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A Randomized Controlled Trial of EEG-Based Motor Imagery Brain-Computer Interface Robotic Rehabilitation for Stroke

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Abstract

Electroencephalography (EEG)–based motor imagery (MI) brain-computer interface (BCI) technology has the potential to restore motor function by inducing activity-dependent brain plasticity. The purpose of this study was to investigate the efficacy of an EEG-based MI BCI system coupled with MIT-Manus shoulder-elbow robotic feedback (BCI-Manus) for subjects with chronic stroke with upper-limb hemiparesis. In this single-blind, randomized trial, 26 hemiplegic subjects (Fugl-Meyer Assessment of Motor Recovery After Stroke [FMMA] score, 4-40; 16 men; mean age, 51.4 years; mean stroke duration, 297.4 days), prescreened with the ability to use the MI BCI, were randomly allocated to BCI-Manus or Manus therapy, lasting 18 hours over 4 weeks. Efficacy was measured using upper-extremity FMMA scores at weeks 0, 2, 4 and 12. ElEG data from subjects allocated to BCI-Manus were quantified using the revised brain symmetry index (rBSI) and analyzed for correlation with the improvements in FMMA score. Eleven and 15 subjects underwent BCI-Manus and Manus therapy, respectively. One subject in the Manus group dropped out. Mean total FMMA scores at weeks 0, 2, 4, and 12 weeks improved for both groups: 26.3 ± 10.3, 27.4 ± 12.0, 30.8 ± 13.8, and 31.5 ± 13.5 for BCI-Manus and 26.6 ± 18.9, 29.9 ± 20.6, 32.9 ± 21.4, and 33.9 ± 20.2 for Manus, with no intergroup differences (P = .51). More subjects attained further gains in FMMA scores at week 12 from BCI-Manus (7 of 11 [63.6%]) than Manus (5 of 14 [35.7%]). A negative correlation was found between the rBSI and FMMA score improvement (P = .044). BCI-Manus therapy was well tolerated and not associated with adverse events. In conclusion, BCI-Manus therapy is effective and safe for arm rehabilitation after severe poststroke hemiparesis. Motor gains were comparable to those attained with intensive robotic therapy (1,040 repetitions/session) despite reduced arm exercise repetitions using EEG-based MI-triggered robotic feedback (136 repetitions/session). The correlation of rBSI with motor improvements suggests that the rBSI can be used as a prognostic measure for BCI-based stroke rehabilitation.

Keywords

stroke, rehabilitation, brain-computer interface, motor imagery, EEG

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Introduction

BCI systems, using noninvasive EEG-based BCI technologies, are able to provide alternative channels using brain signals to support communication and control of assistive devices for subjects with severe motor disabilities.[1,2] Noninvasive BCI systems, based on sensorimotor rhythms, were able to achieve movement restoration in single patients with spinal cord lesions and chronic stroke for reaching and grasping.[3-5] There is now sufficient evidence that MI, the mental rehearsal of physical movement tasks, when combined with physical therapy leads to enhanced motor outcomes for stroke survivors and may represent a new approach to functional recovery after stroke.[6,7]

Because MI is usually concealed within patients, EEG-based BCI can provide online measures of MI as neurofeedback to aid motor task execution.[8,9] An example is the modulation of sensorimotor rhythms, which are oscillations in the EEG occurring in the alpha (8 to12 Hz) and beta (18 to 26 Hz) bands. Modulation of these frequency bands is similarly observed during actual, as well as mentally rehearsed, or imagined movements. Another example is distinct phenomena such as event-related desynchronization (ERD) and synchronization

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(ERS), which are detectable on EEG during MI in healthy subjects.[4,10-13] Recent studies have also revealed that ERD and ERS can be enhanced using BCI with proprioceptive feedback[14] or haptic feedback by closing the sensorimotor loop.[15]

There are currently a few clinical studies or protocols investigating the effects of noninvasive BCI on patients with chronic stroke.[16,17] Tan et al[18] described successful BCI-triggered neuromuscular electrical stimulation of wrist and finger extensors in 4 of 6 stroke survivors with moderate to severe degrees of hand motor paresis. Because of long latency periods to trigger 1 BCI-activated neuromuscular electrical stimulation (42 seconds), fatigue was evident after about 1 hour of BCI practice. Do et al[19] described a BCI functional electrical system to trigger foot dorsiflexion in healthy subjects. Buch et al[20] described 6 of 8 patients >1 year after stroke with severe finger extensor paralysis, who successfully learned to operate a magnetoencephalography (MEG)–based BCI device linked to a hand-opening and hand-closing orthotic system. Kaiser et al[21] measured the ERD or ERS in 29 patients with stroke and found that higher impairment was related to stronger ERD in the unaffected hemisphere, and higher spasticity was related to stronger ERD in the affected hemisphere.[21] However, these studies did not show clinical efficacy measurement on motor functions as a result of BCI-based intervention.

A case study of MEG-based BCI followed by EEG-based BCI combined with physiotherapy found significant clinical outcomes in FMMA scores (+84%).[22] Positive results on functional magnetic resonance imaging (MRI) and diffusion tensor imaging in that case study suggested possible short-term BCI-induced cortical and ipsilesional corticospinal tract neuroplasticity. Mihara et al[23] recently presented the results of a randomized controlled trial in 10 stroke patients who received near-infrared spectroscopy–based BCI with visual feedback, compared with 10 who received near-infrared spectroscopy–based BCI with irrelevant feedback. Compared with the sham group, the patients who received BCI visual feedback showed significantly greater motor improvements, measured using the FMMA score. In addition, Ramos-Murguialday et al[24] recently presented the results of a randomized controlled trial of 16 patients with chronic stroke who received BCI with hand and arm orthotic feedback, compared with 14 who received random orthotic feedback not linked to BCI. Both groups received physiotherapy after the intervention. Patients who received BCI orthotic feedback showed significantly greater motor improvements, measured by combined hand and modified arm FMMA scores.

Hence, preliminary studies suggest that EEG-based MI BCI may be used to objectively assess the performance of MI to restore motor function.

