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RESEARCH REPORT

Newer challenges to restore hemiparetic upper extremity after stroke: HANDS therapy and BMI neurorehabilitation

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Abstract Because recovery of upper extremity (UE) functions to a practical level has been considered difficult in many patients with stroke, compensatory approaches have been emphasised. Recently, based on basic and clinical research indicating a greater potential for plastic changes in the brain, approaches directed toward functional restoration are becoming increasingly popular. Meta-analysis has indicated the effectiveness of constraint-induced movement therapy, electromyography biofeedback, electrostimulation, mental practice, and robot exercise to improve UE functions, but not hand functions. Therefore, we devised two new interventions to improve the paretic hand. One is hybrid assistive neuromuscular dynamic stimulation therapy, designed to facilitate daily use of the hemiparetic UE by combining electromyography (EMG)-triggered electrical stimulation with a wrist splint. We demonstrated improvement of motor function, spasticity, functional scores, and neurophysiologic parameters in chronic hemiparetic stroke. With a randomised controlled trial, we also demonstrated its effectiveness in subacute stroke. The other is brain-machine interface neurofeedback training, which provides real-time feedback based on analysis of volitionally decreased amplitudes of sensory motor rhythm during motor imagery involving extension of the affected fingers. This elicited new voluntary EMG activities, and improved finger functions and neurophysiological parameters. These interventions may offer powerful neurorehabilitative tools for improving hemiparetic UE function after stroke.

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Introduction

Recovery of upper extremity (UE) functions to a practical level has been considered difficult in many patients with stroke [1—3], so emphasis has tended to be placed on compensatory approaches, as opposed to functional restoration of the paretic UE itself. However, based on basic and clinical research indicating a much greater potential for plastic changes in the central nervous system [4—6], recently approaches directed toward functional restoration have been becoming increasingly popular [7].

These approaches include task-oriented training [8,9], repetitive bilateral arm training [10,11], constraint-induced movement therapy (CIMT) [12—14], electromyography (EMG)-triggered neuromuscular stimulation [15—21], repetitive transcranial magnetic stimulation (TMS) [22,23], transcranial direct current stimulation (tDCS) [24,25], robot-assisted training [26—28], and ischemic block [29]. More recently, brain machine interface (BMI) neurorehabilitation has also been proposed [30—37]. Among these approaches, CIMT has gained popularity and long-term effects have been reported [38]. However, the rather strict inclusion criteria and long hours of therapy under supervision limit its wider applicability.

To counter such problems, we devised a therapeutic approach to facilitate use of the hemiparetic UE in daily life by combining EMG-triggered electrical stimulation [39] with a wrist splint [40], calling this approach hybrid assistive neuromuscular dynamic stimulation (HANDS) [20,21]. We also developed an electroencephalography (EEG)-based BMI neurofeedback training system, which can provide real-time visual feedback based on the analysis of volitionally decreased amplitudes in sensory motor rhythm during motor imagery involving extension of the affected fingers [37]. The objectives of this review are first to describe recovery of UE functions in patients with hemiparetic stroke, and then to introduce newer therapeutic interventions for this challenging problem.

Recovery of upper limb functions after stroke

In the Copenhagen study, Nakayama and colleagues [3] assessed 421 patients with stroke weekly from onset using the Scandinavian Stroke Scale and the feeding and grooming items of the Barthel Index. They found that recovery mainly took place within the first 2 months, and full function was achieved by 79% of patients with mild paresis, compared to only 18% of patients with severe paresis. In patients with mild paresis, valid prognostication could be made in 3 weeks and further recovery was not expected later than 6 weeks after stroke. In patients with severe paresis, valid prognostication was possible in 6 weeks and further recovery was difficult beyond 11 weeks after stroke.

However, the above study is limited in that the outcomes were assessed using the UE-related items of the Barthel Index, which does not necessarily reflect the affected-side UE functions themselves, because these activities could also be performed using the unaffected UE. Furthermore, the study was published in 1994, and may not reflect newer advances in rehabilitative interventions. It is therefore important to know the extent to which UE functions recover under a conventional rehabilitation program before attempting to assess the effectiveness of newer therapeutic approaches for paretic UE.

Therefore, we performed a retrospective analysis of the recovery of UE functions in 314 patients (mean age, 60.9 years) with unilateral stroke admitted for rehabilitation [41]. Right hemiparesis was present in 160 patients and left hemiparesis in 154 patients. The cause of stroke was infarction in 147 patients and hemorrhage in 167. Mean days from stroke onset was 61.8 days, about 2 months poststroke, and mean duration of hospitalisation was 127.3 days, meaning that the second assessment was performed at about 6 months poststroke.

