et al., 2008). It has been suggested that intracortical disinhibition is necessary to maintain access to such additional networks, depending on the extent of disruption of the original corticospinal projection (Swayne et al., 2008). This disinhibition was found among patients with chronic stroke (over 6 months). It is suggested that patients with severe hemiparesis have the potential to induce some functional reorganization of the motor cortex even in the chronic phase, though their time window might be limited. Swayne et al. (2008) showed that corticospinal excitability of AH, measured as AMT and RMT, increased in acute phase but this increment became weaker in chronic phase (at 3 month). They also found that increased intracortical excitability continued for 6 month. In our study we assessed AMT, RMT and SICI of AH among patients with chronic stroke, their time from stroke was more than 6 months. We found disinhibition of intracortical inhibition negatively correlated with the time from stroke onset while corticospinal excitability, measures as AMT and RMT, did not correlated with the time from stroke onset. These results suggested that there may remain brain plasticity to induce functional reorganization with aid of disinhibition of intracortical inhibition in chronic phase, over 6 month from stroke onset, while it depends on the time from stroke onset.

Disinhibition of the affected side finger extensor (EDC) was also found in patients with severe hemiparesis. This disinhibition could induce facilitation of finger extension and help improve hand function with severe hemiparesis. For patients who can fully extend their fingers and move their fingers individually, it is not necessary to induce facilitation of finger extension for functional recovery. Therefore, the magnitude of intracortical inhibition may normalize in patients with mild hemiparesis.

The present study showed that disinhibition of intracortical inhibition was observed until 60 months after stroke onset among patients with severe hemiparesis. This might imply that there could be some potential to induce cortical reorganization even in patients with chronic stroke.

Studies have demonstrated that intensive hand rehabilitation changes the SICI of the AH in chronic stoke (Fujiwara et al., 2009; Liepert, 2006). Thus, the change of the SICI in the AH seems to be the result of reorganization in the primary motor cortex. These results also suggest that reorganization can be induced even in the chronic phase.

SICI of the UH had no relationships with motor function and time from stroke onset. The amount of unaffected-side SICI depended on whether the lesion was cortical or subcortical.

The abnormal disinhibition in the UH persisted in patients whose motor function remained poor (Manganotti et al., 2002). However, such a relationship between poor clinical status and increased net intracortical excitability was not observed in patients over a wide range of time points after stroke (Shimizu et al., 2002). In the present study, an increase of the value of SICI of the UH was seen in patients with cortical lesions, but not in those with subcortical lesions. Shimizu et al. (2002) reported the same result, that larger MEP amplitudes when testing SICI were seen in cortical stroke than in subcortical stroke. The change in the SICI of the UH seems to be modulated by compensatory excitation of the ipsilateral corticospinal tract (Caramia et al., 2000; Ziemann et al., 1999) and transcallosally-mediated inhibition (Shimizu et al., 2002; Bütefisch et al., 2008).

Some reports found that SICI in the UH had a correlation with motor recovery (Manganotti et al., 2008; Bütefisch et al., 2008). Di Lazzaro et al. (2009) showed that functional recovery is directly correlated with LTP-like changes in the AH and LTD-like changes in the UH and inversely correlated with the baseline excitability of the UH in acute strokes. These previous studies involved participants in the early or subacute phase of strokes.

The results of the present study did not correspond to these reports. There is a possibility that the SICI of UH is not always disinhibited, but distributed variously, and returns to the normal level over time. The present participants were patients with chronic stroke who had already undergone standardized inpatient rehabilitation during their acute and subacute phases. It was assumed that the state of SICI of the AH in the chronic phase was different from that in the acute phase.

The present study showed that the MEP amplitudes were smaller in the UH than in the control group. Nowak et al. (2007) reported that dexterity was impaired in both hands following unilateral stroke, but the mechanism of bilateral dexterity impairment remains unknown. There could be some relationship between small MEPs in the UH and impaired dexterity.

Recently, repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) have been used as therapeutic modalities to facilitate functional recovery of chronic stroke patients. In these therapies, the basic strategy is to increase the activity of the AH or to decrease the activity of the UH. Many studies have so far adopted low frequency rTMS and cathodal tDCS to the UH to suppress its activity. However, the present study showed that SICI of the UH in the subcortical group was not as high as control SICI. The activities of the AH and UH differed in each patient. Thus, we need to evaluate patients individually to determine whether the activity of the UH is high before instituting therapeutic approaches.

It has been suggested that anatomical localization, type of stroke, and the volume of T2-hyperintense white matter could influence cerebral integrity (Kochunov et al., 2010). In this study, MRI examinations were not performed in all subjects. Furthermore, the number of patients with hemorrhagic stroke was limited. It was not possible to assess the details of lesion location or other neuroimagimg markers. More detailed analyses of lesion and white matter volumes are needed.

5. Conclusion

In conclusion, the present study provided further evidence related to affected-side and unaffected-side SICI in severe chronic stroke patients. SICI of the AH was correlated with functional recovery. However, the reorganization of the motor cortex in stroke patients was not explained solely by SICI. Therefore, further investigations involving inter-hemispheric inhibition and corticospinal activity are needed to learn more about brain plasticity.

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References

Bütefisch CM, Davis BC, Wise SP, Sawaki L, Kopylev L, Classen J, et al. Mechanisms of use-dependent plasticity in the human motor cortex. Proc Natl Acad Sci USA 2000;97:3661–5.

Bütefisch CM, Wessling M, Netz J, Seitz RJ, Hömberg V. Relationship between interhemispheric inhibition and motor cortex excitability in subacute stroke patients. Neurorehabil Neural Repair 2008;22:4–21.

Caramia MD, Palmieri MG, Giacomini P, Iani C, Dally L, Silvestrini M. Ipsilateral activation of the unaffected motor cortex in patients with hemiparetic stroke. Clin Neurophysiol 2000;111:1990–6.

Chino N, Sonoda S, Domen K, Saitoh E, Kimura A. Stroke Impairment Assessment Set (SIAS). In: Chino N, Melvin JL, editors. Functional Evaluation of Stroke Patients. Tokyo: Springer-Verlag; 1995. p. 19–31.