Rationale

Because current BCI neurofeedback systems require pairing with effectors to complete the sensorimotor feedback loop for stroke, we sought to compare the effects of EEG-based BCI with robotic feedback versus manual robotic training using the commercially available MIT-Manus robot, here termed the BCI-Manus system (Interactive Motion Technologies USA, Watertown, MA). This device was chosen for its positive results in hemiplegic stroke and ability to safely deliver high-intensity repetitive training in a supported environment with reduced effort.[25]

The aim of this study was to test the safety and efficacy of BCI-Manus compared with Manus therapy for subjects with chronic stroke with upper-limb hemiparesis. We describe the setup of an integrated BCI-Manus system and a randomized controlled trial comparing the BCI-Manus system with the Manus robot for moderate to severe chronic poststroke upper-limb hemiparesis.

Methods

Study Design

This randomized controlled trial was conducted over an approximately two and a half years period from April 1, 2007, to October 30, 2009, involving subjects who had completed inpatient rehabilitation at Tan Tock Seng Hospital in Singapore. Ethics committee approval was obtained from the institution's Domain Specific Review Board, National Healthcare Group, Singapore. The trial was registered at ClinicalTrials.gov (NCT00955838).

Figure 1 shows a flowchart of the trial. Subjects were first assessed for eligibility. Eligibility criteria included first-ever clinical ischemic or hemorrhagic stroke diagnosed by computed tomography or brain MRI within 3 hours of the event, poststroke duration > 3 months, age 21 to 65 years, and FMMA score of the affected upper limb of 0 to 45.[26] In addition, subjects were required to understand simple instructions and to score >6 of 10 on the Abbreviated Mental Test. Exclusion criteria were: transient ischemic attacks and silent infarctions; severe aphasia; cognitive impairment; severe depression; medical instability, including postural hypotension, unresolved sepsis, epilepsy, end-stage renal failure, and terminal illness; hemispatial neglect or severe visual impairment; skull defects due to craniotomy compromising fitting of the cap for EEG; upper-limb spasticity, with a Modified Ashworth Scale[27] score > 2 in any shoulder, elbow, or wrist or finger region in order to avoid robotic interruptions; shoulder pain (visual analogue scale score > 4 of 10); fixed joint contractures; and skin conditions that could be worsened by robotic exoskeletal or electroencephalographic cap contact. Eligible subjects were then screened for their ability to operate the EEG-based MI BCI system. Details of the BCI screening procedure were reported by Ang et al.[28] Subjects with >60% MI EEG classification accuracy, on the basis of previous local experience in healthy subjects and BCI-naive stroke survivors,[28] were then recruited for randomization.

Randomization and Blinding

Subjects who passed BCI screening, and gave further consent, were randomly assigned to receive 1 of the 2 interventions: (1) BCI-Manus, which consisted of EEG-based MI BCI with Manus robotic feedback,[28] or (2) Manus, which consisted of Manus robotically guided shoulder and elbow reaching exercises with computer screen visual feedback using the clock-face game.[29]

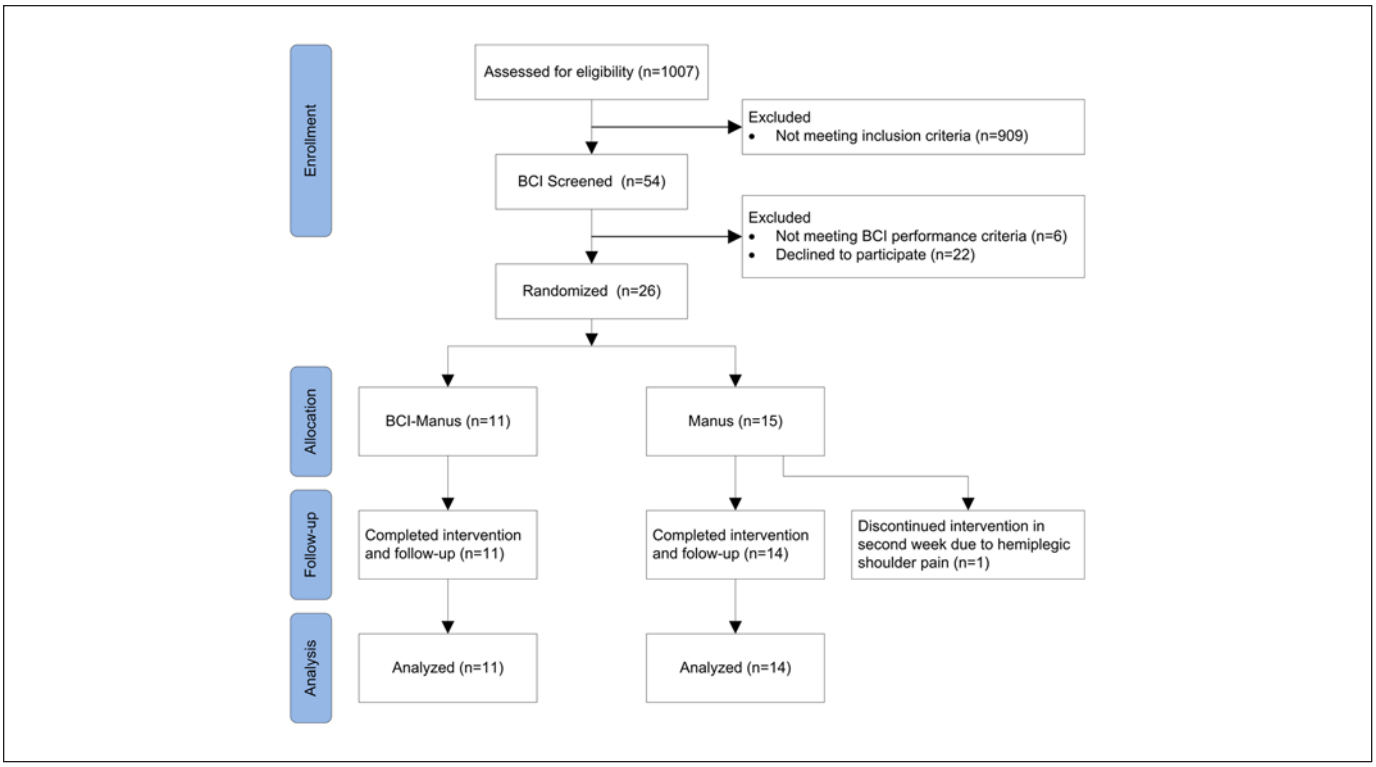

Figure 1. Consolidated Standards of Reporting Trials flow diagram. The diagram shows subject flow from recruitment through follow-up and analysis.

