Because recovery from upper limb paralysis after stroke is challenging, compensatory approaches have been the main focus of upper limb rehabilitation. However, based on fundamental and clinical research indicating that the brain has a far greater potential for plastic change than previously thought, functional restorative approaches have become increasingly common. Among such interventions, constraint-induced movement therapy, task-specific training, robotic therapy, neuromuscular electrical stimulation (NMES), mental practice, mirror therapy, and bilateral arm training are recommended in recently published stroke guidelines. For severe upper limb paralysis, however, no effective therapy has yet been established. Against this background, there is growing interest in applying brain–machine interface (BMI) technologies to upper limb rehabilitation. Increasing numbers of randomized controlled trials have demonstrated the effectiveness of BMI neurorehabilitation, and several meta-analyses have shown medium to large effect sizes with BMI therapy. Subgroup analyses indicate higher intervention effects in the subacute group than the chronic group, when using movement attempts as the BMI-training trigger task rather than using motor imagery, and using NMES as the external device compared with using other devices. The Keio BMI team has developed an electroencephalography-based neurorehabilitation system and has published clinical and basic studies demonstrating its effectiveness and neurophysiological mechanisms. For its wider clinical application, the positioning of BMI therapy in upper limb rehabilitation needs to be clarified, BMI needs to be commercialized as an easy-to-use and cost-effective medical device, and training systems for rehabilitation professionals need to be developed. A technological breakthrough enabling selective modulation of neural circuits is also needed. (DOI: 10.2302/kjm.2022-0002-OA)

Keywords: electroencephalography, neurofeedback, mental practice, hand function, neuroplasticity

Introduction

In Japan, as in many other countries, stroke is a major cause of death (7.5%, third highest cause in 2020) and makes major demands on long-term care (15.1%, third highest in 2017). In 2017, the number of patients in Japan with stroke was estimated at 1.115 million, and stroke accounted for 4.2% of total medical expenses. Stroke therefore imposes significant health and economic impacts on society. Nearly three-quarters of stroke survivors experience upper limb symptoms after the acute episode and, in the first 6 months, only 20% of stroke survivors achieve some functional recovery. Accordingly, the focus to date has been on compensatory approaches as opposed to functional restoration of the paretic upper limb itself. However, based on fundamental and clinical research indicating a much greater potential for plastic changes in the brain than previously thought, approaches oriented...
toward functional restoration have become increasingly common. There is also growing interest in applying brain–machine interface (BMI) technologies to patients with post-stroke severe upper limb paresis that is difficult to treat.\textsuperscript{8–10} In this article, we review the recovery from post-stroke upper limb paresis and the interventions applied to facilitate recovery; we then introduce the current status of BMI neurorehabilitation, including our own work.

**Review Methodology**

This article is a narrative review based on the evidence included in currently available stroke guidelines, systematic reviews and meta-analyses related to motor recovery, and rehabilitative interventions for post-stroke upper limb paresis. The search for relevant guidelines was performed on the PubMed (https://pubmed.ncbi.nlm.nih.gov) and the Alliance for the Implementation of Clinical Practice Guidelines (https://aicpg.org) websites. The search for systematic reviews and meta-analyses was carried out on PubMed and the Cochrane Database of Systematic Reviews (https://www.cochranelibrary.com/cdsr/about-cdsr). Original articles cited in the systematic reviews and meta-analyses were also reviewed, as were the BMI-related publications of our group.

**Recovery of Post-stroke Upper Limb Paresis**

Understanding the natural course of post-stroke upper limb motor recovery and its prediction is important for appropriate goal setting, providing rehabilitation services, and designing clinical trials. To investigate the natural course of motor recovery, Nakayama et al.\textsuperscript{5} assessed 421 patients weekly from the onset of stroke using the Scandinavian Stroke Scale\textsuperscript{11} and the feeding and grooming items of the Barthel Index.\textsuperscript{12} They found that recovery mainly took place within the first 2 months and that full function was achieved by 79% of patients with mild paresis, compared with only 18% of patients with severe paresis. In patients with mild paresis, valid prognostication could be made at 3 weeks, and further recovery was not expected later than 6 weeks post-stroke. In patients with severe paresis, valid prognostication was possible at 6 weeks, and further recovery was difficult beyond 11 weeks post-stroke.