Cramer SC, Sur M, Dobkin BH, O'Brien C, Sanger TD, Trojanowski JQ, et al. Harnessing neuroplasticity for clinical applications. Brain 2011;134:1591–609.
Di Lazzaro V, Profice P, Pilato F, Capone F, Ranieri F, Pasqualetti P, et al. Motor cortex plasticity predicts recovery in acute stroke. Cereb Cortex 2009;5: 1523–8.
Fugl-Meyer AR, Jääskö L, Leyman I, Olsson S, Steglind S. The post-stroke hemiplegic patients 1. A method for evaluation of physical performance. Scand J Rehabil Med 1975;7:13–31.
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;23:125–32.
Jacobs KM, Donoghue JP. Reshaping the cortical motor map by unmasking latent intracortical connections. Science 1991;251:944–7.
Kochunov P, Glahn D, Lancaster J, Winker A, Kent JW, Olvera RL, et al. Whole brain and regional hypertense white matter volume and blood pressure: overlap of genetic loci produced by bivariate, whole-genome linkage analyses. Stroke 2010;41:2137–42.
Kujirai T, Caramia MD, Rothwell JC, Day BL, Thompson PD, Ferbert A, et al. Corticocortical inhibition in human motor cortex. J Physiol 1993;471:501–19.
Liepert J, Storch P, Fritsch A, Weiller C. Motor cortex disinhibition in acute stroke. Clin Neurophysiol 2000;111:671–6.
Liepert J. Motor cortex excitability in stroke before and after constraint-induced movement therapy. Cogn Behav Neurol 2006;19:41–7.
Liu M, Chino N, Tsuji T, Masakado Y, Hase K, Kimura A. Psychometric properties of the Stroke Impairment Assessment Set (SIAS). Neurorehabil Neural Repair 2002;16:339–51.
Manganotti P, Patuzzo S, Cortese F, Palermo A, Smania N, Fiaschi A. Motor disinhibition in affected and unaffected hemisphere in the early period of recovery after stroke. Clin Neurophysiol 2002;113:936–43.
Manganotti P, Acler M, Zanette GP, Smania N, Fiaschi A. Motor Cortical disinhibition during early and late recovery after stroke. Neurorehabil Neural Repair 2008;22:396–403.
Nowak DA, Grefkes C, Dafotakis M, Küst J, Karbe H, Fink GR. Dexterity is impaired at both hands following unilateral subcortical middle cerebral artery stroke. Eur J Neurosci 2007;25:3173–84.
Rossini PM, Barker AT, Berardelli A, Caramia MD, Caruso G, Cracco RQ, et al. Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: basic principles and procedures for routine clinical application. Report of an IFCN committee. Electroencephalogr Clin Neurophysiol 1994;91:79–92.
Sanger TD, Garg RR, Chen R. Interactions between two different inhibitory systems in the human motor cortex. J Physiol 2001;530:307–17.
Shimizu T, Hosaki A, Hino T, Sato M, Komori T, Hirai S, et al. Motor cortical disinhibition in the unaffected hemisphere after unilateral cortical stroke. Brain 2002;125:1896–907.
Smania N, Paolucci S, Tinazzi M, Borgheno A, Manganotti P, Fiaschi A, et al. Active finger extension a simple movement predicting recovery of arm function in patients with acute stroke. Stroke 2007;38:1088–90.
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;131:1381–90.
Swayne OB, Rothwell JC, Ward NS, Greenwood RJ. Stages of motor output reorganization after hemispheric stroke suggested by longitudinal studies of cortical physiology. Cereb Cortex 2008;18:1909–22.
Takeuchi N, Tada T, Toshima M, Ikoma K. Correlation of motor function with transcallosal and intracortical inhibition after stroke. J Rehabil Med 2010;42: 962–6.
Tsuji T, Liu M, Sonoda S, Domen K, Chino N. The stroke impairment assessment set: its internal consistency and predictive validity. Arch Phys Med Rehabil 2000;81:863–8.
Wolf SL, Lecraw DE, Barton LA, Jann BB. Forced use of hemiplegic upper extremities to reverse the effect of learned nonuse among chronic stroke and head injured patients. Exp Neurol 1989;104:125–32.
Ziemann U, Ishii K, Borgheresi A, Yaseen Z, Battaglia F, Hallett M, et al. Dissociation of the pathways mediating ipsilateral and cotralateral motor-evoked potentials in human hand and arm muscles. J Physiol 1999;518:895–906.

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RESEARCH REPORT

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

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KEYWORDS
electrical stimulation;
electroencephalography;
neural plasticity

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

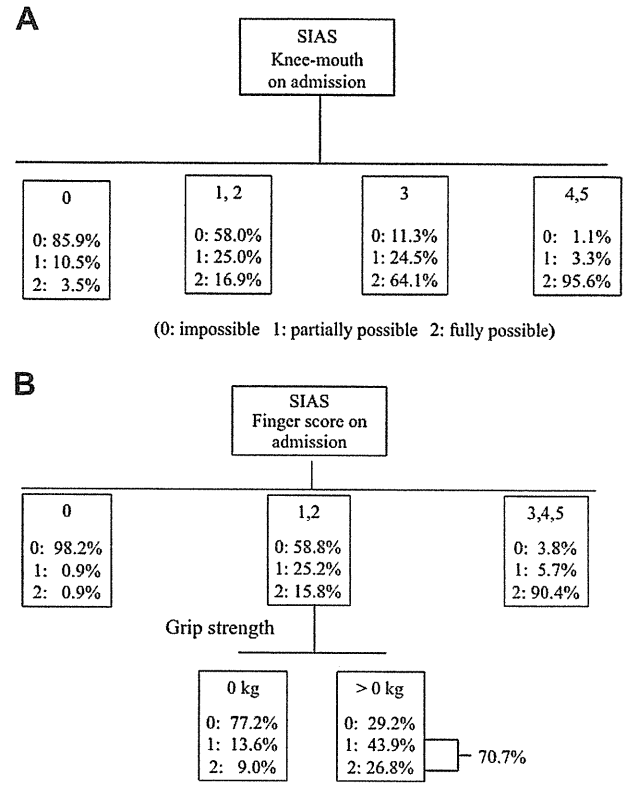

Figure 1 (A) Predicting discharge arm function (hanging a bag item). Using classification and regression tree analysis (CART), we analysed whether we could predict discharge arm function from admission impairment status as assessed using the Stroke Impairment Assessment Set (SIAS). For the hanging a 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

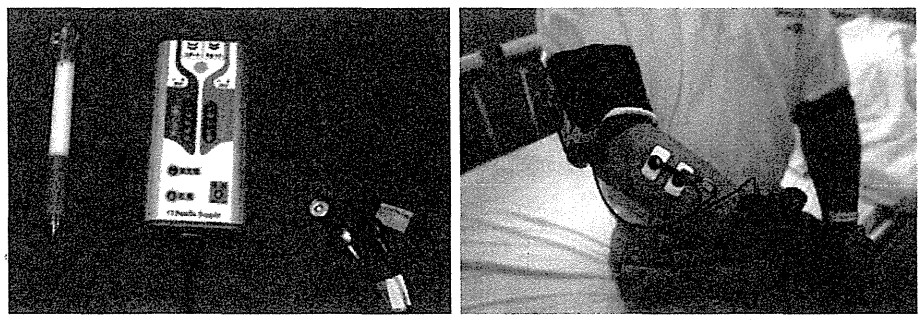

Figure 2 HANDS therapy. HANDS therapy consists of four components: (1) integrated volitional electrical stimulation (IVES), (2) a wrist splint, (3) encouraged use of the affected arm, and (4) occupational therapy (OT) sessions. The HANDS system is used during the daytime to facilitate hand use in daily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

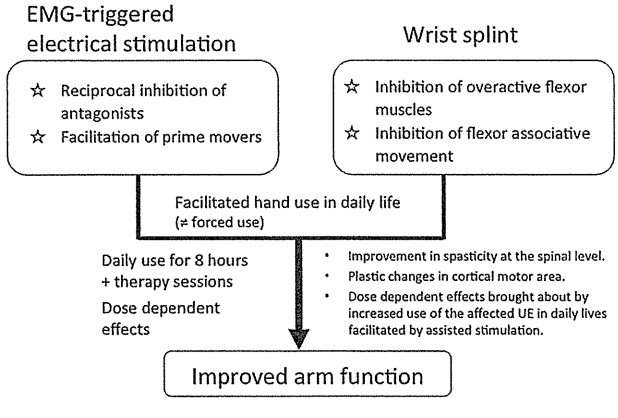

Figure 3 Proposed mechanisms for improvement with HANDS. EMG-triggered electrical stimulation results in reciprocal inhibition of antagonists and facilitation of agonists. The wrist splint brings about inhibition of overactive flexor muscles and flexor associative movement. Together, these changes facilitate 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

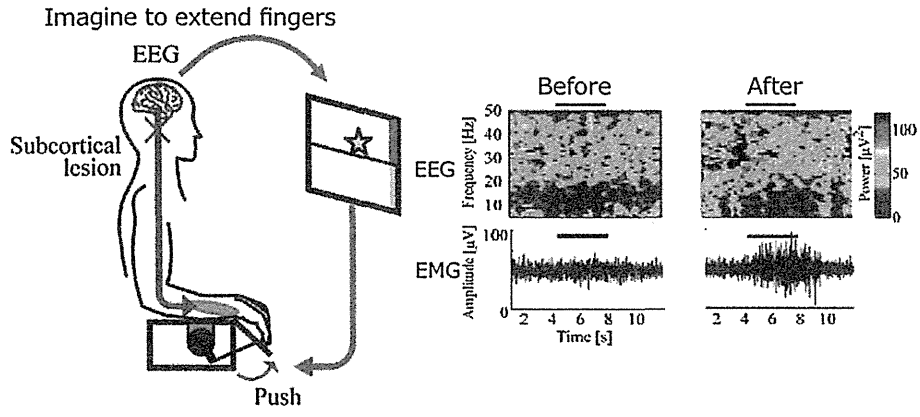

Figure 4 EEG-based BMI neurorehabilitation system. The patient sits on a chair looking at a computer monitor. A star-shaped cursor moves at a fixed rate from left to right, and its position reflects the mu rhythm (frequency range, 8–13 Hz) amplitude during motor imagery. The cursor moves up and down 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.