The randomization allocation sequence was 1:1, generated using Stata version 10.2 (StataCorp LP, College Station, TX) and sealed envelopes. Enrollment and assignment of participants were performed by one investigator. Because subject blinding was not feasible, all outcome assessments for this study were performed by an occupational therapist, who was blinded to allocation. There were no protocol deviations.

Both groups received a total of 18 hours of intervention, delivered over 4 weeks (1.5 hours each, 3 times per week) in the presence of an occupational therapist and an engineer. This included 20 minutes required for initial setup and rest breaks. A shorter 4-week intervention protocol was used in an attempt to reduce subject fatigue and noncompliance. Subject involvement, including follow-up, totaled approximately 4 months. Standard physical therapy was not carried out in combination with BCI-Manus or Manus intervention, and patients' concurrent rehabilitation therapies and medications were maintained during the study period for ethical reasons. Discontinuation criteria for recruited patients included new neurologic or serious adverse events, increase in arm pain or spasticity of >30% from baseline, and severe fatigue related to BCI interventions.

Manus Intervention

The Manus intervention consisted of 12 therapy sessions of a robotically guided protocol with 2 degrees of freedom, involving planar nonresistive, horizontal elbow and forearm reaching exercises within the robotic exoskeletal shell while using an 8-point clock face–drawing interactive video game (Figure 2a).[29] During the study, subjects were seated comfortably in a padded, height-adjustable chair with 2-point chest strapping, without arm rests to reduce compensatory trunk movements. For each subject, allowable pain-free shoulder and elbow ranges of motion were predetermined before training. Visual and movement feedback was provided by the Manus robot, using only passive resistance-free movement of the paretic arm within the exoskeletal arm from the center toward the target displayed on the screen, and back along a predetermined robotic trajectory. A small yellow circle displayed the position of the robotic arm that held the patient's stroke-affected arm, and a large red circle displayed the target position. The subject was instructed to move the stroke-affected arm from the center to the target position and then back to the center position. This to-and-fro movement was considered a single voluntary movement trial. Subsequently, the large red circle was displayed on the next target position in a clockwise manner. Robotically guided movement was initiated if there was no detectable movement from the subject after an interval of 2 seconds. This was progressively withdrawn when arm motor strength was sufficient to generate low-friction robotic arm movement toward the target.[29] The timing for a single movement trial averaged 3 to 5 seconds, as it was self-paced by the subjects. A therapy session consisted of 3 robot-assisted runs of 320 trials, interspersed with 5 nonassisted runs of 16 trials, amounting to 1,040 trials that lasted approximately 1.5 hours, inclusive of breaks for each therapy session.

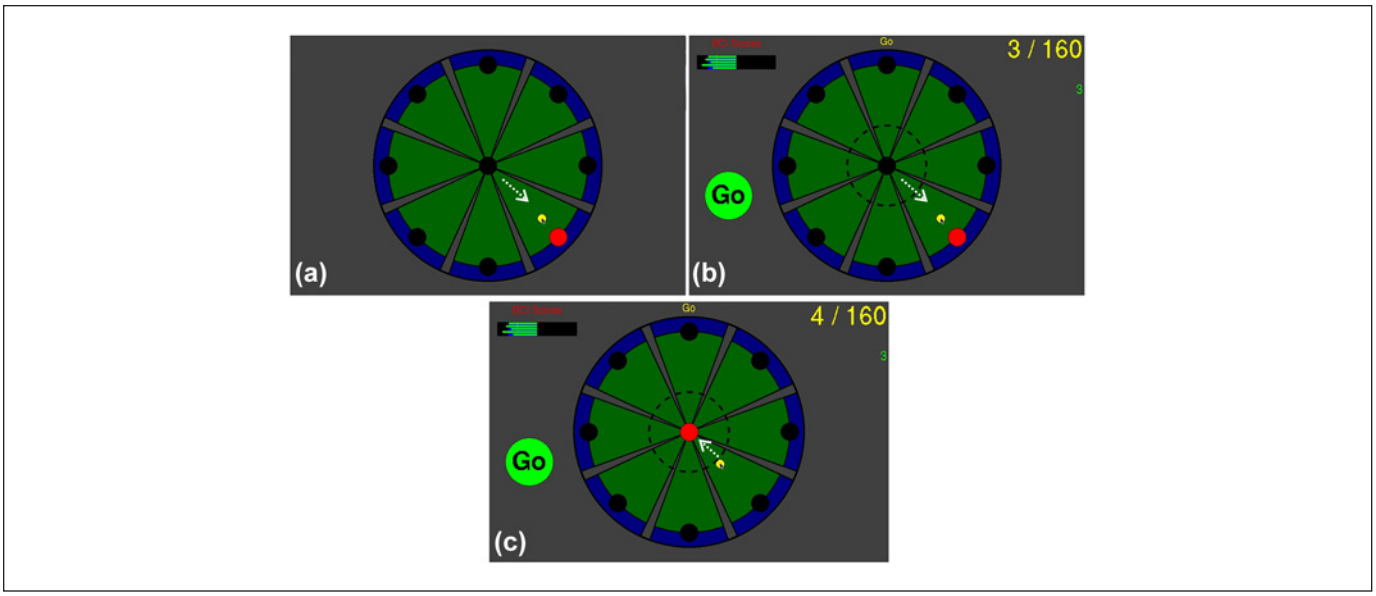

Figure 2. Eight-point clock-face game for Manus and BCI-Manus interventions. (a) Original clock face game used in the Manus intervention, in which a small yellow circle represents the current position of the robotic arm that holds the patient's stroke-affected arm, and a large red circle represents the target position. (b) Modified clock-face game used in the BCI-Manus intervention. If MI is detected, the robotic arm will move the stroke-affected arm to the respective target and (c) back to the center position. The physical distance between the center and the target is approximately 0.15 m.

