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ORIGINAL REPORT

FEASIBILITY OF TASK-SPECIFIC BRAIN-MACHINE INTERFACE TRAINING FOR UPPER-EXTREMITY PARALYSIS IN PATIENTS WITH CHRONIC HEMIPARETIC STROKE

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Objective: **Brain-machine interface training was developed for upper-extremity rehabilitation for patients with severe hemiparesis. Its clinical application, however, has been limited because of its lack of feasibility in real-world rehabilitation settings. We developed a new compact task-specific brain-machine interface system that enables task-specific training, including reach-and-grasp tasks, and studied its clinical feasibility and effectiveness for upper-extremity motor paralysis in patients with stroke.**

Design: **Prospective before–after study.**

Subjects: **Twenty-six patients with severe chronic hemiparetic stroke.**

Methods: **Participants were trained with the brain-machine interface system to pick up and release pegs during 40-min sessions and 40 min of standard occupational therapy per day for 10 days. Fugl-Meyer upper-extremity motor (FMA) and Motor Activity Log-14 amount of use (MAL-AOU) scores were assessed before and after the intervention. To test its feasibility, 4 occupational therapists who operated the system for the first time assessed it with the Quebec User Evaluation of Satisfaction with assistive Technology (QUEST) 2.0.**

Results: **FMA and MAL-AOU scores improved significantly after brain-machine interface training, with the effect sizes being medium and large, respectively ($p<0.01$, d = 0.55; $p<0.01$, d = 0.88). QUEST effectiveness and safety scores showed feasibility and satisfaction in the clinical setting.**

Conclusion: **Our newly developed compact brain-machine interface system is feasible for use in real-world clinical settings.**

Key words: electroencephalogram; cerebrovascular disease; hand function; rehabilitation.

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Stroke is one of the most prevalent neurological conditions worldwide, especially among elderly adults. It has been reported that 30–66% of all stroke patients with hemiparesis have poor arm function 6 months post-stroke (1). Motor recovery relates to: restoration of function in neural tissue that was initially lost; restoration of the ability to perform movement in the same way as before injury; and successful task completion as typically performed by individuals who are not disabled. Types of motor compensation in these 3 areas include the acquisition by neural tissue of a function that it did not have before the injury; performance of a movement in a new way; and successful task completion by using different techniques (2, 3). It has been reported that the major portion of recovery of upper-extremity (UE) motor impairment occurs over the first few months after stroke (4). However, some newly developed approaches for rehabilitation have also improved UE motor function in patients with chronic stroke (5–7).

Recently, a brain-machine interface (BMI) has been developed as a new rehabilitation tool for patients with severe UE paresis (8–14). A BMI detects the increased sensorimotor cortical activity following patient's attempting UE motor activities and provides associated actions with external devices, such as a motor-driven orthosis by functional neuromuscular electrical stimulation (15). Due to such BMI actions, patients begin to exercise UE movement by themselves, even though no volitional signs on EMG or kinematics are found in the innate condition. Several clinical studies have tested the clinical efficacy of BMI-based exercise as motor rehabilitation after stroke and spinal cord injury (16).

BMI is thought to be a novel tool for rehabilitation of patients with severe paresis, for which no intervention has so far been convincingly shown to be effective. A randomized, controlled trial showed that BMI training improved UE motor function even in patients with chronic stroke and severe UE impairment (11). Kawakami and colleagues (17) reported that significant functional recovery from stroke could be induced with BMI training followed by Hybrid Assistive Neuromuscular Dynamic Stimulation (HANDS) therapy in patients with chronic and severe hemiparesis (Fugl-Meyer upper extremity motor (FMA)-gain 14.6

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points). There have been, however, some limitations to clinical application of BMI systems. Most of them were set up in the laboratory and cannot be used in general clinical areas (i.e. therapy rooms). In addition, most of the BMI training in previous reports mainly aimed at improving paretic finger extension (10, 11). To make their paretic UE useful in real-life activities of daily living (ADL), it is necessary to restore hand grip-and-release function combined with arm-reaching function (18).

A new compact BMI system that enables task-specific training, including reach-and-grasp tasks was developed, and applied to a clinical rehabilitation setting. The aim of this study was to investigate the feasibility of this compact BMI system in clinical rehabilitation.