Cooper and colleagues\textsuperscript{13} systematically reviewed the literature available up to November 2011 (58 studies) on prognostic variables related to post-stroke upper limb recovery. The prediction variables extracted were age, gender, lesion site, initial motor impairment, motor evoked potentials (MEPs), and somatosensory-evoked potentials (SEPs). Among these factors, the most important predictors were the initial severity of motor impairment and function. Interpretation of the results of the included studies was complicated by methodological factors, including variations in study populations, outcome measures, timing of baseline and outcome assessments, and predictors selected. Stinear and coworkers\textsuperscript{14} performed a narrative review that summarized the factors known to predict functional outcomes and identified prediction tools that could be used to guide stroke rehabilitation. Models that use demographic, clinical, and neurological variables to predict functional outcomes are frequently reported, and rather than simply providing multivariable regression equations, studies are increasingly using scores, decision trees, and free apps to make predictions. Among the various prediction tools, only PREP\textsuperscript{14} has been externally validated. PREP involves a decision tree to predict 3-month post-stroke upper limb function based on the SAFE (shoulder abduction, finger extension) score evaluated within 72 h after stroke, age, MEP, and National Institute of Health Stroke Scale\textsuperscript{15} score. The impact of its use in routine clinical care and the accuracy of predictions for long-term follow-up have been reported.\textsuperscript{16,17} However, none of the reviewed studies conformed to the guidelines for reporting multivariable prediction models.\textsuperscript{18} Stinear et al.\textsuperscript{14} argue that improvements in the design, testing, and reporting of prediction tools will facilitate their implementation in clinical practice.

**Interventions for Upper Limb Paralysis**

Table 1 summarizes the recommendations for interventions for upper limb paralysis from recently released stroke guidelines.\textsuperscript{19–22} The recommendation grades and evidence levels differ among the guidelines, and although there exist some discrepancies, the strength of recommendation for each intervention is generally consistent. Among the interventions, constraint-induced movement therapy (CIMT) and task-specific training are strongly recommended; robotic therapy, neuromuscular electrical stimulation (NMES), mental practice, mirror therapy, and bilateral arm training are recommended; and virtual reality and repetitive transcranial magnetic stimulation (rTMS)/transcranial direct current stimulation (tDCS) may be considered. BMI therapy is considered only by the Japanese guideline.\textsuperscript{22} Table 1 also shows the target severity of motor paralysis for each intervention. This information was derived from the inclusion criteria of the randomized controlled trials (RCTs) cited in the guidelines. As can be seen, for severe upper limb paralysis, robotic therapy, NMES, mental practice, and mirror therapy are recommended; however, some voluntary function is required for patients to be candidates for most of these therapies. In contrast, BMI therapy can be applied to finger paralysis in patients with no voluntary extension.\textsuperscript{8–10}

**BMI Neurorehabilitation**

There is growing interest in the application of BMI technologies to severe upper limb paresis after stroke,\textsuperscript{8–10,23,24}
### Table 1. Interventions for post-stroke upper limb paralysis: summary from stroke guidelines