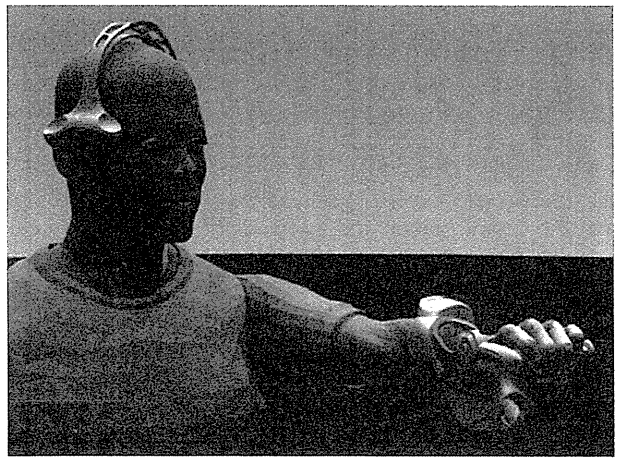

Figure 5 A newly designed EEG-BMI power-assisted orthosis. This system will be wireless, and powered by commercially available AA batteries. Meticulous skin preparation will not be necessary for EEG recordings due to newly developed dry EEG electrodes. The device will therefore be easily applicable to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

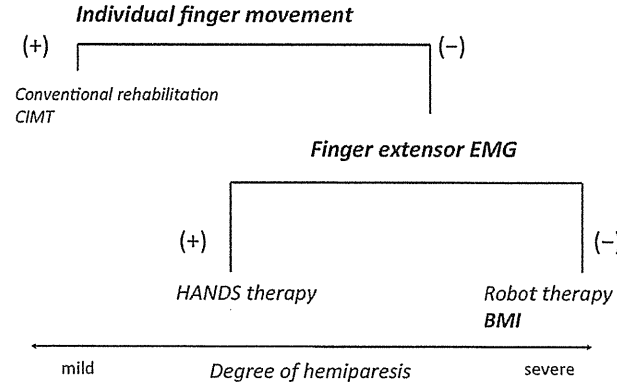

Figure 6 Rehabilitation strategy for the paretic upper limb. If the patient shows individual finger movements, treatment could comprise either conventional rehabilitation or constraint-induced movement therapy. If the patient has no individual finger movement, but a detectable finger extensor on EMG, 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.

Acknowledgements

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References

[1] Hendricks HT, van Limbeek J, Geurts AC, Zwarts MJ. Motor recovery after stroke: a systematic review of the literature. Arch Phys Med Rehabil 2002;83:1629–37.
[2] Duncan PW, Lai SM, Keighley J. Defining post-stroke recovery: implications for design and interpretation of drug trials. Neuropharmacology 2000;39:835–41.
[3] Nakayama H, Jorgensen HS, Raaschou HO, Olsen TS. Recovery of upper extremity function in stroke patients: the Copenhagen stroke study. Arch Phys Med Rehabil 1994;75:394–8.
[4] Nudo RJ, Milliken GW. Reorganization of movement representations in primary motor cortex following focal ischemic infarcts in adult squirrel monkeys. J Neurophysiol 1996;75:2144–9.

[5] Biernaskie J, Chemenko G, Corbett D. Efficacy of rehabilitative experience declines with time after focal ischemic brain injury. J Neurosci 2004;24:1245–54.
[6] Kwakkel G, van Peppen R, Wagenaar RC, Wood Dauphinee S, Richards C, Ashbum A, et al. Effects of augmented exercise therapy time after stroke: a meta-analysis. Stroke 2004;35: 2529–39.
[7] Langhorne P, Coupar F, Pollock A. Motor recovery after stroke: a systematic review. Lancet Neurol 2009;8:741–54.
[8] Dean CM, Shepherd R. Task-related training improves performance of seated reaching tasks after stroke: A randomized controlled trial. Stroke 1997;28:722–8.
[9] Jang Sung HCA, Kim Yun-Hee, Cho Sang-Hyun, Lee Jin-Hee, Park Ji-Won, Kwon Yong-Hyun. Cortical reorganization induced by task-oriented training in chronic hemiplegic stroke patients. Neuro Report 2003;20:137–41.
[10] Whitall J, McCombe Waller MS, Silver KHC, Macko RF. Repetitive bilateral arm training with rhythmic auditory cueing improves motor function in chronic hemiparetic stroke. Stroke 2000;31:2390–5.
[11] Luft Andreas R, McCombe-Waller S, Whitall J, Forrester LW, Macko R, Sorkin JD, et al. Repetitive bilateral arm training and motor cortex activation in chronic stroke: A randomized controlled trial. JAMA 2004;292:1853–61.
[12] Dromerick AW, Edwards DF, Hahn M. Does the application of constraint-induced movement therapy during acute rehabilitation reduce arm impairment after ischemic stroke? Stroke 2000;31:2984–8.
[13] Sterr A, Elbert T, Berthold I, Kolbel S, Rockstroh B, Taub E. Longer versus shorter daily constraint-induced movement therapy of chronic hemiparesis: an exploratory study. Arch Phys Med Rehabil 2002;83:1374–7.
[14] Wolf ST, 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;296:2095–214.
[15] Meilink A, Hemmen B, Seelen HA, Kwakkel G. Impact of EMG-triggered neuromuscular stimulation of the wrist and finger extensors of the paretic hand after stroke: a systematic review of the literature. Clin Rehabil 2008;22:291–305.
[16] de Kroon JR, Ijzerman MJ, Chae J, Lankhorst GJ, Zilvoid G. Relation between stimulation characteristics and clinical outcome in studies using electrical stimulation to improve motor control of the upper extremity in stroke. J Rehabil Med 2005;37:65–74.
[17] Thrasher TA, Zivanovic V, McIlroy W, Popovic MR. Rehabilitation of reaching and grasping function in severe hemiplegic patients using functional electrical stimulation therapy. Neurorehabil Neural Repair 2008;22:706–14.
[18] Mangold S, Schuster C, Keller T, Zimmermann-Schlatter A, Ettlin T. Motor training of upper extremity with functional electrical stimulation in early stroke rehabilitation. Neurorehabil Neural Repair 2009;23:184–90.
[19] Chan MK, Tong RK, Chung KY. Bilateral upper limb training with functional electric stimulation in patients with chronic stroke. Neurorehabil Neural Repair 2009;23:357–65.
[20] 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;23:125–32.
[21] Shindo K, Fujiwara T, Hara J, Oba H, Hotta F, Tsuji T, et al. Effectiveness of ybrid assistive neuromuscular dynamic stimulation (HANDS) therapy in patients with subacute stroke – a randomized controlled trial. Neurorehabil Neural Repair 2011;25:830–7.
[22] Kakuda W, Abo M, Kobayashi K, Takagishi T, Momosaki R, Yokoi A, et al. Baseline severity of upper limb hemiparesis influences the outcome of low-frequency rTMS combined with intensive occupational therapy in patients who have had a stroke. PMR 2011;3:516–22.
[23] Malcolm MP, Triggs WJ, Light KE, Gonzalez Rothi LJ, Wu S, Reid K, et al. Repetitive transcranial magnetic stimulation as an adjunct to constraint-induced therapy: an exploratory randomized controlled trial. Am J Phys Med Rehabil 2007;86:707–15.
[24] Lindenberg R, Renga V, Zhu LL, Nair D, Schlaug G. Bihemispheric brain stimulation facilitates motor recovery in chronic stroke patients. Neurology 2010;24:2176–84.
[25] Hesse S, Werner C, Shonhardt EM, Bardeleben A, Jenrich W, Kirker SG. Combined transcranial direct current stimulation and robot-assisted arm training in subacute stroke patients: a pilot study. Restor Neurol Neurosci 2007;25:9–15.
[26] Volpe BT, Krebs HI, Hogan N, Edelstein L, Diels C, Aisen M. A novel approach to stroke rehabilitation: robot-aided sensorimotor stimulation. Neurology 2000;54:1938–44.
[27] Lum PS, Burgar CG, Shor PC, Majmundar M, Van der Loos M. Robot-assisted movement training compared with conventional therapy techniques for the rehabilitation of upper-limb motor function after stroke. Arch Phys Med Rehabil 2002;83: 952–9.
[28] Fasoli SE, Krebs HI, Stein J, Frontera WR, Hogan N. Effects of robotic therapy on motor impairment and recovery in chronic stroke. Arch Phys Med Rehabil 2003;84:477–82.
[29] Ziemann U, Corwell B, Cohen LG. Modulation of plasticity in human motor cortex after forearm ischemic nerve block. J Neurosci 1998;18:1115–23.
[30] 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;39:910–7.
[31] Daly JJ, Wolpaw JR. brain-computer interfaces in neurological rehabilitation. Lancet Neurol 2008;7:1032–43.
[32] Subramanian SK, Massie CL, Malcolm MP, Levin MF. Does provision of extrinsic feedback result in improved motor learning in the upper limb poststroke? A systematic review of the evidence. Neurorehabil Neural Repair 2010;24:113–24.
[33] Pfurtscheller G, Muller-Putz GR, Scherer R, Neuper C. Rehabilitation with brain-computer interface systems. Computer 2008;41:58–65.
[34] Broetz D, Braun C, Weber C, Soekadar SR, Caria A, Birbaumer N. Combination of brain-computer interface training and goal- directed physical therapy in chronic stroke: a case report. Neurorehabil Neural Repair 2010;24:674–9.
[35] 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;2009:5981–4.
[36] Daly JJ, Cheng R, Rogers J, Litinas K, Hrovat K, Dohring M. Feasibility of a new application of noninvasive brain computer interface (BCI): a case study of training for recovery of volitional motor control after stroke. J Neurol Phys Ther 2009;33: 203–11.
[37] Shindo K, Kawashima K, Ushiba J, Ohta 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;43:951–7.
[38] Wolf SL, Winstein CJ, Miller JP, Thompson PA, Taube E, Uswatte G, et al. Retention of upper limb function in stroke survivors who have received constraint- induced movement therapy: the EXCITE randomised trial. Lancet Neurol 2008;7: 33–40.
[39] Muraoka Y. Development of an EMG recording device from stimulation electrodes for functional electrical stimulation. Frontiers Med Biol Engng 2002;11:323–33.
[40] Fujiwara T, Liu M, Hase K, Tanaka N, Hara Y. Electrophysiological and clinical assessment of a simple wrist-hand splint