We assessed impairment of the UE using the Stroke Impairment Assessment Set (SIAS), a standardised assessment tool for stroke impairment [42] for which the psychometric properties are well described [43,44]. For motor assessment, proximal motor function was evaluated with the knee-mouth item, and distal motor function was assessed with the finger item. These items are rated from 0: no voluntary contraction to 5: full function. We also evaluated paretic UE function with the UE utility score, which consists of the four items of hanging a bag, pressing a sheet of paper on the desk, drinking with a glass and turning over a page. The resulting rating is from 0: impossible to 2: fully possible.

Table 1 demonstrates changes in SIAS UE item scores from admission to discharge. At discharge, significant improvements were observed for the knee-mouth, finger, touch, position and grip strength items. Table 2 illustrates changes in UE function test scores. On admission, the percentages of patients who could hang a bag or press a sheet of paper were 31% and 30%, increasing to 47% and 46% at discharge, respectively. For the items of drinking with a cup and turning over a page, only 20% and 22% of patients could do so on admission, but these percentages increased to 37% and 39% at discharge. As a whole, 49% of patients could not carry out any task item and only 20% could carry out all four task items on admission. At discharge, these percentages changed to 34% and 33%, respectively.

Table 1 Changes in stroke impairment assessment set (SIAS) upper extremity item scores from admission to discharge (n = 314)

Items	On admission (2 mos from onset)	At discharge (6 mos from onset)
Knee-mouth	2[a]	3[a]
Finger	1b[a]	1c[a]
DTR UE	2	2
Tone UE	2	2
Touch UE	2	2
Position UE	2.5[a]	3[a]
Shoulder abduction, degrees	140	140
Affected side GS, kg	5.4[a]	7.0[a]

[a]Wilcoxon signed-ranks test, $p < 0.01$.
DTR = deep tendon reflex; GS = grip strength; UE = upper extremity.

Table 2 Changes in upper extremity utility scores from admission to discharge ($n = 314$)

Hanging a bag	0: Impossible	1: Partially possible	2: Fully possible
Hanging a bag			
On admission	55	14	31
At discharge	38	15	47
Holding a piece of paper			
On admission	53	17	30
At discharge	40	14	46
Bringing a cup to mouth			
On admission	65	15	20
At discharge	52	11	37
Turning a page over			
On admission	65	13	22
At discharge	51	10	39

Figures indicate percentages.

Using classification and regression tree (CART) analysis [45], we examined whether we could predict discharge UE function from the admission impairment status as assessed using the SIAS. As for the hanging a bag item, 85.9% of patients scoring 0 on the SIAS knee-mouth item on admission scored 0 on the UE function test at discharge (Fig. 1A). Sixty-four percent of those scoring 3 on the knee-mouth item achieved full UE function at discharge. This percentage increased to 95.6% if the admission knee-mouth score was 4 or 5. An SIAS knee-mouth item score of 3 thus represented an important cut-off point for achieving practical UE function. The pressing a sheet of paper item showed a similar trend.

With regard to the drinking with a cup item, 98.2% of patients scoring 0 on the SIAS finger item on admission scored 0 on the arm function test at discharge (Fig. 1B). A total of 60% of those scoring 3 or above achieved full arm function at discharge. For those scoring 1 or 2 on admission, 77.2% of patients whose grip strength measured 0 kg scored 0 on the arm function test at discharge, while 70.7% of those whose grip strength measured above 0 kg achieved partial or full arm function at discharge. The turning over a page item showed a similar trend.

To summarize, our study demonstrated that UE functions continued to recover both at the impairment and disability levels from 2 to 6 months after stroke onset. This is in contrast to the Copenhagen study [3], which concluded that recovery could not be expected after 3 months poststroke. Thirty percent of patients achieved practical UE functions at discharge using a conventional rehabilitation program. An SIAS finger score of at least 3 on admission was required to achieve practical UE functions at discharge.