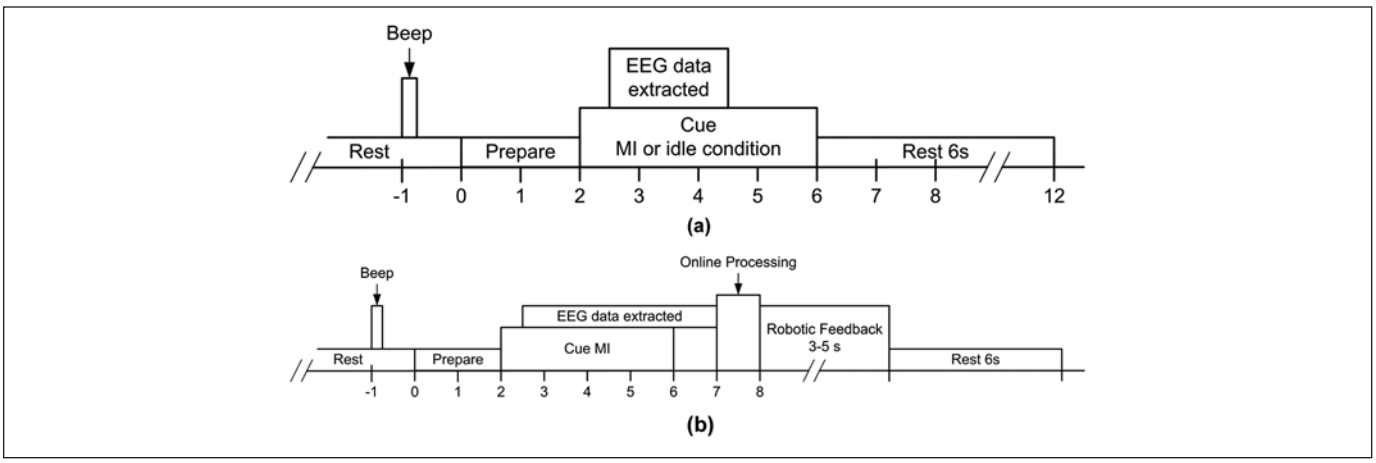

Figure 3. Acquisition of MI EEG for the BCI-Manus system. (a) Timing of the kinesthetic MI of the stroke-affected hand or background rest tasks for the calibration session before commencement of the therapy. (b) Timing of the kinesthetic MI of the stroke-affected hand with online robotic feedback for the therapy session.

BCI-Manus Intervention

The BCI-Manus intervention consisted of a calibration session and 12 therapy sessions of MI with robotic feedback, using a modified 8-point clock face–drawing interactive video game (Figure 2b). During calibration, EEG data were first collected from subjects who performed kinesthetic MI of the stroke-affected hand, while strapped to the Manus robotic exoskeleton. The subjects were instructed to imagine moving the stroke-affected arm and hand forward to reach for an imagery target in front of them and to reach the clock-face target. During MI, voluntary movements were restricted by locking the exoskeletal arm of the Manus robot. Any voluntary movements were countered with static resistance from the Manus robot, which sensed and recorded them. The calibration session consisted of 4 runs of 40 trials, for a total of 160 trials, and a break of ≥2 minutes was given after each run. Each run comprised 20 trials of MI and 20 trials of idiling. Figure 3a shows the timing for a single trial. Each trial lasted about 12 seconds, and each run lasted about 8 minutes. The calibration session lasted about 1 hour, inclusive of EEG setup time. The calibration collected EEG data to train a subject-specific MI detection model, so no

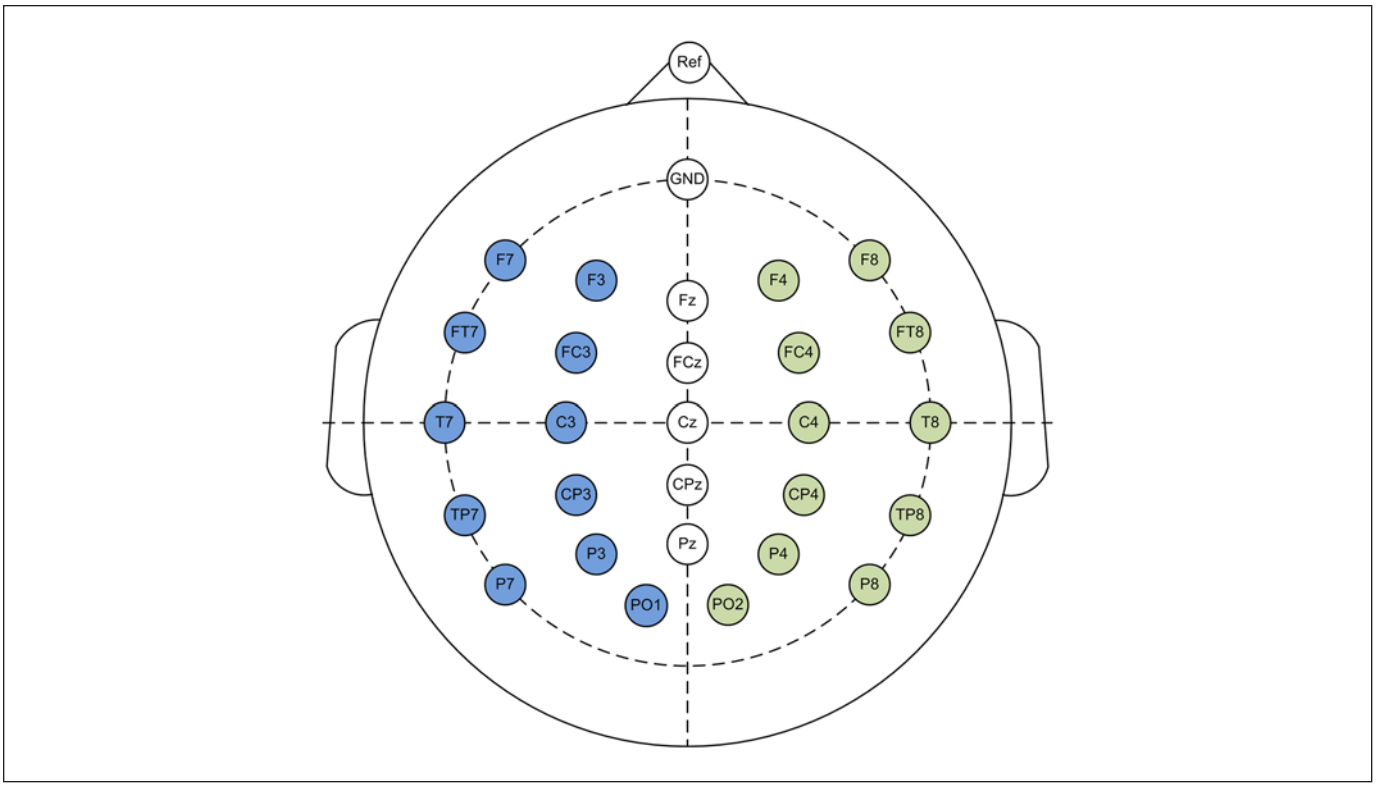

Figure 4. Positions of EEG channel locations. The reference electrode is located on the nasion. Channels on the left and right hemispheres are labeled blue and green, respectively.