for patients with chronic spastic hemiparesis secondary to stroke. Electromyogr Clin Neurophysiol 2004;44:423–42.
[41] Fujiwara T, Liu M, Kasashima Y, Uemura O. Treatment of upper extremity dysfunction in hemiparetic stroke. Jpn J Rehabil Med 2006;43:743–6 [in Japanese].
[42] Chino N, Sonoda S, Domen K, Saitoh E, Kimura A. Stroke impairment assessment set (SIAS). In: Chino N, Melvin JL, editors. Functional evaluation of stroke patients. Tokyo: Springer-Verlag; 1995. p. 19–31.
[43] Tsuji T, Liu M, Sonoda S, Domen K, Chino N. The stroke impairment assessment set: its internal consistency and predictive validity. Arch Phys Med Rehabil 2000;81:863–8.
[44] Liu M, Liu M, Chino N, Tsuji T, Masakado Y, Hase K, et al. Psychometric properties of the stroke impairment assessment set (SIAS). Neurorehabil Neural Repair 2002;16:339–51.
[45] SPSS Answer Tree V3.0 Win App., Tokyo: SPSS Japan Inc.
[46] Bohannon RW, Smith MB. Interrater reliability of a modified ashworth scale of muscle spasticity. Phys Ther 1987;67:206–7.
[47] Day BL, Marsden CD, Obeso JA, Rothwell JC. Reciprocal inhibition between the muscles of the human forearm. J Physiol 1984;349:519–34.
[48] Kujirai T, Caramia MD, Rothwell JC, Day BL, Thompson PD, Ferbert A, et al. Cortico-cortical inhibition in human motor cortex. J Physiol 1993;471:501–19.
[49] 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.
[50] Yozbatiran N, Der-Yeghianian L, Cramer SC. A standard approach to performing the action research arm test. Neurorehabil Nerual Repair 2008;22:78–90.
[51] Li C, Liu T, Inoue Y, Shibata K. Evaluation of a bimanual-coordinated upper-limbs training system based on the near infrared spectroscopic signals on brain. Conf Proc IEEE Eng Med Biol Soc; 2010:6625–8.
[52] Yanagisawa T, Hirata M, Saitoh Y, Kato A, Shibuya D, Kamitani Y, et al. Neural decoding using gyral and intrasulcal electrocorticograms. Neuroimage 2009;45:1099–106.
[53] 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;36:2493–6.
[54] Matsumoto J, Fujiwara T, Takahasi O, Liu M, Kimura A, Ushiba J. Modulation of mu rhythm desynchronization during motor imagery by transcranial direct current stimulation. J Neuro Eng Rehabil 2010;7:27.
[55] Kasahima Y, Fujiwara T, Matsushika Y, Tsuji T, Hase K, Ushiyama J, et al. Modulation of event related desynchronization during motor imagery with transcranial direct current stimulation (tDCS) in patients with chronic hemiparetic stroke. Exp Brain Res 2012;221:263–8.
[56] Mulder T. Motor imagery and action observation: cognitive tools for rehabilitation. J Neural Transm 2007;114:1265–78.
[57] Zimmermann-Schlatter A, Schuster C, Puhan MA, Siekierka E, Steurer J. Efficacy of motor imagery in post-stroke rehabilitation: a systematic review. J Neuroeng Rehabil 2008;14: 5–8.
[58] Caramia MD, Palmieri MG, Giacomini P, Iani C, Dally L, Silvestrini M. Ipsilateral activation of the unaffected motor cortex in patients with hemiparetic stroke. Clin Neurophysiol 2000;111:1990–6.
[59] Woldag H, lukhaup S, Renner C, Hummelsheim H. Enhanced motor cortex excitability during ipsilateral voluntary hand activation in healthy subjects and stroke patients. Stroke 2004;35:2556–9.
[60] Marshall RS, Perera GM, lazar RM, Krakauer JW, Constantine RC, DeLaPaz RL. Evolution of cortical activation during recovery from corticospinal tract infarction. Stroke 2000;31:656–61.
[61] Lindberg P, Schmitz C, Forssberg H, Engardt M, Borg J. Effects of passive-active movement training on upper limb motor function and cortical activation in chronic patients with stroke: a pilot study. J Rehabil Med 2004;36:117–23.
[62] Sharma N, baron JC, Rowe JB. Motor imagery after stroke: relating outcome to motor network connectivity. Ann Neurol 2009;66:604–16.
[63] Bakhei AMO, Thilmann AF, Ward AB, Poewe W, Wissel J, Muller J, et al. A randomized, double-blind, placebo-controlled, dose-ranging study to compare the efficacy and safety of three doses of botulinum toxin type A (Dysport) with placebo in upper limb spasticity after stroke. Stroke 2000;31: 2402–6.