| Intervention                                      | Target severity of motor paralysis | AHS/ASA Guideline (2016) | Australian Guideline (2017) | VA/DoD Guideline (2019) | Japanese Guideline (2021) |
|--------------------------------------------------|------------------------------------|--------------------------|-----------------------------|-------------------------|--------------------------|
|                                                  | Class of recommendation | Level of evidence | Grade of recommendation | Quality of evidence | Grade of recommendation | Level of evidence | Grade of recommendation | Level of evidence |
| ADL training                                     | I                                  | A                        | -                          | -                      | -                        | -                        | -                        | -                        |
| IADL training                                    | I                                  | B                        | -                          | -                      | -                        | -                        | -                        | -                        |
| Constraint-induced movement therapy              | Moderate to mild                   | Ila                      | A                          | Strong                 | Moderate                 | Weak for Very low        | A                        | High                     |
| Task-specific training                           | Moderate to mild                   | I                        | A                          | Weak                   | Low                      | Strong for Moderate      | A                        | High                     |
| Robotic therapy                                  | Severe to moderate                | Ila                      | A                          | Weak                   | Low                      | Weak for Low             | B                        | High                     |
| Neuromuscular electrical stimulation             | Severe to moderate                | Ila                      | A                          | Weak                   | Moderate                 | Weak for Very low        | B                        | Medium                   |
| Mental practice                                  | Severe to mild                    | Ila                      | A                          | Weak                   | Low                      | -                        | -                        | B                        | Medium                   |
| Brain–machine interface therapy                  | Severe to moderate                | -                        | -                          | -                      | -                        | -                        | -                        | B                        | Medium                   |
| Mirror therapy                                   | Severe to moderate                | -                        | -                          | Weak                   | High                     | Neither for nor against  | Low                      | B                        | Medium                   |
| Bilateral arm training                           | Moderate to mild                  | IIb                      | A                          | -                      | -                        | -                        | -                        | -                        | -                        |
| Virtual reality                                  | Severe to mild                    | IIa                      | B                          | Weak                   | Low                      | -                        | -                        | B                        | Medium                   |
| rTMS, tDCS                                       | Severe to mild                    | -                        | -                          | Weak                   | Against                  | Low                      | Neither for nor against  | Very low                 | C                        | Medium                   |
| Strengthening exercises                          | Moderate to mild                  | IIa                      | B                          | Strong                 | Moderate                 | -                        | -                        | -                        | -                        |
| Somatosensory retraining                         | IIb                                | B                        | Weak                      | Low                    | -                        | -                        | -                        | -                        | -                        |
| Acupuncture                                      | III                                | A                        | -                          | -                      | -                        | -                        | -                        | -                        | -                        |
| Splints                                          | -                                  | -                        | Strong                    | against                | High                     | -                        | -                        | -                        | -                        |

AHS/ASA guideline: I, Should be administered; IIa, Reasonable to perform; IIb, May be considered; III, No benefit or harm; A, Multiple RCTs or meta-analysis; B, Single RCT or non randomized studies; C, Consensus opinion of experts, case studies, or standard of care. 
Japanese Guideline: A, Strongly recommended; B, Moderately recommended; C, Weakly recommended; D, No benefit; E, Harmful. 
ADL, activities of daily living; IADL, instrumental ADL; rTMS, repetitive transcranial magnetic stimulation; tDCS, transcranial direct current stimulation.
for which no effective therapy has yet been established. The BMI operates external devices based on brain activities that are detected and measured either noninvasively with surface electroencephalography (EEG),

\[25-39\] functional near-infrared spectroscopy,\[40\] or magnetoencephalography,\[41\] or invasively with intracortical and electrocorticography recordings.\[42\] Among these techniques, EEG-BMI is widely used because of its simplicity, safety, portability, and low cost. BMI is potentially a useful technology in neurorehabilitation, not only to substitute for lost functionality, but also to induce brain plasticity.\[43\] BMI can bypass the normal motor output neural pathways and directly translate brain signals into commands to control external devices.\[43\] Patients’ motor intentions are estimated from the decrease of EEG amplitude in specific frequency bands (8–13 Hz) over the sensorimotor cortex during motor attempt; this decreased EEG amplitude is called event-related desynchronization (ERD).\[43\] These amplitude changes are fed back either visually or kinesthetically to promote motor learning and recovery.\[44\]