MATERIAL AND METHODS

Participants

Patients were recruited from the outpatient rehabilitation clinics of Keio University Hospital. They were included in this study if they met the following criteria: (*i*) a first unilateral subcortical stroke not involving the sensorimotor cortex as confirmed with brain magnetic resonance imaging (MRI) or computed tomography (CT); (*ii*) age between 20 and 80 years; (*iii*) time from stroke onset longer than 180 days; (*iv*) ability to raise the paretic hand to the height of the nipple; (*v*) inability to extend the paretic fingers; (*vi*) no severe proprioceptive deficit in the affected UE; (*vii*) no motor improvement during the 30 days prior to starting the intervention, as confirmed by both the patients and their physicians; (*viii*) ability to walk independently with a cane and/or orthosis in their daily lives; (*ix*) no remarkable pain in the paretic UE; (*x*) no cognitive deficits as determined by a Mini-Mental State Examination score >25; (*xi*) no pacemaker or other implanted stimulator; and (*xii*) no history of seizures within the past 2 years and no use of anticonvulsants at least for 1 month before the intervention.

From 2011 to 2013, 50 patients were seen at the outpatient clinic to be evaluated for eligibility for this study. Twenty-four patients were excluded because they did not meet the inclusion criteria, and 26 patients were enrolled in the study. The study purpose and procedures were explained to the participants, and written, informed consent was obtained from each patient. This study was approved by the institutional ethics review board. This study was registered as a clinical trial with the University Hospital Medical Information Network in Japan (UMIN Critical Trial Registry UMIN000002121).

Electroencephalographic recording

The experiment consisted of BMI training and brain activity assessment using electroencephalography (EEG). EEG was performed with Ag-AgCl electrodes (1 cm in diameter), at C3 and the left ear in patients with right hemiparesis, and at C4 and the right ear in patients with left hemiparesis, according to the international 10–20 system (18). An additional electrode was placed at a position 2.5 cm anterior to C3 or C4. A ground electrode was placed on the forehead, and the reference electrode was placed on either A1 or A2 (ipsilateral to the affected hemisphere). EEGs were recorded in a bipolar manner. The signals were digitized at 256 Hz using a biosignal amplifier (g.MOBIlab+, G.tec Medical Engineering GmbH, Graz Austria).

Event-related desynchronization quantification

As a feature representing the increased excitability of the ipsilesional sensorimotor cortex, event-related desynchronization (ERD), which is a diminution of the alpha band (8–13 Hz) of the mu rhythm amplitude, was calculated as follows, and used as a trigger signal for BMI actions. The ERD was expressed as the percentage of the power decrease related to the 1-s reference interval before the direction of intention. The ERD at a certain frequency was calculated for each time and frequency according to the following equation:

$$\mathrm{ERD}\ (f, t) = \{(R(f) - A(f, t))/R(f)\} \times 100\ (\%);$$

where A(f, t) is the power spectrum density of the EEG at a certain frequency band f [Hz] and time t [s] since the imagery task was started, and R(f) is the power spectrum at the same frequency f [Hz] of the baseline period.

The physiological relevance of the mu rhythm and its ERD on EEG have been reported previously; the mu rhythm amplitude is inversely correlated with the blood oxygen level-dependent signal of the sensorimotor cortex (19), corticospinal tract excitability (20), disinhibition of intra-cortical inhibition in the primary motor cortex (20), and spinal motoneuronal excitability (21). Operating the BMI through this EEG feature is therefore interpreted as an up-conditioning of the ipsilesional corticomuscular pathway involved in motor control.

Task-specific brain-machine interface training

BMI training was carried out for approximately 40 min for 10 days. All of the participants received 40 min of standard occupational therapy per day, which consisted of gentle stretching exercises, active muscle re-education exercises, and introduction to bimanual activities in their daily lives.