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Comparison of the After-Effects of Transcranial Direct Current Stimulation Over the Motor Cortex in Patients With Stroke and Healthy Volunteers

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ABSTRACT

It is known that weak transcranial direct current stimulation (tDCS) induces persistent excitability changes in the cerebral cortex. There are, however, few studies that compare the after-effects of anodal versus cathodal tDCS in patients with stroke. This study assessed the after-effects of tDCS over the motor cortex in patients with hemiparetic stroke and healthy volunteers. Seven stroke patients and nine healthy volunteers were recruited. Ten minutes of anodal and cathodal tDCS (1 mA) and sham stimulation were applied to the affected primary motor cortex (M1) on different days. In healthy subjects, tDCS was applied to the right M1. Before and after tDCS, motor-evoked potentials (MEPs) in the first dorsal interosseous (FDI) muscle and silent period were measured. Anodal tDCS increased the MEPs of the affected FDI in patients with stroke as well as in healthy subjects. Cathodal tDCS increased the MEPs of the affected FDI in patients with stroke. In healthy subjects, however, cathodal tDCS decreased the MEPs. We found no significant change in the duration of the silent period after anodal or cathodal tDCS. We found that both anodal and cathodal tDCS increased the affected M1 excitability in patients with stroke. It is thought that the after-effects of tDCS are different in patients with stroke compared with healthy subjects.

KEYWORDS: cerebrovascular disease, cortical plasticity, hemiparesis, motor-evoked potential (MEP), trancranial direct current stimulation (tDCS), trancranial magnetic stimulation (TMS)

INTRODUCTION

It is known that weak transcranial direct current stimulation (tDCS) induces persistent excitability changes in the cerebral cortex. Anodal stimulation increases and cathodal stimulation decreases cortical excitability [1]. It has been confirmed in animal studies that anodal stimulation increases the excitement frequencies of nerve cells, whereas cathodal stimulation decreases the excitement frequencies of nerve cells [2,3]. Blocking *N*-methyl-D-aspartate (NMDA) receptors prevents the induction of after-effects of tDCS [4]. Therefore the after-effects of tDCS are considered to be related to synapse plasticity due to functions of NMDA receptors in addition to changes in cell membrane potentials [4,5].

Recent studies have shown that non-invasive brain stimulation enhances the beneficial effects of motor training in patients with stroke [6,7]. Hummel et al. [8,9] applied tDCS to patients with mild hemiparesis. They found that anodal tDCS to the affected primary motor cortex (M1) improved the hand function of the paretic hand. It is easy to apply tDCS to the patients

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in clinical settings because electrodes can be set on the head with a band. The after-effects of non-invasive brain stimulation depend on the state of the cortex at the time the stimulation is applied [10]. State-dependency effects of 1 Hz repetitive transcranial magnetic stimulation (rTMS) have been demonstrated in patients with migraine [11]. After a stroke, abnormally increased cortical inhibition contributes to motor dysfunction. It is supposed cathodal tDCS may decrease the excitability of cortical inhibitory interneurons and increase the motor cortex excitability among patients with stroke [12]. There are, however, few studies that compare the after-effects of anodal versus cathodal tDCS in patients with stroke. We hypothesize, therefore, cathodal tDCS may increase the motor cortex excitability in the affected hemisphere.

The aim of this study was to assess the after-effects of cathodal and anodal tDCS over the affected motor cortex in patients with subcortical stroke and healthy volunteers.

METHODS

Participants

Nine healthy volunteers (five males and four females; mean age, 34.4 years; range, 22–65 years) and seven patients with hemiparesis due to stroke (six males and one female; mean age, 64.5 years; range, 58–75 years) were recruited from National Murayama Medical Center. All participants were right-handed. One patient had a cerebral infarction and six had a cerebral hemorrhage; all patients had a subcortical lesion. Two patients had a left-hemisphere lesion and five had a right-hemisphere lesion. Table 1 shows background data on stroke patients. The finger function of the paretic hand was assessed with the Stroke Impairment Assessment Set [13], the validity and reliability of which had been already confirmed [14]. A finger motor function score of 0 means no voluntary finger movement, and score of 5 means normal. A score of 3 means that the patient can perform independent finger movements, with each finger having adequate flexion and extension. A score of 4 means the patient performs independent finger movements with mild clumsiness. The light touch sensation was checked on the palm of the hand. A sensory score of 0 indicated anesthesia and a score of 3 indicated normal. All participants gave written informed consent to the study, which was approved by the local ethical committee and conformed to the requirements of the Declaration of Helsinki. Participants had neither a psychiatric medical history nor contraindications to transcranial magnetic stimulation (TMS) [15].

Recordings

Participants were seated in a comfortable reclining chair so that the whole body, including both arms, was at rest. Surface electrodes were placed at the left first dorsal interosseous (FDI) muscle in healthy subjects and the affected FDI in patients. Signals were amplified and band-pass filtered (10 Hz to 1 kHz) by an amplifier (Neuropack® MEB 2200, Nihon-Kohden Co., Ltd., Tokyo, Japan) and stored at a sampling rate of 5 kHz on a personal computer.

Transcranial Direct Current Stimulation

tDCS was applied for 10 min at a current intensity of 1 mA through rectangular saline-soaked sponge electrodes (50 × 70 mm^2) with a battery-driven stimulator (CX-6650, Rolf Schneider Electronics, Gleichen, Germany). One stimulation electrode was placed over the M1 and the other stimulation electrode was placed above the contralateral supraorbital area. The position of M1 was confirmed through the induction of the largest motor-evoked potentials (MEPs) in the FDI muscle with constant stimulus intensity using TMS with a figure-eight stimulation coil connected to a SMN® 1200 (Nihon-Kohden Co., Ltd.). Among healthy subjects, one electrode was placed over the right M1 and the other was placed over the left side in the supraorbital area. For anodal stimulation, the anodal electrode was

TABLE 1. Demographic information of patients

Patients	Age	Sex	Time from onset (days)	Type of stroke	Affected hemisphere	Lesion	Size of lesion (mL)	SIAS finger score	SIAS sensory score (light touch)
A	62	M	297	CH	R	Putamen	14	4	2
B	60	M	327	CH	R	Putamen	18	3	2
C	58	M	33	CH	R	Putamen	9	4	2
D	75	M	127	CH	R	Thalamus	18	3	3
E	67	F	111	CH	L	Subcortical of frontal	14	4	2
F	65	M	38	CI	L	Corona radiata	4	3	2
G	62	M	70	CH	R	Thalamus	18	4	1

Note: CI, cerebral infarction; CH, cerebral hemorrhage; R, right; L, left.

placed over the right side M1, and the cathodal electrode was placed over the left supraorbital area. For cathodal stimulation, the electrodes were reversed; that is, the cathodal electrode was placed over the right M1 and the anodal electrode was placed over the left supraorbital area. Among patients with stroke, one electrode was placed on affected M1 and the other electrode was placed on contralateral supraorbital area. For anodal stimulation on patients with stroke, anodal electrode was placed on the affected M1. For cathodal stimulation, cathodal electrode was placed on the affected M1. For the sham stimulation, the current was applied for about 10 s to mimic the transient skin sensation at the beginning of actual tDCS without producing any conditioning effects on the brain. Three stimulation conditions (anodal, cathodal, and sham) were applied in each participant with a randomized sequence on different days to minimize carry-over effects. Each condition was separated from the preceding one by more than 24 h in the same participant.

Measurement of MEPs

Resting motor threshold (RMT) of the FDI was measured. For the measurement of RMT, the subject relaxed and electromyographic (EMG) silence was monitored. RMT was defined as the lowest stimulus intensity capable of inducing MEPs greater than 50 μV in at least five of 10 trials [16].