**Clinical Evidence for BMI Therapy**

The number of RCTs examining the effectiveness of BMI neurorehabilitation has recently increased,\[25-40\] and several meta-analyses have been reported.\[8-10,23,24\] In the meta-analysis by Cervera et al.\[8\] (nine RCTs, \(n =235\)), BMI training was associated with a standardized mean difference (SMD) of 0.79 (95% CI: 0.37–1.20) in upper limb Fugl-Meyer Assessment (UL-FMA) scores,\[45\] which indicates a medium to large effect size (ES).\[46\] Subgroup analysis indicated a higher intervention effect for the subacute group compared with the chronic group. The meta-analysis by Bai and colleagues\[8\] (11 RCTs\[25-28,30-34,36-38,40\] and 1 non-randomized controlled trial\[58\] \(n =318\)) reported a medium ES favoring BMI (SMD 0.42; 95% CI 0.18–0.66), but the long-term effects (5 studies) were not significant (SMD 0.12; 95% CI −0.28 to 0.52). With subgroup analyses, using movement attempts as the trigger task in BMI training appeared to be more effective than using motor imagery, and using NMES as the external device produced a larger effect than using other devices. A more recent meta-analysis by Mansour et al.\[10\] (12 RCTs\[25-28,30-35,39,40\] \(n =298\)) demonstrated that BMI therapy yielded significantly superior short-term and long-term efficacy in improving the upper limb motor function compared to the control therapies (Hedge’s g =0.73 and 0.33). Subgroup analyses revealed that using movement attempt had a higher ES compared with using motor imagery (Hedge’s g =1.21 and 0.55), using band power features had a significantly higher ES than using filter bank common spatial pattern features (Hedge’s g =1.25 and −0.23), and using NMES as the feedback had a higher ES than the other devices (Hedge’s g =1.2). Table 2 shows the ES of various interventions for upper limb paralysis.\[8\] Compared with other interventions, BMI therapy can induce fairly large improvements.

Although evidence on the effects of BMI neurorehabilitation on post-stroke upper limb dysfunction is still accumulating, the studies included in the meta-analyses discussed here are highly heterogenous with respect to patient characteristics, the BMI system used for training, methods of mental practice, mode of feedback, rehabilitation protocol, and outcome measures used (Fig. 1). Important information is not specified in some RCTs adopted in the meta-analyses, e.g., the lesion site, severity of finger paralysis, degree of spasticity, sensory impairment, and cognitive impairment. These factors will be important in the design of future clinical trials.

**Studies from the Keio BMI Team**

The Keio University Medical and Engineering team has developed an EEG-based BMI neurorehabilitation system (Fig. 2) and reported its clinical and neurophysiological effects. With our system, the patient sits on a chair and looks at a computer monitor. A star-shaped cursor moves at a fixed rate from left to right, the position reflecting the mu rhythm (8–13 Hz frequency range) amplitude during motor imagery. The cursor moves up and down depending on the degree of success of the motor imagery. When successful, the fingers are extended by down depending on the degree of success of the motor imagery.
provided. In the following sections, we present the clinical and neurophysiological studies performed with our EEG-based BMI system.

**Pilot Study**

Our pilot study provided eight patients with chronic hemiparetic stroke (age: 46–68 years; duration of stroke: 1.3–12 years); the Stroke Impairment Assessment Set (SIAS) finger score was 1A (mass flexion possible but no extension) in five patients, 1B (mass flexion and extension) in two patients, and 2 (incomplete individual finger movement) in one patient. Patients were asked to imagine paretic finger extension for 5 s in every 10 s. The subjects performed 50–100 trials/day, once or twice a week for 4–7 months as outpatients (12–20 training days). After the training, voluntary finger extensor electromyogram (EMG) activities newly appeared in four of six patients. In two patients showing voluntary contractions at baseline, involuntary EMG activities during the rest phase decreased. Event-related desynchronization (ERD) became significantly stronger in both hemispheres, suggesting increased ipsilesional cortical excitability. Five patients exhibited improvement of their paresis (as measured using the SIAS finger test) and spasticity [as assessed using the modified Ashworth scale (MAS)]. As for daily use of the paretic upper limb, the Motor Activity Log Amount of Use (MAL-AOU) score improved in five patients. In the TMS study, the resting motor thresholds for the first dorsal interosseous muscle decreased after the training, indicating enhanced ipsilesional cortical excitability.

**Single Case Study**

Mukaino et al. compared BMI-driven NMES (epoch B) with conventional NMES (epoch A) using an A-B-A-B withdrawal single-case design. A 38-year-old man with severe hemiplegia participated in the study. In epoch A, he attempted to open his fingers during the application of NMES, irrespective of his actual brain activity.
In epoch B, NMES was applied only when a significant motor-related cortical potential was observed in the EEG. The patient initially showed diffuse functional magnetic resonance imaging (fMRI) activation and small EEG responses while attempting finger movement. Epoch A was associated with few signs of improvement. In contrast, epoch B was associated with marked lateralization of EEG and blood oxygen level-dependent (BOLD) responses. Voluntary EMG activity, with significant EEG–EMG coherence, was also prompted. Clinical improvement in upper limb function and muscle tone was observed. The results indicated that self-directed BMI training may induce activity-dependent cortical plasticity and promote functional recovery.