Newer rehabilitation approaches to the paretic UE

A recent meta-analysis examining the effectiveness of various interventions targeted at UE paresis indicated that CIMT, EMG biofeedback, electrostimulation, mental practice, and robot exercise are all effective for improving arm

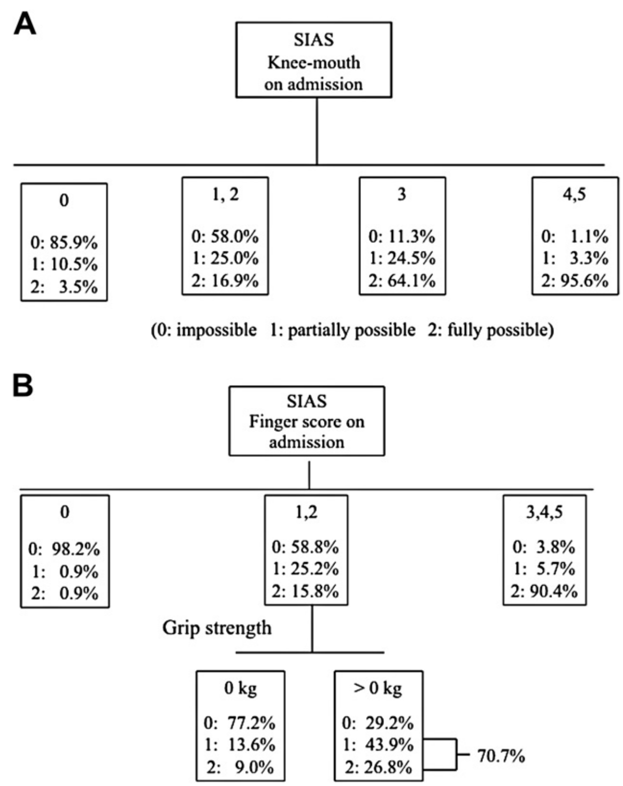

Figure 1 (A) Predicting discharge arm function (hanging a bag item). Using classification and regression tree analysis (CART), we analysed whether we could predict discharge arm function from admission impairment status as assessed using the Stroke Impairment Assessment Set (SIAS). For the hanging a bag item, 85.9% of patients scoring 0 on the SIAS knee-mouth item on admission scored 0 on the arm function test at discharge. Sixty-four percent of those scoring 3 on the knee mouth item achieved full arm function by discharge. This percentage increased to 95.6% if the admission knee mouth score was 4 or 5. The SIAS knee mouth item score of 3 represented an important cut-off point for achieving practical arm function; (B) predicting discharge arm function (bringing a cup to mouth item). Among the patients scoring 0 for the SIAS finger item on admission, 98.2% scored 0 on the arm function test at discharge. Of those scoring $\geq$3, 90.4% achieved full arm function at discharge. For those scoring 1 or 2 on admission, 77.2% of those patients with grip strength measuring 0 kg scored 0 on the arm function test at discharge, while 70.7% of those with grip strength >0 achieved partial or full arm function at discharge. SIAS knee mouth items: 0, no muscle contraction; 1, muscle contraction, but not to the level of the nipple; 2, can lift the hand to the level of the nipple; 3, can barely lift the hand to the mouth; 4, can lift the hand to the mouth with some clumsiness; and 5, can carry out the task smoothly. SIAS finger item. 0, no voluntary finger movement; 1A, mass finger flexion; 1B, mass finger extension; 1C, minimal individual finger movement; 2, incomplete individual finger movement; 3, individual finger movement with moderate clumsiness; 4, individual finger movement with mild clumsiness; 5, can carry out the task smoothly.

functions, but no intervention is known to be effective for improving hand functions [7]. There is thus a strong need for innovative therapeutic approaches to the paretic hand. The following is a description of our attempts to tackle this difficult problem, in the form of HANDS therapy and BMI-based neurorehabilitation.

HANDS therapy

The concept of HANDS therapy

As mentioned above, the effectiveness of CIMT has been widely recognised. This method emphasises forced use of the affected arm to combat the so-called "learned non-use," and its effectiveness has been documented [12–14]. However, CIMT is both time- and personnel-intensive, and candidates must be able to voluntarily extend the fingers and wrist to some extent.

To counter these limitations, Fujiwara and others [20] developed HANDS therapy as a new alternative therapeutic approach to facilitate use of the affected UE in daily living for patients with insufficient mass or individual extension of the paretic fingers. HANDS therapy has four components: (a) integrated volitional electrical stimulation (IVES) [39], (b) a wrist splint [40], (c) encouraged use of the affected arm, and (d) occupational therapy (OT) sessions (Fig. 2).

The effectiveness of EMG-TES has been suggested in several meta-analyses [15,16]. Muraoka and colleagues [39] developed IVES as a new EMG-triggered electrical stimulator. With IVES, we can automatically adjust stimulation intensity in proportion to the amplitude of voluntary EMG. Using this assistive stimulation, patients can extend the fingers at will.

As for the splint, Fujiwara and coauthors [40] previously demonstrated that use could reduce overactive finger flexors and facilitate voluntary finger extension. These effects are considered to be brought about by reducing monosynaptic excitability in the flexors, possibly through stretching effects. This mechanism is suggested by a significant reduction in the H wave to M wave ratio elicited from the flexor carpi radialis. Combining IVES with the splint appears to facilitate paretic hand use in daily living.