Corticospinal excitability was evaluated using suprathreshold stimulation (110% RMT). MEPs were recorded at the left FDI muscle in healthy subjects and at the paretic side in patients with stroke. Seventeen MEPs were measured and averaged at each time point, that is, before tDCS, immediately after tDCS, 10 min after tDCS, and 30 min after tDCS. The stimuli were delivered using SMN® 1200 (Nihon-Kohden Co., Ltd.) machine and a figure-eight coil with an outer winding diameter of 9 cm.

Silent Period

Six of nine healthy volunteers and six patients participated in silent period and F-wave study. A single TMS pulse was applied during isometric index finger abduction with a force of about 10%–20% maximum voluntary contraction with the help of visual feedback of the EMG activity. The duration of the silent period was defined as the time from the MEP to the return of voluntary EMG activity. Stimulus intensity was set at 110% of the RMT. Ten silent periods were measured and averaged before tDCS, immediately after tDCS, 10 min after tDCS, and 30 min after tDCS.

F-wave

In all subjects, changes in resting amplitudes of TMS-evoked MEPs following tDCS were compared with changes in the size of F-waves evoked in the relaxed FDI by supramaximal electrical stimulation of the ulnar nerve at the wrist before and after tDCS. The peak-to-peak amplitude of each of 16 F-waves was measured and then averaged before tDCS, immediately after tDCS, 10 min after tDCS, and 30 min after tDCS.

Data Analysis

We compared the baseline values of MEP with repeated measure ANOVA. All data were analyzed with the general linear model three-way mixed ANOVA with factors of time (before and at intervals after tDCS), stimulation (anodal, cathodal, and sham tDCS), and category (healthy subjects and stroke subjects). Conditional on a significant F value, post-hoc tests were performed with using paired and unpaired t-tests. Values were considered statistically significant when $p < 0.05$. Statistical analysis was performed with SPSS 15.0J (SPSS Japan, Tokyo, Japan).

RESULTS

Motor-Evoked Potentials

No participant experienced any side effects from the stimulation. RMTs were expressed as the percentage of maximum output of the magnetic stimulator. The mean (SE) RMT value of healthy subjects was 49.1% (2.3%), and the mean RMT value of the stroke group was 70.2% (4.2%). The difference was significant with unpaired t-test ($p = 0.001$).

The mean amplitude of MEPs (SE) in healthy subjects before anodal, cathodal, and sham tDCS were 0.40 (0.03), 0.61 (0.11), and 0.59 (0.11) mV, respectively. The mean amplitude of MEPs (SE) in patients with stroke before anodal, cathodal, and sham tDCS were 0.22 (0.07), 0.24 (0.06), and 0.22 (0.05) mV, respectively. There were no significant differences in mean MEP amplitude before anodal, cathodal, and sham tDCS in healthy subjects ($F_{2,16} = 1.644, p = 0.224$) and patients with stroke ($F_{2,12} = 0.13, p = 0.877$).

The changes of MEPs were expressed as the ratio to the mean value of before tDCS in each subject. Figure 1 shows the change of MEPs induced by anodal and cathodal tDCS and sham stimulation among the nine healthy subjects. Figure 2 shows the change of MEPs induced by anodal and cathodal tDCS and sham stimulation among the seven patients with stroke. Three-way mixed ANOVA showed significant interaction of time

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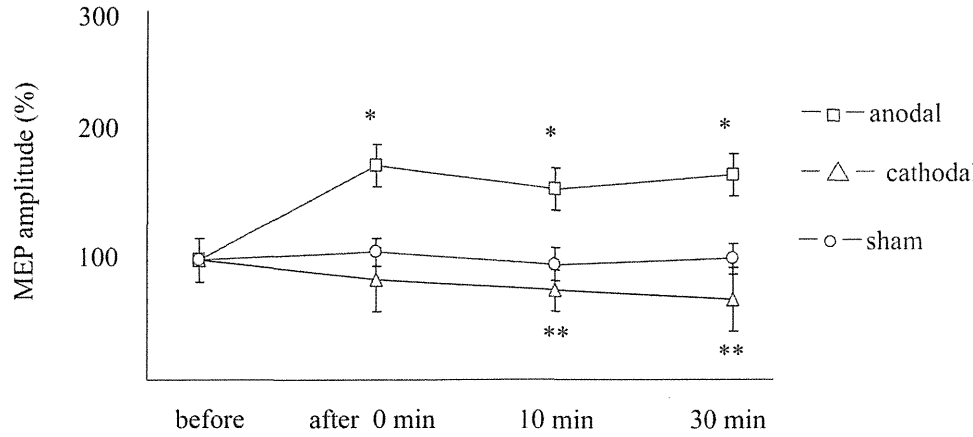

FIGURE 1. Change of the MEP amplitudes before and after (after: 0 min, 10 min, 30 min) the anodal tDCS (open square), cathodal tDCS (open triangle), and sham tDCS (open circle) among healthy subjects. The size of the amplitude is expressed as a percentage of the preconditioning control. Anodal tDCS increased MEPs in 0, 10, and 30 min after stimulation and cathodal tDCS decreased MEPs at 10 and 30 min after stimulation. $^{*}p < 0.001$; $^{**}p < 0.05$.

(before and at intervals after tDCS), stimulation (anodal, cathodal, and sham), and category (healthy subjects and stroke subjects; $F_{6,9} = 5.369$, $p = 0.013$).

In healthy subjects, anodal tDCS increased MEPs at 0 min ($p < 0.001$), 10 min ($p < 0.001$), and 30 min after stimulation ($p < 0.001$). Cathodal tDCS decreased the MEPs at 10 min ($p = 0.023$) and 30nin ($p = 0.04$) after stimulation compared with before stimulation. Sham stimulation did not induce any significant changes of MEPs.

In stroke patients, anodal tDCS increased the MEPs significantly at 0 min ($p = 0.024$) and 10 min ($p = 0.031$) after tDCS. In cathodal tDCS, the MEPs were significantly increased at 0 min after tDCS compared with before tDCS ($p = 0.016$). Sham stimulation did not induce any significant change.

Silent Period and F-Wave Amplitude

Table 2 shows the mean duration of the silent period and mean amplitudes of the F-wave. There was no significant interaction of time, stimulation, and category in the duration of the silent period ($F_{6,66} = 0.816$, $p = 0.562$) and F-wave amplitude ($F_{6,66} = 0.348$, $p = 0.909$).

DISCUSSION

We found that both anodal and cathodal tDCS increased cortical excitability in patients with subcortical stroke. Cathodal tDCS, however, decreased cortical excitability in healthy volunteers. Our results showed that MEP change induced with tDCS has significant interaction

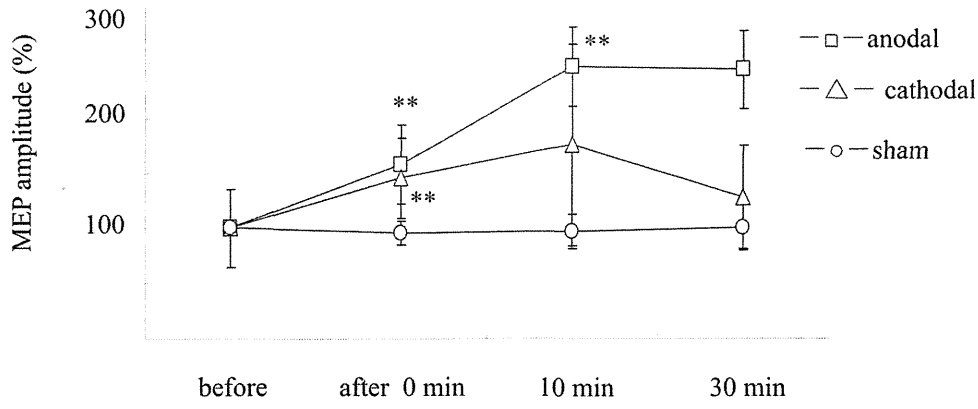

FIGURE 2. Change of the MEP amplitudes before and after (after: 0 min, 10 min, 30 min) the anodal tDCS (open square), cathodal tDCS (open triangle), and sham tDCS (open circle) among patients with stroke. The size of the amplitude is expressed as a percentage of the preconditioning control. Post-hoc paired *t*-test showed significant increased MEPs in 0 and 10 min after anodal and 0 min after cathodal tDCS. $^{**}p < 0.05$.