**Case Series Studies**

To improve the feasibility of BMI training in real-world rehabilitation settings, we developed a new compact BMI system that enables task-specific training, including reach-and-grasp tasks, and studied its clinical feasibility and effectiveness. The participants were 26 patients with severe chronic hemiparetic stroke [age: 38–72 years; duration of stroke: 169–5391 days (median 772.5); SIAS finger score: 1A; and FMA-total median: 17.5 (inter quartile range 14.0–22.5)]. The subjects were trained with the BMI system to pick up and release pegs during 40-min sessions in addition to 40 min of standard occupational therapy per day for 10 days. After the BMI training, the UL-FMA total score, C (hand/finger) score, and MAL-AOU scores improved significantly. Effectiveness and safety were assessed using Quebec User Evaluation of Satisfaction with Assistive Technology (QUEST) 2.0 scores and showed feasibility and satisfaction in the clinical setting.

Kawakami et al. studied the efficacy of BMI training followed by Hybrid Assistive Neuromuscular Dynamic Stimulation (HANDS) therapy in 29 patients with chronic hemiparetic stroke [age: 50.6 ± 10.9 years; duration of stroke: 48.0 ± 41.4 months; SIAS finger score in all patients: 1A; FMA total score: 19.2 ± 6.4]. After the BMI training for 40 min a day for 10 days, finger extensor activity had appeared in 21 patients (80.8%). Eighteen of them then participated in 3 weeks of HANDS therapy, in which the participants received closed-loop, EMG-controlled NMES combined with a wrist–hand splint 8 h a day for 3 weeks. FMA (total, A, B, and C), MAL-AOU, and MAS (elbow, wrist and finger) scores improved significantly after the BMI training and showed further improvement immediately after and at 3 months after the HANDS therapy. This study indicated the possibility of seamlessly treating severe finger paralysis by starting...
with BMI and moving on to HANDS therapy.

Modulation of ERD with Anodal tDCS

It is sometimes difficult to detect stable ERD used to trigger the BMI system from the affected hemisphere. In healthy individuals, we demonstrated that anodal tDCS (10 min, 1 mA) could potentiate ERD. Based on this finding, we then studied whether ERD could also be enhanced with anodal tDCS in six patients with severe hemiparetic stroke [age: 56.8 ± 9.5 years; duration of stroke: 70.0 ± 19.6 months; UL-FMA total score: 30.8 ± 16.5]. We applied anodal and sham tDCS over the affected primary motor cortex in a random order, and assessed mu ERD with motor imagery of affected finger extension. The affected side mu ERD increased significantly after anodal tDCS but remained unchanged after sham stimulation. This suggested the possibility of using tDCS as a conditioning tool for BMI training. Based on these results, we performed a nonrandomized controlled trial involving 18 patients with chronic hemiparetic stroke [11 in the tDCS-BMI group (age: 53.5 ± 9.7 years; duration of stroke: 46.2 ± 20.2 months; FMA total: 27.6 ± 11.2) and 7 in the BMI group (age: 48.0 ± 12.4 years; duration of stroke: 56.4 ± 36.4 months; FMA total: 23.4 ± 13.9, no significant difference at baseline)] After 10 days of each intervention, ERD increased significantly only in the tDCS-BMI group. The FMA total and C scores rose significantly in both groups; however, the FMA improvement was maintained at 3 months only in the tDCS-BMI group. Ang et al. also suggested a role for tDCS in facilitating motor imagery in stroke.

Investigator-initiated RCT

We conducted a single-blind RCT in chronic post-stroke patients with severe hemiparesis (no voluntary finger extension) more than 90 days after onset (n = 40). Participants were randomly allocated to the BMI group (n = 20) or the control group (n = 20). Patients in the BMI group repeated 10-s motor imagery to operate EEG-BMI for 40 min per day followed by 40 min of conventional occupational therapy for 2 weeks. Control participants performed simple motor imagery without servo-action of the orthosis for 40 min, followed by 40 min of conventional occupational therapy for 2 weeks. The primary outcome was the UL-FMA score. The results of this RCT will be available soon.