The participants wore a headset with 2 brush-type electrodes that recorded the ipsilesional mu rhythm (Fig. 1a). With this headset electrode system, it is easy to set the electrode on C3 or C4 (i.e. the corticocerebral motor area) to record the EEG by adjusting the headset to the relative positions of both ears. It takes only 5 min to set the electrodes. The motor-driven orthosis was attached to the affected hand to achieve finger extension movement at the metacarpophalangeal and proximal interphalangeal joints. The affected forearm was placed on a balanced forearm orthosis (Fig. 1b). The participants were seated in front of a desk. Thirty pegs were set on the desk peg board. Participants were asked to pick up a peg with the affected hand with the orthosis (Fig. 1c). A star-shaped cursor began to move at a fixed rate from left to right across the monitor over an 8-s period. Participants were instructed to rest for 5 s and then to either imagine extending their affected fingers or remain relaxed for the next 3 s, depending on the task cue on the monitor. If the mu ERD was detected after the cue instruction to imagine finger extension, the star-shaped cursor moved down on the screen as visual feedback, and then the motor-driven hand orthosis extended the affected fingers and stimulated the extensor digitorum communis muscle (EDC) by electrical stimulation weaker than its motor threshold (frequency 100 Hz, pulse width 200 μs) for 3 s (Fig. 2). If ERD was not detected after the cue, which meant that the motor imagery was not successfully performed, the orthosis did not move, and electric stimulation was not applied.

Fig. 1. Task-specific brain-machine interface (BMI) system. (a) A pair of dry electroencephalographic (EEG) electrodes with a headset: event-related desynchronization (ERD) during motor imagery of paretic finger extension is detected on the affected sensory motor cortex (C3 or C4) using this pair of dry electrodes. (b) Motor-driven hand orthosis: patients wear the motor-driven hand orthosis for picking up and releasing a peg. This orthosis fixes the form of the paretic hand. If ERD is detected after cue instruction of motor imagery of finger extension, then the orthosis extends the participant's paretic fingers. (c) Overview of task-specific BMI system: computer screen, peg task, motor-driven hand orthosis on the affected hand, and headset with a pair of dry electrodes on the head.

Feasibility of the newly developed BMI system for professional users

The time needed to set up this BMI training system every day was measured, and the mean time calculated. Four occupational therapists who had not operated the BMI system previously were asked to set up and operate the system, and a questionnaire survey with the Quebec User Evaluation of Satisfaction with assistive Technology 2.0 (QUEST 2.0) (22) was conducted after the intervention. The QUEST survey comprises 12 satisfaction items whose scores range from 1 (very satisfied) to 5 (not satisfied at all). The QUEST 2.0 was used to evaluate the usability of a BMI-based system in a previous report (23). The time needed for each therapist to set up the system was also measured.

Outcome measures

The following clinical assessments were conducted one day before (pre) and the day after the intervention (post). The number of times that a participant

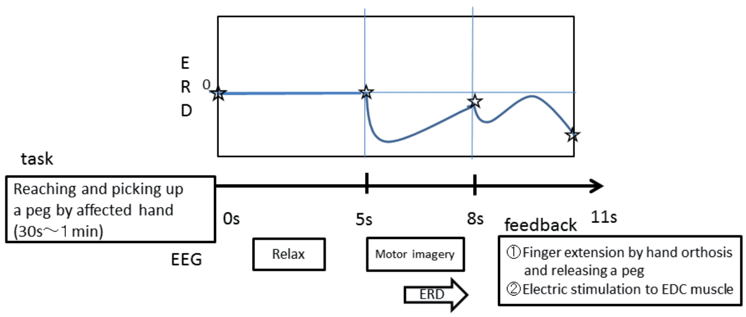

Fig. 2. Illustration of an event-related desynchronization (ERD)-electrical stimulation protocol. A star-shaped cursor began to move at a fixed rate from left to right across the monitor over an 8-s period. Participants were instructed to rest for 5 s and then to either imagine extending their affected fingers or remain relaxed for the next 3 s, depending on the task cue on the monitor. If the mu ERD was detected after the cue instruction to imagine finger extension, the star-shaped cursor moved down on the screen as visual feedback, and then the motor-driven hand orthosis extended the participants' affected fingers and stimulated the extensor digitorum communis muscle (EDC) by electrical stimulation weaker than its motor threshold (frequency 100 Hz, pulse width 200 μs) for 3 s. If the mu ERD was not detected, the motor-driven hand orthosis did not move for the extension of the participants' fingers.

produced appropriate ERD (number of ERD detections) during BMI training was reported each day.