Effectiveness of HANDS therapy in chronic stroke

We first performed a before-and-after trial in patients with chronic hemiparetic stroke [20]. The eligibility criteria included: (a) time from onset >150 days, (b) no cognitive deficit, (c) no pain, severe proprioceptive deficit or contractures, (d) EMG detectable from extensor digtorum communis (EDC), (e) independent ambulation, and (f) no motor improvement in the last 1 month. Participants comprised 20 patients with chronic hemiparetic stroke and a mean age of 51 years. Median duration from onset was 17.5 months (range, 5.3–32.5 months). Nine patients had right hemiparesis and 11 had left hemiparesis.

The intervention consisted of combined use of a wrist splint and IVES for 8 hours a day for a mean of 21 days. A pair of electrodes for EMG detection and stimulation (30×12 mm) placed 5 mm apart, and one electrode (30×30 mm) for reference and stimulation were placed on the affected EDC muscle. Three trains of biphasic square-wave pulses with duration of 300 μs were applied at 20 Hz. Stimulus intensity was continuously changed in proportion to the detected EMG amplitude of the target muscle. Supervised OT was provided 40 minutes a day, 5 days a week during the intervention period. Before and immediately after completing a 3-week course of HANDS therapy, clinical and neurophysiological measures were assessed. A follow-up clinical assessment was performed 3 months later.

As a result, UE utility scores, SIAS finger and knee-mouth scores, modified Ashworth scale [46] for elbow, wrist and finger flexors, affected-side grip strength, pen pressure and EMG measurements improved after the intervention [20].

Neurophysiologically, the intervention induced restoration of presynaptic and long-loop inhibitory connections, as well as disynaptic reciprocal inhibition [47]. A paired pulse TMS study [48] indicated disinhibition of short intracortical inhibition in the affected hemisphere.

The follow-up assessment at 3 months postintervention showed that improved UE functions had been maintained.

Effectiveness of HANDS therapy in subacute stroke

Our second trial investigated the effects of HANDS therapy in the subacute phase [21]. Participants were 24 inpatients with hemiparetic stroke who were within 60 days post-stroke, randomly assigned to two groups. The HANDS group ($n = 12$) used IVES combined with a wrist splint for 8 hours a day for 3 weeks. The control group ($n = 12$) used a wrist splint for 8 hours a day for 3 weeks. Outcome measures included Fugl-Meyer Assessment (FMA) of UE

Figure 2 HANDS therapy. HANDS therapy consists of four components: (1) integrated volitional electrical stimulation (IVES), (2) a wrist splint, (3) encouraged use of the affected arm, and (4) occupational therapy (OT) sessions. The HANDS system is used during the daytime to facilitate hand use in daily activities. HANDS = hybrid assistive neuromuscular dynamic stimulation.

function [49], the action research arm test (ARAT) [50], and motor activity log-14 (MAL-14) [53].

Ten patients in each group completed the interventions. Compared with the control group, the HANDS group showed significantly greater gains in FMA score for the distal (wrist/hand) portion ($p < 0.01$) and improvement of ARAT ($p < 0.05$). The gains in MAL did not reach the level of statistical significance in favor of the HANDS group over the control group. In summary, HANDS therapy induced improvements in motor functions, particularly for the distal portion, in patients with subacute stroke.

Mechanisms underlying HANDS therapy

Fig. 3 depicts the proposed mechanisms for the improvement of arm function observed with HANDS. EMG-TES brings about reciprocal inhibition of antagonists and facilitation of agonists. The wrist splint contributes to the inhibition of overactive flexor muscles and flexor-associated movements. Together, these two facets of HANDS make it easier for the patient to use their paretic hand in daily life, leading to improved arm function. The combined effects of improvement in spasticity at the spinal cord level, plastic changes in cortical motor area and dose-dependent effects brought about by increased use of the affected arm in daily life are postulated as the mechanisms underlying improvement.