Visual versus Somatosensory Feedback

Contingent feedback is important for motor learning. Ono et al. compared the efficacy of visual and somatosensory feedback in 12 patients with severe hemiparetic stroke who received 1-h/day BMI training for 2–3 weeks. In the 6 patients for whom visual feedback was provided by displaying ERD intensities, no changes in SIAS finger scores or EMG activities were observed. In contrast, in the 6 patients for whom somatosensory feedback was provided by extending the paretic fingers in proportion to the ERD intensity, functional recovery was observed in 3 patients and voluntary EMG newly appeared in 4 patients. These results indicated that somatosensory feedback is important for motor recovery.

The Significance of ERD

To clarify the neurophysiological basis of BMI-based neurorehabilitation, Takemi et al. studied the relationship of ERD with primary motor cortex (M1) excitability during motor imagery of right wrist movement as assessed using MEPs, short-interval intracortical inhibition (SICI), and intracortical facilitation (ICF) with TMS. Twenty healthy participants performed 7 s of rest followed by 5 s of motor imagery and received online visual feedback of the ERD magnitude of the contralateral hand M1 while performing the motor imagery task. TMS was applied to the right hand M1 when ERD exceeded predetermined thresholds during motor imagery, and MEP amplitudes, SICI, and ICF were recorded from the agonist muscle of the imagined hand movement. It was observed that the large ERD during wrist motor imagery was associated with significantly increased MEP amplitudes and reduced SICI but no significant changes in ICF; these findings indicated that the ERD magnitude during wrist motor imagery represents M1 excitability. This study provided electrophysiological evidence that a motor imagery task involving ERD may induce changes in corticospinal excitability similar to changes accompanying actual movements. Takemi et al. further examined the association of ERD during motor imagery with the excitability of spinal motoneurons in 15 healthy participants. The results indicated that the ERD magnitude during hand motor imagery was associated with an increase in F-wave persistence but not with the response average of F-wave amplitude or F-wave latency. These findings suggest that the ERD magnitude may be a biomarker representing increases in the excitability at both cortical and spinal levels. Using brain state-dependent TMS, Takemi et al. also showed that motor imagery-based BMI can selectively disinhibit the corticomotor output to the agonist muscle, enabling effector-specific training in patients with motor paralysis.

EEG-ERD and BOLD Signals

To study whether the ERD observed during motor attempt in stroke survivors can be regarded as a neural marker representing M1 excitability, Ono et al. investigated the association between ERD and the BOLD fMRI signal during attempted movement of a paralyzed finger in nine patients with chronic stroke. The subjects received
BMI training for finger extension movement 1 h daily for 1 month. After the BMI training, an increased ERD over the damaged hemisphere was confirmed in all participants during extension attempt of the affected finger, and this increase was associated with a BOLD response in the primary sensorimotor area. Whole-brain MRI revealed that the primary sensorimotor and supplementary motor areas were activated in the damaged hemisphere after the training. These findings suggest the reliability of EEG-ERD (based on the association with the affected side M1 BOLD signals) and functional reorganization of the cortex (based on the increased BOLD signals in M1 and SMA).

A Simultaneous EEG-fMRI Study

Blockade of the scalp EEG sensorimotor rhythm (SMR) is a well-known phenomenon following attempted or executed movements. Such a frequency-specific power attenuation of the SMR occurs in the alpha and beta frequency bands and is spatially registered at primary somatosensory and motor cortices. Tsuchimoto et al.65 employed fMRI to investigate the neural regions where activities were correlated with the simultaneously recorded SMR power fluctuations. These fluctuations were convolved with a canonical hemodynamic response function and correlated with BOLD signals obtained from the entire brain. The results show that the alpha and beta power components of the SMR correlate with activities of the pericentral area. Furthermore, brain regions with correlations between BOLD signals and the alpha-band SMR fluctuations were located posterior to those with correlations between BOLD signals and the beta-band SMR. These findings are consistent with those of event-related studies of SMR modulation induced by sensory input or motor output and may help to understand the role of sensorimotor cortex activity in contributing to the amplitude modulation of SMR during the resting state.