Clinical assessments

UE motor function was assessed with the FMA (range 0–66 points, total score) (24, 25). The FMA consists of test A (shoulder/elbow/forearm: 36 points, A score), test B (wrist: 10 points, B score), test C (hand/finger: 14 points, C score), and test D (coordination: 6 points, D score). The D score was excluded because not all of the patients in this study could touch their nose with their index finger fully extended, and they had no voluntary finger extension. The FMA was assessed according to the scoring manual (26), and the validity and reliability of this method have been confirmed previously (25, 27). It was reported that the estimated clinically important difference of the UE-FM scores ranged from 4.25 to 7.25 points in individuals with stable, mild to moderate UE hemiparesis (28). However, the minimal clinically important difference (MCID) for patients with severe hemiparesis remains to be shown. Because it was considered that a greater than 10% change in FM motor scores may represent a clinically meaningful improvement based on clinical experience (29), it is conceivable that the MCID for severe hemiparesis is lower than that for mild hemiparesis. A minimal detectable change of 3.2 points was reported in 31 patients with stroke (30).

UE disability in ADL was assessed with the Motor Activity Log-14 (MAL), which uses a structured interview (31). MAL includes 14 items, scored on an 11-point amount of use scale (range 0–5) to rate how much the arm is used (MAL-AOU) and an 11-point quality of movement scale (range 0–5) to rate how well the participants are using their affected upper extremity (31). We selected only the MAL-AOU score in this study because it was difficult for patients with a severely paretic hand to change the quality of movements. High construct validity and reliability have been demonstrated in patients with chronic stroke (31, 32).

The capability to pick-up and release pegs with the reaching task was assessed by the number of pegs picked up and released in 1 min (peg number). Participants tried to pick up from the board and release pegs out of the board as many time as possible for 1 min (board: width 300 mm × 250 mm × height 25 mm; peg: diameter 21 mm, height 70 mm; 30 pegs were set on the board).

FMA and MAL-AOU were assessed by an independent assessor who did not know which patients were recruited for this study to receive the BMI training. This assessor scored all of the participants with stroke who were admitted to the department during the study period, including participants not recruited for this study, and the peg number was assessed by an occupational therapist who was not engaged in the BMI training.

Relationship between the number of times of appropriate motor imagery in BMI training and clinical assessment scores

BMI intervention forces the patient to perform repetitive motor tasks and monitors the activity of the ipsilesional SM1 through EEG. It should be noted here that the actual neural activity of the ipsilesional SM1 is unstable and fluctuated, irrespective of the patients' attempts. Thus, the timing of the volitionally increased SM1 activity can be determined only by the somatosensory signals for neural conditioning through motor-driven orthosis action and neuromuscular electrical stimulation. Such somatosensory feedback associated with proper cortical motor activity is presumably a driving factor for Hebbian-like neural plasticity and sensorimotor learning (33, 34). To empirically give evidence related to this theoretical frame, the association between the number of times of appropriate motor imagery in BMI training and the gain of clinical motor functions was also assessed. A positive correlation in this analysis indicates that the therapeutic effect of BMI intervention is dose-dependent due to the above-mentioned mechanisms.

The number of times that a participant produced appropriate ERD (number of ERD detections) in the BMI training was counted each day. We evaluated the relationships between the total numbers over 10 days and the gain with intervention in the FMA and MAL-AOU scores as well as the peg number.

Statistical analyses

Effect of BMI training. The Wilcoxon signed-rank test was used to compare the total FMA score (FMA-total), FMA category A score (FMA-A), FMA category B score (FMA-B), FMA category C score (FMA-C), MAL-AOU score, and the peg number with a between-subjects factor of time (pre- and post-BMI training). Effect sizes were calculated using Cohen's d statistics, with the magnitude of group differences defined as small if $d=0.2$, medium if $d=0.5$, or large if $d=0.8$ considering the clinical significance of the variables. "FMA-gain" was the mean value obtained by subtracting FMA-total before the intervention from FMA-total after the intervention for each participant.

Relationship between number of times of appropriate motor imagery in BMI training and clinical assessments.

Correlations between the total number of ERD detections during BMI training over the 10 days and gain with the intervention in the FMA-total and MAL-AOU scores and peg number were statistically tested with Spearman's rank correlation test.

Differences were considered significant if $p<0.05$. All statistical analyses were performed with SPSS, version 21.0 J (SPSS, Japan).

RESULTS

Feasibility of the newly developed BMI system for professional users

All patients were fully compliant with the BMI training programme with no adverse events. For all participants, there was no interruption in training due to any cause including fatigue. Skilled BMI system users could set it up in approximately 10 min, while the 4 therapists who set it up for the first time could do so within 15 min. They all answered "more than somewhat satisfied" for the weight, facility, safety, and effectiveness, and 3 therapists answered "more than somewhat satisfied" for the size and ease of adjustment (Table I). They felt that it would be easy to operate the system after operating it continuously.