The above two studies suggest that HANDS therapy can induce corticospinal plasticity and may offer a promising option in the management of a paretic UE for patients with stroke in both the chronic and subacute phases. However, to be candidates, EMG must be recorded from finger extensors, which means that this approach is not applicable

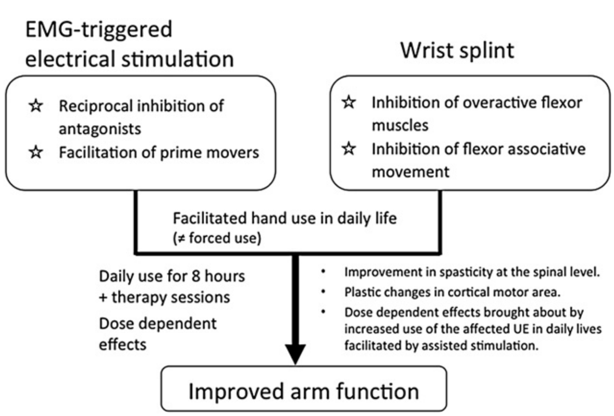

Figure 3 Proposed mechanisms for improvement with HANDS. EMG-triggered electrical stimulation results in reciprocal inhibition of antagonists and facilitation of agonists. The wrist splint brings about inhibition of overactive flexor muscles and flexor associative movement. Together, these changes facilitate use of the paretic hand in daily life, leading to improved arm function. The combined effects of improvement in spasticity at the spinal cord level, plastic changes in the cortical motor area and dose-dependent effects brought about by increased use of the affected arm in daily lives are postulated as mechanisms involved in improvement. EMG = electromyography; HANDS = hybrid assistive neuromuscular dynamic stimulation.

to patients with complete paralysis. For these patients, the BMI technology described in the next section might offer some benefits.

BMI neurorehabilitation

Background

Newer neurorehabilitation techniques using BMI technology have been proposed for patients with severe paresis after stroke [30—37]. BMI operates external devices based on brain activities. Brain signals can be detected and measured in many ways, either noninvasively with surface EEG [34—37], magnetoencephalography (MEG) [30,34], functional near-infrared spectroscopy (fNIRS) [51], or invasively with intracortical and electrocorticography (ECoG) recordings [52]. Among the various types of BMI, EEG-BMI is widely used because of the simplicity, safety, portability, and low cost.

BMI is a potentially useful technology in rehabilitation, not only to substitute for lost functions, but also to induce brain plasticity. BMI can bypass the normal motor output neural pathways and directly translate brain signals into commands for the control of external devices [31]. As extrinsic feedback is expected to promote motor learning and improve UE motor recovery after stroke [32], approaches using BMI technology might facilitate neural network plasticity and restoration of function. The motor intentions of the patient are usually estimated from changes in brain activity over the primary sensorimotor cortex (termed the sensory motor rhythm; SMR), and are displayed through visual feedback [37]. Various studies have examined the possibility of MEG-based BMI [30,34] and EEG-based BMI [34—37] for neurorehabilitation in patients with chronic stroke, and some neuroplastic changes have been suggested (Table 3 [30,34—37]). BMI systems are thus expected to help guide cortical reorganisation by motor learning, and to make neurorehabilitative approaches more effective. However, how neurofeedback training with BMI systems induces clinical and neurophysiological changes in stroke patients remains unclear.

Our BMI neurorehabilitation system

We developed an EEG-based BMI neurorehabilitation system (Fig. 4) and studied its clinical and electrophysiologic effectiveness [37]. With our system, the patient sits on a chair looking at a computer monitor. A star-shaped cursor moves at a fixed rate from left to right, with the position reflecting the mu rhythm (in the frequency range of 8—13 Hz) amplitude during motor imagery. The cursor moves up and down according to the degree of success of motor imagery. Upon successful motor imagery, the fingers are extended by an electrically powered orthosis, which is triggered as a result of the EEG classification.

Using this system, we undertook a preliminary case-series study [37], selecting patients with first-ever unilateral stroke. Duration from onset in these patients was longer than 180 days, and finger test scores on the SIAS were equal to or less than 2 on a five-point scale, meaning that the paresis was fairly severe. The participants

Table 3 Studies on brain machine interface (BMI)-based neurorehabilitation for patients with stroke

Author	Year	Patients	Intervention	Results
Buch E [30]	2008	8	MEG-BMI + hand orthosis 13–20 sessions	Successful control in 6/8 Improved ipsi-lesional (n = 4) and contra-lesional (n = 2) ERD No improvement in hand function
Ang KK [35]	2009	8 10	EEG-BMI + MIT-Manus MIT-Manus only 12 sessions	Increase in FMA in both groups; no significant difference. Significant difference with subgroup analysis
Daly JJ [36]	2009	1	EEG-BMI + FES 9 sessions	Recovery of volitional isolated index finger extension
Broetz D [34]	2010	1	EEG-BMI-robot + PT for 1 y	Improved hand and arm function (FMA, WMFT), and gait. Increased μ-oscillations in the ipsilesional motor cortex
Shido K [37]	2010	8	EEG-BMI + hand orthosis 12–20 sessions	Appearance of EMG in 4/6 Decrease in involuntary EMG in 2/2 Improved motor function in 5/8 Improved spasticity in 5/8 Increase in MAL-14 in 5/8

