, as increased synaptogenesis and axonal sprouting within the deafferented brain regions has been well documented during recovery [57]. However, by providing a relevant feedback signal in the absence of movement, BMI may enhance plasticity by reinforcing the sensory aspects of the sensorimotor loop. Corroborating this, there is evidence that BMI-triggered exoskeleton movements increase the excitability of cortical projections to extensor muscles in the forearm [58]. There is also evidence of a shift in haemodynamic activity from contralesional to ipsilesional motor cortex in patients who could control a robotic arm orthosis using ipsilesional SMR signals [59]. Functional connectivity between ipsilesional M1 and contralesional Brodmann area 6 (premotor cortex and SMA) also significantly increased after several sessions of BMI robot hand training [60]. Plasticity evaluated using both functional and structural MRI appeared to be immediate, even after just one hour of training [61]. These physiological changes were accompanied by a remodelling of the corticospinal and transcallosal fibre tracts evident on DTI-derived metrics [62], suggesting that better functional outcomes were dependent on the structural integrity of connecting white matter.

Invasive BMI

The main disadvantage of scalp recordings is that electrical signals are significantly attenuated in the process of passing through the dura, skull, and scalp. Given this limitation, recent BMI work has explored ways of recording intracranially [63-67]. A 96-mircoelectrode array was implanted into the arm/hand region of right M1 in a man with tetraplegia caused by spinal cord injury. He was asked to modulate cortical spiking patterns by imagining limb motions. After 9-months of training, decoders were created and successfully used for 2D control of a computer cursor and prosthetic hand [63]. Similarly, in an individual with non-spastic C5/C6 quadriplegia caused by spinal cord injury, a microelectrode array was implanted in the left M1 hand area [68]. The participant attended three sessions weekly for 15-months and was trained to control a neuromuscular electrical stimulator connected to the right forearm using motor cortical

spiking activity. This was continuously decoded as the participant attempted to perform six wrist and hand movements, as cued by an animated virtual hand on a computer monitor. The participant achieved continuous cortical control of these movements and was able to use the system to complete functional tasks relevant to daily living. Clinical assessments of upper limb sensorimotor function were also performed; muscle strength improved from C6 to C7-C8 level, gross grasping ability improved from C7-C8 to C8-T1 level, and prehensile skills improved from C5 to C6 level. This study is important as it shows that people with quadriplegia can regain volitional and functional movement.

Combining functional electrical stimulation (FES) and intracortical BMI has also been explored (ClinicalTrials.gov: NCT00912041) [69]. A patient with traumatic high-cervical spinal cord injury received two 96-channel microelectrode arrays in M1 (hand area), in addition to percutaneous electrodes in their right upper and lower arm for muscle stimulation. They were first asked to control a virtual reality arm on a screen, and then their own reaching and grasping movements during simple single-joint and functionally meaningful multi-joint actions. By decoding intentions and translating cortical activity into commands, the patient was able to successfully engage in both tasks with 80-100% accuracy. With their paralysed arm, they also performed voluntary self-paced reaches to hold a cup or feed themselves. These findings have important real-world implications as they demonstrate that users can modulate their own neural activity and use visual feedback to perform meaningful arm movements guided by FES.

These results are promising and demonstrate the feasibility of therapeutic BMI to improve or regain motor function, yet there are limitations surrounding the utilization of spiking activity. The sorted data can be unstable over time [70], and signals from individual neurons are sometimes lost as a result of small movements in the microelectrode arrays. The number of well discriminated neurons can also diminish over time due to a variety of mechanical and biological failures such as degradation of electrode materials, connector issues, and progressive meningeal reactions that separate the array from parenchymal brain tissues [71]. To partly overcome these methodological limitations, many studies perform frequent or daily recalibration of neural decoders to maintain high-level performance. However, this is time consuming and impractical for everyday use. As such, other studies have employed adaptive decoding mechanisms [72], but this too poses challenges as it requires regular involvement of highly trained engineers. Utilisation of local field potentials, however, may be the answer to reliable and long-term BMI control.