Effect of BMI training. Table II shows the patients' clinical characteristics (age, time from onset of stroke, sex, type of stroke, paretic side, lesion). Twenty-six patients were included in the current analyses. The mean age of all patients was 50.3 years (SD=11.1,

Table I. QUEST scores of the newly developed brain-machine interface (BMI) system assessed by 4 therapists

	Very satisfied	Satisfied	Somewhat satisfied	Not very satisfied	Completely dissatisfied
Size	1	2	0	1	0
Weight	2	2	0	0	0
Easy adjustment	0	1	2	1	0
Facility	1	2	1	0	0
Safeness	3	0	1	0	0
Effectiveness	1	2	1	0	0

QUEST: Quebec User Evaluation of Satisfaction with Assistive Technology.

range = 25–72 years), and their mean time from stroke onset was 1,421.5 days (SD = 1,318.1). Twelve patients had hemiparesis affecting their right UEs.

After the BMI training, Wilcoxon signed-rank testing showed significant differences in the FMA-total, FMA-A score, FMA-C score, MAL-AOU score, and peg number (Table III). The effect sizes for FMA-total, FMA-A score, and peg number were moderate. The effect size for the FMA-C score was small, and the MAL-AOU score showed a large effect size. FMA-gain was 3.3 (SD = 2.9).

Relationship of accuracy in BMI training and clinical assessments

Spearman's signed-rank test showed a significant correlation between the total number of ERD detections and peg number gain ($\rho = 0.5$, $p = 0.02$). However, no significant correlations were observed between the number of ERD detections and FMA-total and MAL-AOU gain (FMA-total: $\rho = 0.24$, $p = 0.29$; MAL-AOU: $\rho = 0.11$, $p = 0.59$) (Table IV).

Table II. Clinical characteristics of participants

Age, years	Stroke type	Stroke lesion	Paretic side	Time from onset of stroke, days
49	CI	Corona radiata	Left	262
53	CH	Putamen	Right	1,050
66	CI	MCA	Right	3,046
52	CH	Putamen	Right	3,567
39	CH	Putamen	Left	635
65	CH	Putamen	Right	5,391
50	CH	Putamen	Left	3,611
55	CH	Putamen	Right	491
47	CH	Putamen	Left	732
72	CI	Corona radiata	Left	2,866
45	CH	Putamen	Left	873
71	CI	Corona radiata	Left	169
46	CH	Putamen	Right	773
42	CH	Thalamus	Right	739
53	CH	Putamen	Left	736
25	CH	Putamen	Right	983
51	CH	Putamen	Right	566
36	CI	MCA	Left	3,077
48	CH	Putamen	Right	2,468
43	CH	Putamen	Left	454
64	CI	MCA	Left	915
63	CH	Putamen	Left	605
41	CH	Putamen	Right	532
52	CH	Putamen	Left	1,018
43	CH	Putamen	Right	629
38	CH	Putamen	Left	772

CI: cerebral infarction; CH: cerebral hemorrhage; MCA: middle cerebral artery.

Table III. Changes in clinical assessment scores

	Pre-BMI Median (IQR)	Post-BMI Median (IQR)	*p*-value	Effect size
FMA-A	14.5 (12.25–17.75)	17.0 (14.0–22.0)	< 0.01	0.51
FMA-B	0 (0–0)	0 (0–0)	0.53	0.16
FMA-C	2.0 (1.0–3.0)	3.0 (2.0–4.0)	< 0.01	0.30
FMA-total	17.5 (14.0–22.75)	19.5 (17.25–25.75)	< 0.01	0.55
Peg number	5.0 (4.0–7.0)	7.0 (5.0–10.5)	< 0.01	0.68
MAL-AOU	2.0 (0–2.0)	4.0 (2.0–7.0)	< 0.01	0.88

Effect sizes were calculated using Cohen's d statistic and an effect size less than 0.5 was regarded as small, 0.5–0.8 as medium and above 0.8 as large. Pre-BMI: before brain-machine interface training; post-BMI: after brain-machine interface training; FMA: Fugl-Meyer upper extremity score: A, shoulder/elbow/forearm, 36 points; B, wrist, 10 points; C, hand/finger, 14 points; MAL-AOU: motor activity log amount of use; peg number: number of pegs picked up and released in 1 min; IQR: interquartile range.