EEG = electroencephalography; EMG = electromyography; ERD = event-related desynchronisation; FES, functional electrical stimulation; FMA = Fugl-Meyer assessment; MAL = motor activity log; MEG = magnetoencephalography; PT = physical therapy; WMFT = Wolf motor function test.

comprised eight patients with chronic hemiparetic stroke, ranging in age from 46 to 68 years and with a duration from onset of 1.3 to 12 years. The degree of finger voluntary control as assessed with the SIAS was 1A in five patients, meaning mass flexion, 1B in two patients, meaning mass extension, and two in 1 patient, meaning incomplete finger individual movement. All patients showed mild to moderate spasticity in the paretic fingers.

As for the training protocol, patients were asked to imagine extending the paretic fingers for 5 s in every 10 seconds. They performed 50–100 trials/day, once or twice a week, for 4–7 months as outpatients. Each participant thus had 12–20 training days. We compared the results of clinical and neurophysiological examinations pre- and postintervention.

After BMI training, five patients with moderate-to-severe hand paresis exhibited improvement of hand paresis, as measured with the SIAS finger test. No change in motor impairment was seen in the other three patients with severe hand paresis. We measured the use of the paretic upper extremity with the MAL [53], a structured interview with known psychometric properties. The MAL amount of use (AOU) was zero in five patients before the intervention. After the intervention, this was increased in the five patients who exhibited some improvement in motor paresis. Through participation in the BMI training, all patients indicated that they became more aware of the use of their paretic UE in daily activities, and felt that they could relax it more easily. In four patients, voluntary EMG activities of the affected finger extensors that were absent

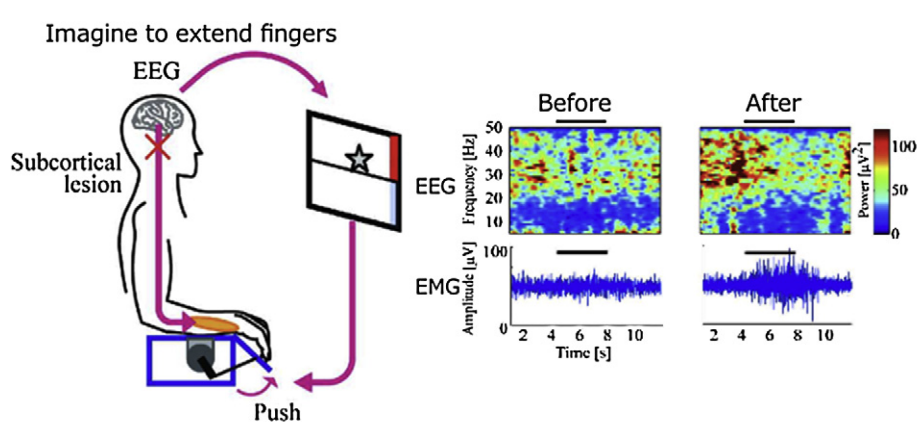

Figure 4 EEG-based BMI neurorehabilitation system. The patient sits on a chair looking at a computer monitor. A star-shaped cursor moves at a fixed rate from left to right, and its position reflects the mu rhythm (frequency range, 8–13 Hz) amplitude during motor imagery. The cursor moves up and down according to the degree of success of motor imagery. Upon successful motor imaging, the fingers are extended using an electrically powered orthosis, which is triggered as a result of the EEG classification. After the training, event-related desynchronisation (ERD) became stronger during motor imagery, and EMG became newly recordable from finger extensor muscles. BMI = brain machine interface; EEG = electroencephalography.

at the initial session newly appeared at the final session. In patients with voluntary contractions, involuntary EMG activities during the resting phase decreased after the training. Consequently, all patients showed improvements in motor function or voluntary EMG. After training, event-related desynchronisation (ERD) became significantly stronger over both hemispheres, suggesting increased ipsi-lesional cortical excitability. The majority of stroke patients showed changes in SMR during motor imagery over the affected hemisphere after BMI training, although some showed changes over the unaffected hemisphere.

To assess changes in corticospinal excitability, we applied TMS over the ipsi-lesional hemisphere, and compared resting motor thresholds (RMTs) for the first dorsal interosseous muscle (FDI) at 1 week before and 1 week after neurofeedback training. RMT was found to be decreased after the training, indicating enhanced ipsilesional cortical excitability. This finding suggests that BMI neurofeedback training facilitated corticospinal excitability as a lasting effect, even in patients with severe hemiparesis.