robotic feedback was provided. The trained MI detection model was then used in the subsequent 12 therapy sessions to detect MI of the stroke-affected limb for this subject.[28]

During the BCI-Manus therapy sessions, the subjects performed single-trial kinesthetic MI of the stroke-affected hand with online Manus robotic feedback. The modified clock-face exercise from the Manus robotic protocol was used during these BCI-Manus therapy sessions (Figure 2b). During MI, the subjects were instructed to imagine moving the stroke-affected hand toward the target indicated on the 8-point clock-face video game. Voluntary movements during this period were restricted by locking the Manus robot. Subjects were instructed to minimize voluntary head and body movements, and any small voluntary arm movements were countered with resistance from the Manus robot, which recorded them. If MI was detected, visual and movement feedback was provided, by the Manus robot, through passive movement of the paretic arm from the center toward the target and back to the target along a predetermined robotic trajectory.[29] The BCI-Manus therapy session consisted of 4 runs of 40 trials, for a total of 160 trials, and an interrun break of 3 to 5 minutes was given after each run. Figure 3b shows the timing for a single trial. Each trial lasted about 17 to 19 seconds, and each run lasted about 13 minutes. Each BCI-Manus therapy session lasted about 1.5 hours, inclusive of 20 minutes for setup for EEG recordings. Although there was a total of 160 trials, there were trials in which MI was not detected and robotic feedback was not provided (about 15% of the total number of trials estimated from the median online MI detection rate across subjects). Thus, on average, there were about 136 instances of MI-triggered robotic feedback for each therapy session in the BCI-Manus group.[28]

EEG Signal Processing

During the BCI-Manus calibration and therapy sessions, EEG measurements from 27 channels (Figure 4) were collected using the Nuamps EEG acquisition hardware (Compumedics, Charlotte, NC) with unipolar Ag/AgCl electrodes channels, digitally sampled at 250 Hz with a resolution of 22 bits for voltage ranges of ± 130 mV. EEG recordings from all channels were band-pass filtered from 0.05 to 40 Hz by the acquisition hardware. The challenge in the detection of MI from the EEG recordings was the huge intersubject variability with respect to brain signal characteristics.[30] Hence, we used the filter bank common spatial pattern (FBCSP) algorithm[31] to construct a subject-specific MI detection model from the calibration session to detect MI in the therapy sessions.

The FBCSP algorithm comprises 4 progressive stages of EEG processing to construct a subject-specific MI detection model. The first stage uses a filter bank that decomposes the EEG signal into multiple frequency pass bands using a total of 9 band-pass filters, namely, 4 to 8 Hz, 8 to 12 Hz, 12 to 16 Hz, 16 to 20 Hz, 20 to 24 Hz, 24 to 28 Hz, 28 to 32 Hz, 32 to 36 Hz, and 36 to 40 Hz.

The second stage performs common spatial pattern (CSP) spatial filtering,[32] whereby each pair of band-pass and spatial filters computes the CSP features that are specific to the band-pass frequency range by linearly transforming the EEG signal using

$$\mathbf{Z}_{b,i} = \mathbf{W}_b^T \mathbf{E}_{b,i}, \quad (1)$$

where $\mathbf{E}_{b,i} \in \mathbb{R}^{c \times t}$ denotes the single-trial EEG from the bth band-pass filter of the ith trial, $\mathbf{W}_b \in \mathbb{R}^{c \times c}$ denotes the CSP projection matrix, c is the number of channels, t is the number of EEG samples per channel; and the superscript T denotes the transpose operator.

The spatial filtered signal $\mathbf{Z}_{b,i}$ in equation 1 using $\mathbf{W}_b$ maximizes the differences in the variance of the 2 classes of band-pass-filtered EEG. The m pairs of CSP features for the bth band-pass-filtered EEG is given by

$$\mathbf{v}_{b,i} = \log\left(\mathrm{diag}(\bar{\mathbf{W}}_b^T \mathbf{E}_{b,i} \mathbf{E}_{b,i}^T \bar{\mathbf{W}}_b) / \mathrm{tr}[\bar{\mathbf{W}}_b^T \mathbf{E}_{b,i} \mathbf{E}_{b,i}^T \bar{\mathbf{W}}_b]\right), \quad (2)$$

where $\mathbf{v}_{b,i} \in \mathbb{R}^{2m}$, $\bar{\mathbf{W}}_b$ represents the first and last m columns of $\mathbf{W}_b$, diag(·) gets the diagonal elements of the square matrix, and tr[·] gets the sum of the diagonal elements in the square matrix.

The FBCSP feature vector for the ith trial is formed using $\mathbf{v}_i = [\mathbf{v}_{1,i}, \mathbf{v}_{2,i}, \ldots, \mathbf{v}_{9,i}]$ such that the FBCSP feature matrix from training data is $\mathbf{V} = [\mathbf{v}_1^T \mathbf{v}_2^T \cdots \mathbf{v}_n^T]^T$, whereby n denotes the total number of trials in the training data, and $\mathbf{V} \in \mathbb{R}^{n \times (9*2m)}$.

The third stage selects discriminative CSP features from $\mathbf{V}$ for the subject's task using the mutual information–based best individual feature algorithm to select $k = 4$ best features from a total of $9*2m$ features.[33] Because CSP features are paired, the corresponding features that are paired with the selected k features are included. The training data after feature selection are denoted as $\bar{\mathbf{X}} \in \mathbb{R}^{n \times d}$, where d ranges from 4 to 8. For example, $d = 4$ if all 4 features selected are from 2 pairs of CSP features, and $d = 8$ if all 4 features selected are from 4 pairs of CSP features, because their corresponding pair is included.