DISCUSSION

Feasibility of the newly developed BMI system for professional users

When using a new rehabilitation device in clinical settings, it is necessary to consider the time to set up the system, the space required for its operation, and its usability from the point of view of therapists (23). Our results showed that the QUEST effectiveness and safety scores were comparable to or better than those of Morone's report (23). This indicates that our BMI system is feasible for use in real clinical situations.

Task-specific BMI training on upper extremity limb in patients with severe score

To our knowledge, this is the first study to demonstrate the efficacy of task-specific BMI training for severe UE paresis. In previous reports, the FMA score of severe arm paresis was defined as 35 or less (35, 36). All participants in this study met this definition. There was improvement in UE function, peg pick-up and release task performance, and the amount of use of the paretic hand in their ADL. The gain in FMA in this report was comparable to that in previous reports, (10, 11) even though the hand paralysis of our participants was more severe.

Table IV. Correlations between total number of event-related desynchronization (ERD) detections and changes in clinical assessment scores

	Spearman's rank correlation coefficient	*p*-value
FMA-total gain	0.24	0.26
MAL-AOU gain	0.11	0.59
Peg number gain	0.50*	0.02

*Significant result. FMA: Fugl-Meyer upper extremity score; MAL-AOU, motor activity log-14 amount of use.

In addition, there was significant improvement in peg pick-up and release task performance and the amount of use of the affected UE in daily life assessed with the MAL-AOU. To the best of our knowledge, the MCID of MAL-AOU had not been reported previously. The present data showed a large effect size for MAL-AOU. Although it is necessary to further investigate whether this result is due to the characteristics of the measurement method, we are considering the following 2 hypotheses: (*i*) since participants were severely paralysed and had not used the paralysed hand before the intervention, the use frequency of the paralysed hands was likely to increase because the "learned non-use" was improved by the intervention; (*ii*) our BMI training might affect not only arm function but also use of the paretic hand in their ADL, because our system consists of task-specific tasks (i.e. pinch and release). Task-specific BMI training induced task-specific improvements of hand function and reaching function of the paretic UE. Picking up and releasing objects while reaching are basic UE movements in ADL. These improvements may have increased the MAL-AOU score.

In this study, there was a significant correlation between the total number of ERD detections (successful trials) during the BMI training and peg numbers. It was supposed that electrical stimulation and actual paretic finger movement triggered by motor intention increased motor cortex excitability. The increase in motor cortex excitability might be dose-dependent.

Kasashima-Shindo et al. (14) reported that the accuracy rate of ERD detection increased significantly after BMI training. Shindo and colleagues (10) found that increased cortical excitability in the affected hemisphere was confirmed by transcranial magnetic stimulation after BMI training. Li and co-workers (12) also suggested that the activation of the affected sensorimotor cortex and the parietal lobe may contribute to effective motor function improvement assessed with the action research arm test in stroke patients. In addition to these previous reports, our results might support a relationship between the change in brain activity (especially neural excitation in the affected hemisphere) and functional recovery.

Study limitations

In this study, we cannot convincingly discuss the effectiveness of the BMI intervention because the number of patients treated was small, and there was no age-matched control or sham treatment group. Furthermore, our protocol included not only BMI training but also occupational therapy. Therefore, one cannot differentiate the effects brought about by the 2 interventions. In previous randomized, controlled trials, the BMI training group showed a greater improvement in the paretic UE than the control group (11–13). The pilot data presented here provide a basis for designing and conducting a larger scale trial with more rigorous study design, including masking and randomization, to test the task-specific BMI training effects. This research was performed as a phase 1–2 clinical trial. However, the effect was not large. Thus, this protocol might need revision before moving to stage 3 trials.

Conclusion

Our newly developed compact BMI system is feasible for use in real-world clinical settings, and BMI training is potentially a useful technology in rehabilitation, not only to substitute for lost functions, but also to induce brain plasticity and improve paresis. According to the phased approach to the development of clinical rehabilitation evidence (37), the present study was positioned as a phase 1–2 clinical trial. The present study confirmed that the proposed treatment was clinically feasible from the perspective of both efficacy and safety, and it ensured that the effects of the treatment are in the desired direction. The results now encourage us to compare its effectiveness with that of existing standardized treatments. A phase 3 clinical trial with a larger sample is needed for further development of clinical BMI interventions.