Modulation of ERD with anodal tDCS

As mentioned above, our EEG-based BMI was developed as a new neurorehabilitative tool for patients with severe hemiparesis. However, it is sometimes difficult to detect the stable brain signal changes (ERD) used to trigger the BMI system from the affected hemisphere. We have already demonstrated that anodal tDCS (10 minute, 1 mA) could modulate ERD in healthy individuals [54]. We therefore studied whether we could also enhance ERD with anodal tDCS in patients with severe hemiparetic stroke [55]. The participants were six patients with chronic hemiparetic stroke (age, 56.8 $\pm$ 9.5 years; time from onset, 5.8 $\pm$ 1.6 years; FMA UE motor score, 30.8 $\pm$ 16.5). We applied anodal (10 minutes, 1 mA) and sham tDCS over the affected primary motor cortex in a random order. ERD of the mu rhythm (mu ERD) with motor imagery of extension of the affected finger was assessed before and after anodal tDCS and sham stimulation. As a result, mu ERD of the affected hemisphere increased significantly after anodal tDCS, but remained unchanged after sham stimulation. This kind of stimulation could thus represent a conditioning tool for BMI training for such individuals.

Mechanism of improvement

With our EEG-based BMI training, we observed the following changes [37]: (a) improvements in motor function of the affected fingers and surface EMG activity of the affected finger extensors, (b) greater suppression of the SMR over both hemispheres during motor imagery, (c) facilitation of cortical excitability as assessed with the TMS in the affected hemisphere in patients with greater changes in SMR over the affected hemispheres, and (d) increased daily usage of the paralysed hand in some patients. Particularly promising was the induction of voluntary muscle activity in patients with little or no remaining motor function, because this can open up the possibility of reinforcement with other established interventions, such as HANDS therapy [20,21].

As for the mechanisms underlying such recovery, motor imagery is known to activate the damaged brain in a manner similar to motor execution, and to induce corticospinal excitability in both healthy individuals and post-stroke patients [56]. Although clinical effectiveness has been so far limited to mild-to-moderate hemiparesis [57], motor imagery coupled with visual and kinesthetic feedbacks as utilised in our BMI neurofeedback training might have helped to induce cortical excitability even in patients with complete loss of motor function.

The majority of stroke patients reportedly show changes in SMR during motor imagery over the affected hemisphere after BMI training, although some show changes over the unaffected hemisphere [30]. Our TMS results were consistent with the findings of the previous study [30], and supported the notion that changes in SMR over the affected hemisphere might relate to improvements in motor control of the affected side, with decreased RMT of the affected hemisphere. On the other hand, ipsilateral activation of the unaffected motor cortex, shown during movement of the paretic hand [58,59], was considered to play an important role in the recovery of motor function after stroke [60]. These results might explain the relationship between changes in SMR over the unaffected hemisphere and improvements in motor control of the affected side in some cases.

Other possible mechanisms include: (a) increased awareness of and attempts to use the paretic UE, (b) passive stretching of the paretic fingers [61], (c) correction of hemispheric inhibition, (d) neuroplastic changes toward more optimal reorganisation induced by visual feedback of brain activity, and (e) alterations in connectivity of the prefrontal lesion [62].

To further clarify the mechanisms underlying improvement, we are now studying changes in activation patterns of the brain before and after BMI training with functional magnetic resonance imaging (fMRI). Although only preliminary results have been obtained, several different activation patterns seem to exist among individual patients. Some patients show activation of the primary and supplementary motor areas after BMI training, while others demonstrate activation of the cerebellum or more focused activation of the supplementary motor area instead of the diffuse brain activation seen before training. We plan to study how these differences in the pattern of activation arise in relation to factors such as time from onset, lesion site and size, and degree of intracortical and interhemispheric inhibition.

In addition, by measuring fMRI and EEG simultaneously, we identified a correlation between blood flow changes and EEG changes. This finding indicates that the changes in EEG (ERD) used in EEG-based BMI reflect cortical excitability, an important finding to explain the mechanisms underlying EEG-BMI neurofeedback training.

Furthermore, using a navigation TMS system, with which we could stimulate the desired area of the brain with a space resolution accuracy of 5 mm, we found that the cortical areas demonstrating significant increases in blood flow on fMRI correlated well with areas of low excitability threshold with TMS. When we applied TMS according to the intensity of EEG changes during motor attempts, we found that the degree of ERD correlated with motor evoked potentials (MEP) amplitude. These findings are useful to clarify the physiological significance of EEG changes, and are important in explaining the mechanisms underlying EEG-BMI neurofeedback training.