The fourth stage uses the naive Bayesian Parzen window classification algorithm to model and classify the selected CSP features. Given that $\mathbf{x} = [x_1, x_2, \ldots, x_d]$ denotes a random evaluation trial, the naive Bayesian Parzen window classifier estimates $p(\mathbf{x}|\omega)$ and $P(\omega)$ from training data samples and predicts the class ω with the highest posterior probability $p(\omega|\mathbf{x})$ using

$$\omega = \arg\max_{\omega=1,2} p(\omega \mid \mathbf{x}). \quad (3)$$

Outcomes

Outcomes were measured at 4 time points: at baseline (week 0), at week 2, on completion of training (week 4), and after 8 weeks of follow-up (week 12). All assessments were performed by a blinded occupational therapist (J.L.) not involved in the training. The primary outcome was the total FMMA score (range, 0-66) for the affected hemiplegic upper limb at week 4 for both groups upon completion of training. No changes were made after the trial commenced.

EEG Analysis

EEG data collected during the BCI-Manus therapy sessions were also analyzed using the following rBSI to detect inter-hemispheric asymmetry[34]:

$$rBSI(t) = \frac{1}{n_k} \sum_{n=k_1}^{k_2} \left| \frac{R_n^*(t) - L_n^*(t)}{R_n^*(t) + L_n^*(t)} \right|, \quad (4)$$

where $R_n^*(t) = \frac{1}{n_c} \sum_{c=1}^{n_c} a_n^2(c,t)$ evaluates the averaged Fourier coefficient of $n_c = 11$ channels from the right hemisphere shown in Figure 4, a similar $L_n^*(t)$ for the left hemisphere, $a_n(c, t)$ is the Fourier coefficient of index n of channel c evaluated at time t that corresponds to a particular time segment $[t - T, t]$ with duration T, the Fourier coefficient index $[k_1, k_2]$ corresponds to the frequency band 4 to 40 Hz, and n_k is the number of Fourier coefficients evaluated that correspond to the frequency band.

For the current study, the rBSI at $t = 4.5$ seconds from the MI time segment of 2.5 to 4.5 seconds with duration $T = 2$ seconds from all 12 BCI-Manus therapy sessions was computed using a routine implemented in MATLAB (The MathWorks, Natick, MA).

Sample Size

Assuming a 15 ± 8% gain in total FMMA score for the BCI-Manus group compared with the Manus group, the recommended sample size was 20 subjects in each group to achieve statistical power of 80% for this study. Sample size calculation was performed in PS Power and Sample Size version 1.0.

Statistical Methods

Data were collected using SPSS version 14 (SPSS, Inc, Chicago, IL) and analyzed using Stata. Because of the small sample size, nonparametric tests were used for univariate and multivariate analyses. For continuous outcome measures, we used the analysis of covariance model to examine differences in mean values at each follow-up period, between the 2 groups, after adjusting for baseline differences. Data analysis was performed in Stata VII, and the level of significance was set at 5%.

Results

Patient Enrollment

Twenty-six subjects were randomized, with 11 and 15 allocated to the BCI-Manus and Manus groups, respectively (Figure 1). In the Manus group, there was 1 dropout after 6 training sessions because of transient nausea. The dropout rate was thus 1 in 26 (3.8%). The study was terminated in 2009 because of cessation of research funding, and hence not all 40 intended subjects could be recruited.

Table 1. Demographics and Baseline Characteristics of Subjects by Intervention.

Variable	Total	Intervention	
		BCI-Manus	Manus
n	26	11	15
Age (y)	51.4 ± 11.6	48.5 ± 13.5	53.6 ± 9.5
Gender			
Male	16 (61.5%)	9 (81.8%)	7 (46.7%)
Female	10 (38.5%)	2 (11.2%)	8 (53.3%)
Handedness			
Right	23 (88.5%)	10 (90.9%)	13 (86.7%)
Left	3 (11.5%)	1 (9.1%)	2 (13.3%)
Race			
Chinese	21 (80.8%)	9 (81.8%)	12 (80.0%)
Others	5 (19.2%)	2 (18.2%)	3 (20.0%)
Stroke type			
Infarction	10 (38.5%)	5 (45.5%)	5 (33.3%)
Hemorrhage	16 (61.5%)	6 (54.4%)	10 (66.7%)
Stroke nature			
Cortical	8 (30.8%)	3 (27.3%)	5 (33.3%)
Subcortical	18 (69.2%)	8 (72.7%)	10 (66.7%)
Affected limb			
Right	11 (42.3%)	5 (45.5%)	6 (40.0%)
Left	15 (57.7%)	6 (54.5%)	9 (60.0%)
CVA to intervention (days)	297.4 ± 238.7	383.0 ± 290.8	234.7 ± 183.8
BCI screening	75.4 ± 11.8	77.6 ± 6.4	73.8 ± 14.9
FMMA score	26.4 ± 14.8	26.3 ± 10.3	26.5 ± 18.2

Abbreviations: BCI, brain-computer interface; CVA, cerebrovascular accident; FMMA, Fugl-Meyer Assessment of Motor Recovery After Stroke.

Altogether, there were 16 men and 10 women (mean age, 51.4 years; mean stroke duration, 297.4 days). In the Manus group, 5 subjects had cortical strokes involving the frontal or temporal-parietal region, and 10 had subcortical strokes involving the corona radiata, basal ganglia, and thalamus. In the BCI-Manus group, 2 subjects had cortical strokes involving mainly the temporal-parietal regions, and 8 had subcortical strokes involving the basal ganglia. None had brain-stem involvement. There were no significant baseline differences between the 2 groups in demography, stroke impairment, or functional data (Table 1).

Efficacy Measurements

At week 4, upon completion of both interventions, both groups demonstrated significant gains in the primary outcome, total FMMA score, compared with baseline FMMA score, with mean total FMMA score gains of +6.3 (+23.7%) for the Manus group and +4.5 (+17.1%) for the BCI-Manus group ($P < .05$). However, there were no significant intergroup differences at any time point during the study ($P > .05$) (Table 2).

Positive gains in FMMA scores from week 0 to week 4 for the Manus group were observed in 10 of 14 subjects (71.4%). For the nonresponders, their baseline FMMA scores ranged from 4 to 13. For the BCI-Manus group, 7 of 11 subjects (63.6%) demonstrated positive gains in FMMA scores from week 0 to week 4. Their baseline FMMA scores were slightly higher, ranging from 2 to 19.

Intervention was administered up to week 4 for both groups. Further gains in FMMA scores from week 4 to week 12 were observed in 5 of 14 subjects (35.7%) in the Manus group and 7 of 11 subjects (63.6%) in the BCI-Manus group.