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REFERENCES

1. Kwakkel G, Kollen BJ, van der Grond J, Prevo AJ. Probability of regaining dexterity in the flaccid upper limb: impact of severity of paresis and time since onset in acute stroke. Stroke 2003; 34: 2181–2186.
2. Levin MF, Kleim JA, Wolf SL. What do motor "recovery" and "compensation" mean in patients following stroke? Neurorehabil Neural Repair 2008; 23: 313–319.
3. Langhorne P, Coupar F, Pollock A. Motor recovery after stroke: a systematic review. Lancet Neurol 2009; 8: 741–754.
4. Kwakkel G, Kollen B, Twisk J. Impact of time on improvement of outcome after stroke. Stroke 2006; 37: 2348–2353.
5. Wolf SL, Winstein CJ, Miller JP, Taub E, Uswatte G, Morris D, et al. Effect of constraint-induced movement therapy on upper extremity function 3 to 9 months after stroke: the EXCITE randomized clinical trial. JAMA 2006; 296:

2095–2104.
6. Stinear CM, Barber PA, Coxon JP, Fleming MK, Byblow WD. Priming the motor system enhances the effects of upper limb therapy in chronic stroke. Brain 2008; 131: 1381–1390.
7. Fujiwara T, Kasashima Y, Honaga K, Muraoka Y, Tsuji T, Osu R, et al. Motor improvement and corticospinal modulation induced by hybrid assistive neuromuscular dynamic stimulation (HANDS) therapy in patients with chronic stroke. Neurorehabil Neural Repair 2009; 23: 125–132.
8. Buch E, Weber C, Cohen LG, Braun C, Dimyan MA, Ard T, et al. Think to move: a neuromagnetic brain-computer interface (BCI) system for chronic stroke. Stroke 2008; 39: 910–917.
9. Ang KK, Guan C, Chua KS, Ang BT, Kuah C, Wang C, et al. A clinical study of motor imagery–based brain-computer interface for upper limb robotic rehabilitation. Conf Proc IEEE Eng Med Biol Soc 2009; 2009: 5981–5984.
10. Shindo K, Kawashima K, Ushiba J, Ota N, Ito M, Ota T, et al. Effects of neurofeedback training with an electroencephalogram-based brain-computer interface for hand paralysis in patients with chronic stroke: a preliminary case series study. J Rehabil Med 2011; 43: 951–957.
11. Ramos-Murguialday A, Broetz D, Rea M, Läer L, Yilmaz O, Brasil FL, et al. Brain-machine interface in chronic stroke rehabilitation: a controlled study. Ann Neurol 2013; 74: 100–108.
12. Li M, Liu Y, Wu Y, Liu S, Jia J, Zhang L. Neurophysiological substrates of stroke patients with motor imagery-based brain-computer interface training. Int J Neurosci 2014; 124: 403–415.
13. Ang KK, Chua KS, Phua KS, Wang C, Chin ZY, Kuah CW, et al. A randomized controlled trial of EEG-based motor imagery brain-computer interface robotic rehabilitation for stroke. Clin EEG Neurosci 2015; 46: 310–320.
14. Kasashima-Shindo Y, Fujiwara T, Ushiba J, Matsushika Y, Kamatani D, Oto M, et al. Brain-computer interface training combined with transcranial direct current stimulation in patients with chronic severe hemiparesis: proof of concept study. J Rehabil Med 2015; 47: 318–324.
15. Daly JJ, Wolpaw JR. Brain-computer interfaces in neurological rehabilitation. Lancet Neurol 2008; 7: 1032–1043.
16. Chaudhary U, Birbaumer N, Ramos-Murguialday A. Brain-computer interfaces for communication and rehabilitation. Nat Rev Neurol 2016; 12: 513–525.
17. Kawakami M, Fujiwara T, Ushiba J, Nishimoto A, Abe K, Honaga K, et al. A new therapeutic application of brain-machine interface (BMI) training followed by hybrid assistive neuromuscular dynamic stimulation (HANDS) therapy for patients with severe hemiparetic stroke: a proof of concept study. Restor Neurol Neurosci 2016; 34: 789–797.
18. Klem GH, Luders HO, Jasper HH, Elger C. The ten-twenty electrode system of the international federation. The International Federation of Clinical Neurophysiology. Electroencephalogr Clin Neurophysiol Suppl 1999; 52: 3–6.