Future prospect

Although our BMI neurorehabilitation system demonstrated preliminary effectiveness for inducing motor improvements in patients with severe hemiparetic stroke, study of the clinical effectiveness with a larger sample in a controlled study with elucidation of the mechanisms resulting in improvement will be necessary.

Based on the experience with our preliminary device for EEG-based BMI neurofeedback, we are now developing a new EEG-BMI power-assisted orthosis (Fig. 5). This orthosis will be wireless, and powered by commercially available AA batteries. Meticulous skin preparation will not be necessary for EEG recordings due to our newly developed dry EEG electrodes. The device will therefore be more easily applicable in daily clinical settings. In the near future, we are thinking of spreading our cutting-edge rehabilitation technology based on information technology communication platforms. Through a central server operated from our laboratory, patients will be able to receive BMI neurorehabilitation training at local hospitals and clinics, at home and in welfare facilities.

Therapeutic strategy for the hemiparetic UE

Fig. 6 summarizes our current treatment strategy for UE paresis in patients with stroke. If the patient demonstrates individual finger movement, treatment could be provided as either conventional rehabilitation or CIMT. If no individual finger movement is shown, but finger extensor EMG is detectable, HANDS therapy can be applied. When no finger extensor EMG is detectable, robot-assisted therapy or BMI neurorehabilitation might be an option. In other words, for individuals with severe hemiparesis showing no detectable EMG activities, we will first start with BMI neurofeedback training to induce EMG activities in the paretic muscles, sometimes in combination with tDCS to increase cortical excitability in the absence of contraindications such as seizures. Once EMG activities become recordable, we will then move on to HANDS therapy to further improve motor function and performance. If spasticity interferes with the movement, then we would use botulinum toxin [63] as an adjunctive therapy. By wisely selecting and combining currently available therapeutic tools including HANDS and BMI neurofeedback training, we believe we can open up new possibilities for the restoration of function in the hemiparetic UE.

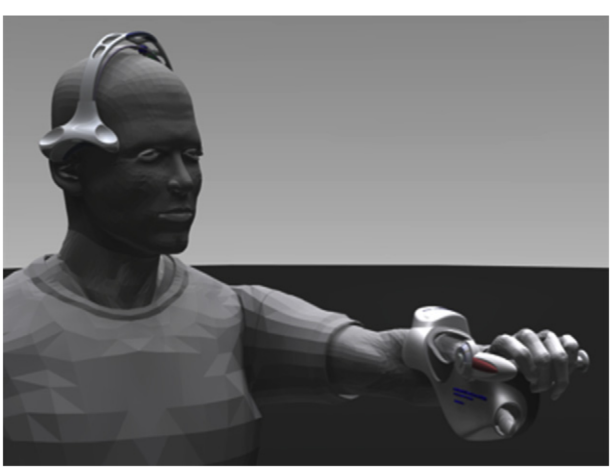

Figure 5 A newly designed EEG-BMI power-assisted orthosis. This system will be wireless, and powered by commercially available AA batteries. Meticulous skin preparation will not be necessary for EEG recordings due to newly developed dry EEG electrodes. The device will therefore be easily applicable to daily clinical settings. BMI = brain machine interface; EEG = electroencephalography.

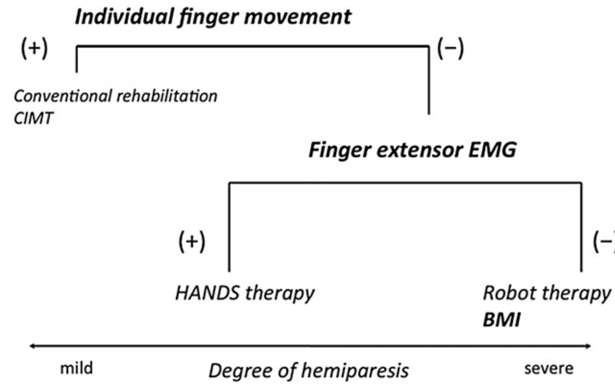

Figure 6 Rehabilitation strategy for the paretic upper limb. If the patient shows individual finger movements, treatment could comprise either conventional rehabilitation or constraint-induced movement therapy. If the patient has no individual finger movement, but a detectable finger extensor on EMG, the HANDS therapy can be applied. If no finger extensor EMG can be detected, robot-assisted therapy or BMI might be an option. BMI = brain machine interface; EEG = electroencephalography; EMG = electromyography; HANDS = hybrid assistive neuromuscular dynamic stimulation.

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