Changes in M1-S1 Connectivity

To elucidate the mechanisms underlying BMI neurofeedback, Tsuchimoto et al.66 assessed resting-state functional connectivity with MRI imaging (rsfMRI) between the ipsilesional sensory and motor cortices before and after a single 1-h intervention. Eighteen stroke patients were randomly assigned to crossover interventions in a double-blind and sham-controlled design. The neurofeedback intervention consisted of motor imagery, robotic assistance, and NMES administered to the affected finger extensors contingent on desynchronized ipsilesional EEG oscillations during motor imagery. The control intervention delivered sensorimotor stimulations that were independent of EEG oscillations. The results indicated that contingent EEG-SMR-based neurofeedback adjuvant to standard motor imagery of the affected hand resulted in significant increases in rsfMRI in post-stroke hemiparetic patients that were not found in the sham-controlled intervention. This study showed neurophysiological evidence that EEG-contingent neurofeedback is a promising strategy to induce intrinsic ipsilesional sensorimotor reorganization, thereby supporting the importance of integrating closed-loop sensorimotor processing at the neurophysiological level.

Technological Advances in BMI

Guiding spatially specific activation is important for facilitating neurorehabilitation. Hayashi et al.67 tested whether users could explicitly guide sensorimotor cortical activity to the contralateral or ipsilateral hemisphere using spatially bivariate EEG-based neurofeedback that monitors bi-hemispheric sensorimotor cortical activities in healthy participants. Two different motor imageries (shoulder and hand motor imageries) were selected to see how differences in intrinsic corticomuscular projection patterns might influence activity lateralization. They showed that sensorimotor cortical activities during shoulder motor imagery, but not during hand motor imagery, can be brought under ipsilateral control with guided EEG-based neurofeedback. These results are compatible with neuroanatomy; shoulder muscles are innervated bi-hemispherically, whereas hand muscles are mostly innervated contralaterally. The neuroanatomically inspired approach enables us to investigate the potent neural remodeling functions that underlie EEG-BMI-based neurofeedback.

To elucidate which brain regions are implicated in generating and coordinating voluntary movements, Iwama et al.68 employed a physiologically inspired two-stage method to decode relaxation and three patterns of contraction in unilateral finger muscles (i.e., extension, flexion, and co-contraction) from high-density scalp EEG. They demonstrated that weighted EEG features enabled a deeper understanding of human sensorimotor processing as well as offering a more naturalistic control of BMIs.

Conclusions

The restoration of post-stroke severe upper limb paralysis is challenging. Various interventions have been tried to facilitate motor recovery but so far with limited success. Among these interventions, BMI-based neurorehabilitation seems promising, and positive evidence of its effectiveness is accumulating, as demonstrated in recent meta-analyses. The neuroscientific mechanisms for its effects have also been investigated using electrophysiological and neuroimaging measurements. For the broader clinical application of BMI, the following problems need to be addressed: (1) Positioning of BMI therapy in post-stroke upper limb rehabilitation with clear-cut indications and pipelining with other interventions; (2) Development of an efficient program to generalize the motor functional
gain achieved with BMI intervention to daily activities; (3) Marketing as user-friendly and cost-effective medical devices; (4) Development of education and training systems for rehabilitation professionals to facilitate appropriate use; and (5) Technological breakthroughs that will enable selective modulation of neural circuits. It is confidently expected that BMI technologies will open a new frontier in neurorehabilitation.

Conflicts of Interest

Author Meigen Liu (ML) is a co-founder and an advisor of a research result utilization company LIFESCAPES Inc. and receives advisory fees. ML also holds shares in LIFESCAPES Inc. Author Junichi Ushiba (JU) is a co-founder and Representative Director of LIFESCAPES Inc. and receives advisory fees. JU also holds founder and Representative Director of LIFESCAPES Inc. Author Junichi Ushiba (JU) is a co-founder and Representative Director of LIFESCAPES Inc. and receives advisory fees. ML also holds shares in LIFESCAPES Inc. Both ML and JU have patents licensed to LIFESCAPES Inc. (PCT/JP2017/018216 for ML and JU, JP-5283065, 5813981, 6536869, 6536870, 6840343, 6917600, 6960619 and Design JP-1608029 for JU).

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