Two patients with tetraplegia (caused by either brainstem stroke or secondary to amyotrophic lateral sclerosis) were enrolled into a BrainGate clinical trial and received a 96-channel intracortical electrode array in the arm area of dominant precentral gyrus [73, 74]. They interacted with a text-entry application, which first required them to 'click' on a displayed option by attempting to, or executing, a chosen movement. Local field potentials elicited during 'click' actions were recorded from the motor cortex and decoded by the BMI. The decoder remained unchanged for 76 and 138 days in each patient, and both were able to independently communicate by typing messages or writing emails without recalibration.

Taken together, BMI enables the volitional control and translation of motor brain activity in patients with severe disability. It appears to depend on long-term functional plasticity changes, transpiring at both the cortical and subcortical level [75]. Supporting this, Koralek and colleagues implemented an operant task to investigate the role of corticostriatal plasticity in abstract skill learning. By receiving contingent food rewards, rodents learned to control the pitch of an auditory cursor which moved between two different targets in response to self-modulation of M1 activity. An improvement in behavioural performance was accompanied by a significant amplification in dorsal striatal firing during late learning compared with early learning. Striatal neurons also increasingly changed their activity when rodents volitionally controlled M1, and dynamic changes in functional interactions involving M1 and striatum were noted during skill learning. The crux of this study, however, was that acute pharmacological blockage of NMDA acid receptors in striatal medium spiny neurons led to learning deficits. Because these mice were still able to perform the skill but showed no improvement with training, the authors suggested that corticostriatal plasticity must be essential for intentional neuromodulation [76]. Thus, volitional neural control does not just evoke functional changes but also morphological or cellular alterations. For example, there is evidence that EEG neurofeedback training can lead to significant increases in blood brain-derived neurotrophic factor levels [77]. This signalling protein is a major regulator of synaptic transmission and plasticity at adult synapses within the CNS.

CONCLUSION, LIMITATIONS AND FUTURE DIRECTIONS

Neurofeedback training facilitates self-regulation of the neural substrates that underlie a particular behaviour or pathology. This has been demonstrated using various neuroimaging methods and with different features of brain activity. Perhaps most

importantly, neurofeedback has been associated with clinical improvements in motor function and could therefore be particularly useful in rehabilitation settings where physically strenuous interventions are not possible. Beyond this however, the neural control of external devices has been achieved with neurofeedback-driven BMI, although it is important to mention that successful BMI control can take months of training to achieve. Neural plasticity appears to play a large role in these processes, either by triggering a functional reorganisation within structurally intact parts of the brain to compensate for lesions or by evoking microstructural changes in both white and grey matter. Synaptogenesis and changes in dendrite spine morphology are speculated to underlie these changes, as they have been associated with motor skill learning in rodents.

While the current findings are promising and offer an interdisciplinary approach to motor rehabilitation, there are several limitations to consider. The current literature reports mainly positive findings from a small number of participants, and often specific data have not been replicated so the question of reproducibility remains open. The effect of durability is also unclear due to the small amount of long-term data available. Similarly, most BMI systems decode signals from the motor cortex even though this region represents a subset of substrates involved in goal-directed behaviours. As successful movement depends on the collective contribution of several high-level and widespread neural mechanisms, it may be beneficial to enlarge the repertoire of brain signals exploited for BMI. The prefrontal and posterior parietal cortices, for example, have both been identified as target areas for future BMI systems due to their role in the cognitive aspects of movement [78, 79]. Taking these factors into consideration may facilitate a larger percentage of end users to successfully control the BMI.

Of course, these limitations most likely reflect the early stage of neurofeedback application in motor rehabilitation. Further research is needed, as well as pragmatic randomised clinical trials to provide the evidence base to allow such paradigms to move into routine clinical practice.

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