EEG Quantification

The averaged rBSI from all 12 sessions for the 11 subjects in the BCI-Manus group was analyzed for correlation with FMMA score improvements (Figure 5). A negative correlation was found ($r = -0.616$, $P = .044$).

Adverse Events

There were no serious adverse events or deaths related to interventions during the 4-month study. All subjects, except for 1 dropout from the Manus group, completed training and follow-up. The reason for discontinuation was hemiplegic shoulder pain which led to subject dropout in the second week of training. During the trial, 5 of 15 subjects (33.3%) in the Manus group reported transient, mild arm fatigue, and 2 of 11 subjects (18.2%) in the BCI-Manus group reported transient nausea and headache after the training sessions, which stopped after the interventions. Central fatigue was not reported after training. It is noteworthy that 2 subjects in the BCI-Manus group reported subjective increases in concentration and lower limb strength during the 4-week training. In general, there was a high degree of subject acceptability (80%) of both interventions and willingness to undergo further similar related interventions.

Discussion

We report a large-scale randomized controlled study comparing EEG-based MI BCI with Manus robotic therapy for moderate to severe chronic stroke upper-extremity impairment. For chronic hemiplegic subjects, previously reported gains after 36 hours of Manus shoulder-elbow robotic therapy were approximately +2.17 FMMA points after 12 weeks of training and approximately +2.88 points after 36 weeks.[35] This study yielded FMMA score increases of approximately +6.3 points for subjects in the Manus group and +4.5 points for the BCI-Manus group, with relatively shorter therapy of 18 hours, illustrating the reproducible nature of upper-limb robotic training. Despite a shorter 4-week training duration, compared with other distributed arm robotic protocols over 12 to 36 weeks, significant positive gains in FMMA scores were observed in both groups after 4 weeks. This is consistent with productive gains seen with shorter training robotic protocols for those with more severe degrees of upper-extremity impairment.[36-38] Subjects who trained with intensive Manus robotic therapy

Table 2. Efficacy Measures by FMMA Score for Each Intervention Group (n = 14 for Manus, n = 11 for BCI-Manus).

Outcome	Group	Week 0	Week 2	Week 4	Week 12
Shoulder	Manus	19.9 ± 11.2	22.4 ± 12.7	22.8 ± 12.8	23.9 ± 12.7
	BCI-Manus	20.8 ± 7.2	22.0 ± 8.4	22.9 ± 7.8	23.0 ± 8.1
Wrist	Manus	6.7 ± 8.6	7.4 ± 8.9	10.1 ± 9.8	10.1 ± 8.4
	BCI-Manus	5.5 ± 3.5	5.4 ± 4.3	7.8 ± 6.5	8.5 ± 6.4
Upper extremity	Manus	26.6 ± 18.9	29.9 ± 20.6	32.9 ± 21.4	33.9 ± 20.2
	BCI-Manus	26.3 ± 10.3	27.4 ± 12.0	30.8 ± 13.8	31.5 ± 13.5

Abbreviation: BCI, brain-computer interface; FMMA, Fugl-Meyer Assessment of Motor Recovery After Stroke.

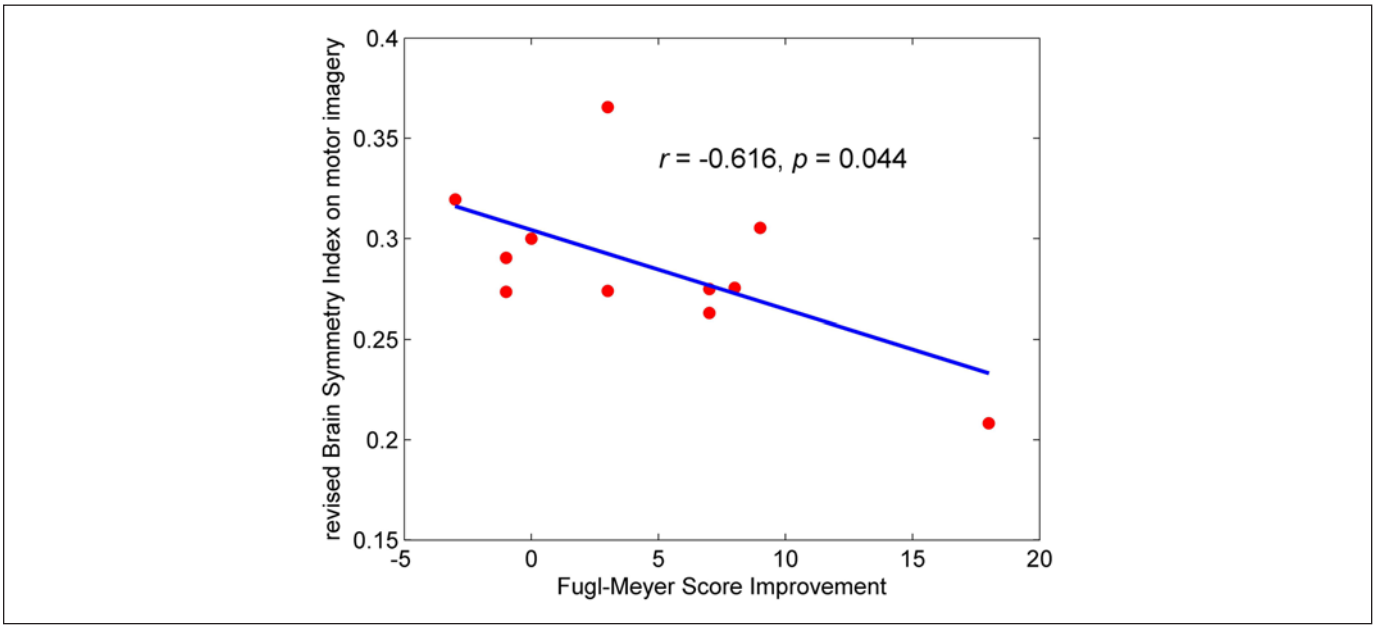

Figure 5. Plot of rBSI on MI EEG against FMMA score improvement in the BCI-Manus group (n = 11).

achieved the majority of their gains in FMMA scores in the first 2 weeks, compared with those in the BCI-Manus group, who gained during weeks 2 to 4. Both groups achieved similar FMMA scores at week 4, and further gains were observed in more subjects from the BCI-Manus group compared with the Manus group. Generalization of proximal shoulder and elbow training effects was observed in the positive gains from the wrist-hand FMMA subscores. This is likely due to the reproducible effects related to arm robotic training, concomitant outpatient rehabilitation therapies, and increased ease of use of the affected wrist and hand due to improved proximal motor control.[36,38]