TABLE 2. The mean values (SD) of silent period and F-wave amplitude

Group	Parameter	Stimulation	Before	After 0 min	After 10 min	After 30 min
Healthy group	Silent period (ms)	Anodal tDCS	98.8 (47.0)	103.0 (32.0)	102.7 (46.7)	109.4 (48.9)
		Cathodal tDCS	130.7 (19.5)	133.2 (22.5)	131.5 (19.7)	135.1 (24.1)
		Sham	124.4 (39.8)	124.3 (43.6)	125.4 (39.5)	125.1 (39.9)
	F-wave amplitude (mV)	Anodal tDCS	0.24 (0.14)	0.18 (0.05)	0.24 (0.10)	0.22 (0.10)
		Cathodal tDCS	0.21 (0.16)	0.21 (0.11)	0.18 (0.04)	0.19 (0.10)
		Sham	0.22 (0.15)	0.22 (0.12)	0.23 (0.11)	0.24 (0.08)
Stroke group	Silent period (ms)	Anodal tDCS	188.1 (78.8)	190.5 (79.1)	192.3 (78.6)	189.5 (80.3)
		Cathodal tDCS	196.1 (71.2)	196.7 (71.9)	203.8 (75.0)	202.8 (76.0)
		sham	178.9 (72.4)	175.8 (72.1)	179.3 (78.3)	174.1 (70.9)
	F-wave amplitude (mV)	Anodal tDCS	0.31 (0.05)	0.33 (0.06)	0.30 (0.08)	0.34 (0.10)
		Cathodal tDCS	0.27 (0.12)	0.23 (0.11)	0.26 (0.09)	0.27 (0.15)
		Sham	0.30 (0.11)	0.32 (0.13)	0.30 (0.11)	0.35 (0.14)

of category (stroke and healthy), stimulation (anodal, cathodal, and sham), and time (before and at intervals after tDCS). It implies that the modulation of motor cortex excitability with tDCS depends on the state of motor cortex.

All patients recruited in this study had a subcortical lesion. Liepert et al. [17] reported that motor cortex excitability of patients with subcortical stroke had been decreased. Neuronal circuits within the basal ganglia facilitate the motor cortex either through antidromic excitation of cortical-basal ganglia fibers or through orthodromic activation of a basal ganglia-thalamocortical pathway. Therefore, a stroke-induced disturbance of basal ganglia may result in change of motor cortex excitability. It was hypothesized that the condition of projection from the basal nucleus to M1 in these patients would be different from conditions in healthy subjects. Therefore, cortical modulation by tDCS would be different in the affected hemisphere.

The differential effects of cathodal tDCS between healthy subjects and patients with stroke underline the point that the effects of brain stimulation depend on the physiological state of neuronal populations at the time the stimulus is applied. This is evident in concepts such as "homeostatic" plasticity [18,19], where the state of neural activity determines the production of LTP/LTD-like synaptic effects. Siebner et al. [18] showed that inhibitory preconditioning with cathodal tDCS resulted in 1 Hz repetitive TMS (rTMS) increasing corticospinal excitability, whereas 1 Hz rTMS alone induced reduction in corticospinal excitability. The baseline corticospinal excitability in patients with stroke should be reduced in the affected hemisphere because the mean RMT value of the affected hemisphere was significantly higher than that of healthy subjects. The after-effect of noninvasive brain stimulation should depend on the state of excitability before stimulation. According to the homeostatic hypothesis, cathodal tDCS should increase corticospinal excitability in a reduced-excitability state affected hemisphere, such as stroke, whereas it should decrease corticospinal excitability in healthy subjects.

When changes that bring about membranal potential excitement or stimuli that would induce changes in synaptic transmission occur at a time when excitability is lowered by the state of the precondition, as with homeostatic plasticity, there is a possibility for cortical excitability to be increased after cathodal tDCS in the direction of homeostatic plasticity.

The mechanism how cathodal tDCS increases the motor cortex excitability may be explained by cathodal tDCS-induced depression of cortical inhibitory interneuron, which is abnormally increased in the affected hemisphere among patients with stroke.

It should be, however, noted that it is not always the case for the opposite phenomena to occur in anodal and cathodal tDCS [20,21].

Age difference between healthy subjects and patients with stroke might be other mechanism, which explains the different after-effect induced cathodal tDCS. Normal aging is associated with relative decrease in the excitability of inhibitory circuits within motor cortex. Peinemann et al. [22] showed that short-interval intracortical inhibition correlated negatively with age, whereas intracortical facilitation (ICF) was preserved in the elderly persons. It is, therefore, supposed that cathodal tDCS induces facilitatory effect more than inhibitory effect in elderly person.

Hummel et al. [8] found decreases of short intracortical inhibition (SICI) with anodal tDCS. Liepert et al. [23] conducted TMS with stroke patients as subjects. Compared with the unaffected side, SICI decreased in a significant manner, which suggests disinhibition among stroke patients. They reported that the cortical silent period was significantly prolonged among stroke patients, which suggests that different inhibition mechanisms are at work in SICI and the silent period.

With our current assessment, no changes were seen in the silent period with anodal or cathodal tDCS. With

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1 mA tDCS for 10 min, it is possible that the effects were not large enough to bring about changes in the silent period. It should be noted, however, that there are many unknown elements in the mechanisms of occurrences during the silent period. In the case of stroke patients, effects of excitement and inhibition between hemispheres must be considered. It is necessary, therefore, to carry out in future assessments on SICI and ICF during the silent period and double stimuli (paired pulse TMS) after conducting anodal and cathodal tDCS on both the affected and unaffected areas.

As for the F-wave, results from our study showed no significant changes before or after anodal or cathodal tDCS. Nitsche et al. [5] reported that no changes occurred on the spinal level as no change was seen in H-reflex amplitudes before and after tDCS. Nitsche et al. [24] reported no change in the assessment of F-wave. When combining these reports with our assessment on F-wave of stroke patients, it is considered that MEP changes are caused by changes on the cortex level and not on the spinal level. However, it has been pointed out that effects on the spinal level cannot be completely excluded when examining F-waves [25]. Thus, future studies are warranted.

We found no relationships between the change of corticospinal excitability induced by tDCS and time from onset in this study. We could not find consistent differences between the subjects with putaminal lesions, the subjects with thalamic lesions, and the subjects with subcortical white matter lesions. Patients with hypertensive hemorrhages and ischemic stroke often have small vessel microangiopathic changes on MRI. Extensive small vessel ischemic disease affects cognition and motor function [26]. We did not find extensive microangiopathic changes on MRI. We could not, however, exclude the effect of microangiopathic changes. However, we had a limited number of subjects in this study, so further studies are needed. In particular, we need to study factors that influence the change of corticospinal excitability induced by tDCS, such as lesion size, location, time after events, and impairment level.

Hummel et al. [9] reported that tDCS of the motor cortex improve motor function in the paretic hand of patients with chronic stroke. We did not find whether anodal and cathodal tDCS have beneficial effect on motor and sensory function of the affected hand or not. Future studies are necessary to study the relationship to the behavioral consequences of stimulation in patients with stroke.