19. Tsuchimoto S, Shibusawa S, Mizuguchi N, Kato K, Ebata H, Liu M, Hanakawa T, Ushiba J. Resting-state fluctuations of EEG sensorimotor rhythm reflect BOLD activities in the pericentral areas: a simultaneous EEG-fMRI Study. Front Hum Neurosci 2017; 11: 356.
20. Takemi M, Masakado Y, Liu M, Ushiba J. Event-related desynchronization reflects downregulation of intracortical inhibition in human primary motor cortex. J Neurophysiol 2013; 110: 1158–1166.
21. Takemi M, Masakado Y, Liu M, Ushiba J. Sensorimotor event-related desynchronization represents the excitability of human spinal motoneurons. Neuroscience 2015; 297: 58–67.
22. Demers L, Weiss-Lambrou R, Ska B. The Quebec User Evaluation of Satisfaction with Assistive Technology (QUEST 2.0): an overview and recent progress. Technol Disabil 2002; 14: 101–105.
23. Morone G, Pisotta I, Pichiorri F, Kleih S, Paolucci S, Molinari M, et al. Proof of principle of a brain-computer interface approach to support poststroke arm rehabilitation in hospitalized patients: design, acceptability, and usability. Arch Phys Med Rehabil 2015; 96: S71–S78.
24. Fugl-Meyer AR, Jääskö L, Leyman I, Olsson S, Steglind S. The post-stroke hemiplegic patient. 1. a method for evaluation of physical performance. Scand J Rehabil Med 1975; 7: 13–31.
25. Wood-Dauphinee SL, Williams JI, Shapiro SH. Examining outcome measures in a clinical study of stroke. Stroke 1990; 21: 731–739.
26. Duncan PW, Propst M, Nelson SG. Reliability of the Fugl-Meyer assessment of sensorimotor recovery following cerebrovascular accident. Phys Ther 1983; 63: 1606–1610.
27. Platz T, Pinkowski C, van Wijck F, Kim IH, di Bella P, Johnson G. Reliability and validity of arm function assessment with standardized guidelines for the Fugl-Meyer Test, Action Research Arm Test and Box and Block Test: a multicentre study. Clin Rehabil 2005; 19: 404–411.
28. Page SJ, Fulk GD, Boyne P. Clinically important differences for the upper-extremity Fugl-Meyer Scale in people with minimal to moderate impairment due to chronic stroke. Phys Ther 2012; 92: 791–798.
29. Gladstone DJ, Danells CJ, Black SE. The Fugl-Meyer assessment of motor recovery after stroke: a critical review of its measurement properties. Neurorehabil Neural Repair 2002; 16: 232–240.
30. See J, Dodakian L, Chou C, Chan V, McKenzie A, Reinkensmeyer DJ, Cramer SC. A standardized approach to the Fugl-Meyer assessment and its implications for clinical trials. Neurorehabil Neural Repair 2013; 27: 732–741.
31. Uswatte G, Taub E, Morris D, Vignolo M, McCulloch K. Reliability and validity of the upper-extremity Motor Activity Log-14 for measuring real-world arm use. Stroke 2005; 36: 2493–2496.
32. Van der Lee JH1, Beckerman H, Knol DL, de Vet HC, Bouter LM. Clinimetric properties of the motor activity log for the assessment of arm use in hemiparetic patients. Stroke 2004; 35: 1410–1414.
33. Ushiba J, Soekadar SR. Brain-machine interfaces for rehabilitation of poststroke hemiplegia. Prog Brain Res 2016; 228: 163–183.
34. Soekadar SR, Birbaumer N, Slutzky MW, Cohen LG. Brain-machine interfaces in neurorehabilitation of stroke. Neurobiol Dis 2015; 83: 172–179.
35. Hesse S, Heß A, Werner C C, Kabbert N, Buschfort R. Effect on arm function and cost of robot-assisted group therapy in subacute patients with stroke and a moderately to severely affected arm: a randomized controlled trial. Clin Rehabil 2014; 28: 637–647.
36. Platz T, Eickhof C, van Kaick S, Engel U, Pinkowski C, Kalok S, Pause M. Impairment-oriented training or Bobath therapy for severe arm paresis after stroke: a single-blind, multicentre randomized controlled trial. Clin Rehabil 2005; 19: 714–724.
37. White DK, Wagenaar RC, Ellis TD, Tickle-Degnen L. Changes in walking activity and endurance following rehabilitation for people with Parkinson disease. Arch Phys Med Rehabil 2009; 90: 43–50.