There were no significant differences in primary outcome (total FMMA score) between the 2 groups at each of the 4 time points. At the completion of training (week 4), subjects in the BCI-Manus group (+4.5 FMMA points) fared slightly worse than those in the Manus group (+6.3 FMMA points) (P = .51). This may have been due to the reduced training intensity for the BCI-Manus group (136 repetitions/session) due to latencies in the BCI-Manus system compared with the Manus group (1,040 repetitions/session). However, the subjects in the BCI-Manus group received higher training intensity compared to local standard therapy, whereby about 100 human-based repetitions are possible per treatment. Yet with only 13% of repetitions in the BCI-Manus group, their gains were comparable with those in the Manus group. Although current stroke rehabilitation strategies to improve motor function are focused on high-intensity, repetitive, and task-specific practice,[39,40] this result suggests that BCI-induced functional recovery[10,12,17,41] could be another promising strategy.

Broetz et al[42] reported 84% gains in FMMA arm scores and functional gains in gait speed in a single subject with chronic stroke treated with 3 blocks of MEG-based BCI paired with a rehabilitation robot and followed by intensive goal-directed physiotherapy over 1 year. Increased cortical activation was suggested by increased EEG-based cortical activity, albeit without lateralization. Similar clinical benefits and increases in functional MRI ipsilesional corticospinal tract plasticity and posttraining lateralization were seen in another single case study after MEG-based BCI training paired with physiotherapy, suggesting a possible role for BCI in long-term cortical plasticity.[22]

Moderate BCI classification during EEG-based BCI did not impede positive rehabilitation trends reported in 5 chronic hemiplegics. Despite variability in the ERD and ERS changes in 2 of 5 subjects, all showed gains that approached minimally clinically important differences in Action Research Arm Test scores and grip strength after 6 weeks (12 sessions) of EEG-based BCI paired with physical practice.[43] Further support for BCI-induced cortical reorganization was reported in an uncontrolled clinical trial of 8 subjects with chronic stroke, whereby low-intensity BCI training over 4 to 7 months (12-20 sessions), coupled with mechanical hand-opening orthotic training, resulted in new voluntary severe finger flexor extensor activity, detected by EEG in all 8 trained subjects, with 5 demonstrating gains in Action Research Arm Test score. Short-term increased cortical excitability over the lesioned hemisphere was measured by transcranial magnetic stimulation in 4 of 8 subjects within 1 week of training.[44]

The results of the EEG analysis of MI from the BCI-Manus group showed a negative correlation between rBSI and FMMA score. The rBSI captures the asymmetry in spectral power between the 2 cerebral hemispheres and is normalized between 0 for perfect symmetry and 1 for maximal asymmetry.[45] The results show that patients with higher asymmetry on EEG tend to gain less motor improvement. Studies had shown that bilateral changes in hemispheric reorganization were observed chronically after unilateral stroke.[46,47] The results of this study are consistent with recent findings of activity-dependent competition between the lesioned and nonlesioned corticospinal systems, resulting in persisting asymmetry and associated with poor recovery.[48] Because EEG was not recorded in the Manus group, we cannot comment on the use of rBSI as a predictor of motor response. Nevertheless, the results suggest a promising direction for the use of rBSI as a prognostic measure for BCI-based stroke rehabilitation.

To date, studies reporting side effects related to EEG-based BCI are limited.[43,44] Fatigue related to MI-based BCI practice has been reported after conventional ball-basket neurofeedback training sessions of >1.5 to 2 hours.[18,43] Fatigue was not a major problem in our study, likely because of frequent brief rest periods during the 1.5-hour training program, the abbreviated 4-week training duration, and interactive feedback given by the Manus robot. Interestingly, more issues were observed in the Manus group with regard to training-related arm fatigue (33.3%) compared with central fatigue related to BCI-Manus training (18.2%).

Study Limitations

The major limitations of our study were its small sample size, heterogeneity within subjects and training repetitions between the 2 intervention groups, lack of functional neuroimaging outcomes, and multiple factors contributing to the functional gains in both groups. The gain in FMMA score in the BCI-Manus group as a result of BCI-based intervention could not be discerned in this study, because Manus was used in both groups, and concurrent rehabilitation therapies of the patients were maintained. Despite optimization of inherent latencies in EEG acquisition, differences in training repetitions between the Manus and BCI-Manus systems could not be minimized, hence underpinning the ongoing limitations for BCI as a tool for intensive upper-extremity training.

Subject prerequisites for BCI include sustained attention, active participation, and upright postural tolerance for 1.5 to 2 hours, so it may not be suitable for patients with acute stroke. However, it is noteworthy that Tan et al[17] reported partial successes in a small cohort of patients with acute and subacute strokes. Although the Abbreviated Mental Test was used to screen for cognitive deficits, tests for specific attention processing, relevant in MI BCI, could be more ideal. Because of current heterogeneity of clinical BCI protocols, suitable candidates for MI BCI, dosing, duration, intensity, and predictors of outcomes and appropriate pairing with arm rehabilitation need further study.[16]

Currently, EEG-based MI BCI robotic rehabilitation is not without its drawbacks; it requires setup time, there is latency in the performance and detection of MI, and specialized staff and hair washing are needed after each session because of the use of wet EEG electrodes, adding to paretic subjects' and caregivers' burdens. Although the EEG-based MI BCI system is portable, the Manus robot is not. Nevertheless, BCI could potentially be deployed as an objective measurement and feedback tool for accurate MI detection for inducing functional recovery and as an alternative for subjects intolerant of intensive robotic training. In the future, suitable BCI tools for rehabilitation may involve portable EEG-based systems with dry electrodes with visual feedback. Finally, prefunctional and postfunctional neuroimaging is important to identify suitable neural substrates for MI BCI practice and objectively quantify the nature of BCI-related neuroplasticity.

Conclusions

This study of EEG-based MI BCI-Manus therapy achieved positive results, with >60% of subjects safely achieving significant motor function improvements (+17.1% FMMA score), comparable with more intensive and repetitive Manus therapy. The finding of a correlation between rBSI on EEG and motor impairment reduction suggests the promise of research on the use of rBSI as a prognostic measure for BCI-based stroke rehabilitation.

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Declaration of Conflicting Interests

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