CONCLUSION

In this study, we found that both anodal and cathodal tDCS increased the affected MI excitability in patients with stroke. It is thought that the after-effect of tDCS is different in patients with stroke, compared with healthy subjects. In applying tDCS to patients with stroke, we further need to study factors that influence the after-effect induced by tDCS.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

REFERENCES

1. Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol. 2000;527:633–9.
2. Bindman LJ, Lippold OCJ, Redfearn JWT. The action of brief polarizing currents on the cerebral cortex of the rat (1) during current flow and (2) in the production of long-lasting after-effects. J Physiol. 1964;172:369–82.
3. Purpura DP, McMurtry JG. Intracellular activities and evoked potential changes during polarization of motor cortex. J Neurophysiol. 1965;28:166–85.
4. Liebetanz D, Nitsche MA, Tergau F, Paulus W. Pharmacological approach to the mechanisms of transcranial DC-stimulation-induced after-effects of human motor cortex excitability. Brain. 2002;125:2238–47.
5. Nitsche MA, Nitsche MS, Klein CC, Tergau F, Rothwell JC, Paulus W. Level of action of cathodal DC polarization induced inhibition of the human motor cortex. Clin Neurophysiol. 2003;114:600–4.
6. Suzuki K, Tsuji T, Masakado Y, Ota T, Kimura A, Chino N. Long lasting effects of 0.1Hz rTMS paired with motor point stimulation in hemiparetic stroke patients. Jpn J Rehabil Med. 2004;41:302–6.
7. Takeuchi N, Chuma T, Matsuo Y, Watanabe I, Ikoma K. Repetitive transcranial magnetic stimulation of contralesional primary motor cortex improves hand function after stroke. Stroke. 2005;36:2681–6.
8. Hummel F, Celink P, Giraux P, Floel A, Wu W-H, Gerloff C, Cohen LG. Effects of non-invasive cortical stimulation on skilled motor function in chronic stroke. Brain. 2005;128:490–9.
9. Hummel F, Cohen LG. Improvement of motor function with noninvasive cortical stimulation in a patient with chronic stroke. Neurorehabil Neural Repair. 2005;19:14–9.
10. Fujiwara T, Rothwell JC. The after effects of motor cortex rTMS depend on the state of contraction when rTMS is applied. Clin Neurophysiol. 2004;115:1514–8.
11. Brighina F, Piazza A, Daniele O, Fierro B. Modulation of visual cortical excitability in migraine with aura: effects of 1 Hz repetitive transcranial magnetic stimulation. Exp Brain Res. 2002;145:177–81.
12. Monti A, Cogiamanian F, Marceglia S, Ferrucci R, Mameli F, Mrakic-Sposta S, Vergari M, Zago S, Priori A. Improved naming after transcranial direct current stimulation in aphasia. J Neurol Neurosurg Psychiatry. 2008;79:451–3.
13. Chino N, Sonoda S, Domen K, Saitoh E, Kimura A. Stroke Impairment Assessment Set (SIAS). Jpn J Rehabil Med. 1994;31:119–25.
14. Tsuji T, Liu M, Sonoda S, Domen K, Chino N. The stroke impairment assessment set: its internal consistency and predictive validity. Arch Phys Med Rehabil. 2000;81:863–8.

15. Wassermann EM. Risk and safety of repetitive transcranial magnetic stimulation: report and guidelines. Electroenceph Clin Neurophysiol. 1998;108:1–16.
16. Rossini PM, Barker AT, Berardelli A, Caramia MD, Caruso G, Cracco RQ, Dimitrijević MR, Hallett M, Katayama Y, Lücking CH. Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: basic principles and procedures for routine clinical application. Report of an IFCN committee. Electroencephalogr Clin Neurophysiol. 1994;91:79–92.
17. Liepert J, Restemeyer C, Kucinski T, Zittel S, Weiller C. Motor strokes: the lesion location determines motor excitability changes. Stroke. 2005;36:2648–53.
18. Siebner HR, Lang N, Rizzo V, Nitsche MA, Paulus W, Lemon RN, Rothwell JC. Preconditioning of low-frequency repetitive transcranial magnetic stimulation with transcranial direct stimulation: evidence for homeostatic plasticity in the human motor cortex. J Neurosci. 2004;24:3379–85.
19. Ziemann U, Ilić TV, Pauli C, Meintzschel F, Ruge D. Learning modifies subsequent induction of long-term potentiation-like and long-term depression-like plasticity in human motor cortex. J Neurosci. 2004;24:1666–72.
20. Matsunaga K, Nitche MA, Tsuji S, Rothwell JC. Effect of transcranial DC sensorimotor cortex stimulation on somatosensory evoked potentials in humans. Clin Neurophysiol. 2004;115:456–60.
21. Priori A. Brain polarization in humans: a reappraisal of an old tool for prolonged non-invasive modulation of brain excitability. Clin Neurophysiol. 2003;114:589–95.
22. Peinemann A, Lehner C, Conrad B, Siebner HR. Age-related decrease in paired-pulse intracortical inhibition in the human primary motor cortex. Neurosci Lett. 2001;313:33–6.
23. Liepert J, Kucinski T, Tüscher O, Pawlas F, Bäumer T, Weiller C. Motor cortex excitability after cerebellar infarction. Stroke. 2004;35:2484–8.
24. Nitsche MA, Fricke K, Henschke U, Schlitterlau A, Liebetanz D, Lang N, Henning S, Tergau F, Paulus W. Pharmacological modulation of cortical excitability shifts induced by transcranial direct stimulation in humans. J Physiol. 2003;533:293–301.
25. Hultborn H, Nielsen JB. H-reflex and F-responses are not equally sensitive to changes in motoneuronal excitability. Muscle Nerve. 1995;18:1471–4.
26. Mok VC, Wong A, Lam WW, Fan YH, Tang WK, Kwok T, Hui AC, Wong KS. Cognitive impairment and functional outcome after stroke associated with small vessel disease. J Neurol Neurosurg Psychiatry. 2004;75:560–6.

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RESEARCH ARTICLE

Modulation of event-related desynchronization during motor imagery with transcranial direct current stimulation (tDCS) in patients with chronic hemiparetic stroke

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Abstract Electroencephalogram-based brain–computer interface (BCI) has been developed as a new neurorehabilitative tool for patients with severe hemiparesis. However, its application has been limited because of difficulty detecting stable brain signals from the affected hemisphere. It has been reported that transcranial direct current stimulation (tDCS) can modulate event-related desynchronization (ERD) in healthy persons. The objective of this study was to test the hypothesis that anodal tDCS could modulate ERD in patients with severe hemiparetic stroke. The participants were six patients with chronic hemiparetic stroke (mean age, 56.8 ± 9.5 years; mean time from the onset, 70.0 ± 19.6 months; Fugl-Meyer Assessment upper extremity motor score, 30.8 ± 16.5). We applied anodal tDCS (10 min, 1 mA) and sham stimulation 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. Mu ERD of the affected hemisphere increased significantly after anodal tDCS, whereas it did not change after sham stimulation. Our results show that anodal tDCS can increase mu ERD in patients with hemiparetic stroke, indicating that anodal tDCS could be used as a conditioning tool for BCI in stroke patients.

Keywords Electroencephalography · Cerebrovascular disease · Rehabilitation · Noninvasive brain stimulation

Introduction

The functional recovery of the upper extremity is limited in patients with hemiparetic stroke. Most patients with stroke have difficulty performing activities of daily living (ADL) using their weakened upper extremity. The functional recovery depends on the severity of their motor impairment (Hendricks et al. 2002). Therefore, therapeutic options for patients with a severely hemiparetic upper extremity are limited.

Recently, technological innovations such as the brain–computer interface (BCI) have been developed. Buch et al. (2008) reported the possibility of using the sensorimotor mu rhythm over the affected primary motor cortex (M1) recorded with magnetoencephalography (MEG) for neurorehabilitation. Using this signal, the patients learned to use motor imagery to control the mu rhythm and to operate an orthotic device that opened and closed their paretic hand. The mu rhythm is a spontaneous characteristic feature of the EEG/MEG pattern that has 8- to 13-Hz activity and appears maximally over the central rolandic or sensorimotor area

Yuko Kasashima and Yayoi Matsushika contributed equally to the study.

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