Full Title

A Randomized Controlled Trial on EEG-based motor imagery Brain-Computer Interface robotic rehabilitation for stroke

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Competing Interests

The authors have declared that no competing interests exist.

Abstract

Electroencephalograpy-based (EEG) Motor Imagery Brain-Computer Interface (MI-BCI) technology has the prospects of restoring 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 MANUS shoulder-elbow robotic feedback (BCI-MANUS) for chronic stroke subjects with upper limb hemiparesis.

In this single-blind, randomized trial, 26 hemiplegic subjects (Fugl-Meyer Motor Assessment (FMMA) scores 4-40/66, 15 males, mean age 50.5 years, mean stroke duration 313.9 days) pre-screened with the ability to use MI-BCI, were randomly allocated to the BCI-MANUS or MANUS therapy, which consisted of total 18 hours over 4 weeks. Efficacy was measured using upper extremity FMMA scores at weeks 0, 2, 4 and 12. EEG 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.

11 and 15 subjects underwent BCI-MANUS and MANUS therapies respectively. One subject for MANUS dropped out. Total FMMA scores (mean (SD)) at weeks 0, 2, 4, 12 weeks improved for both groups: 26.3 (10.3), 27.4 (12.0), 30.8 (13.8), 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, without inter-group differences (P=0.51). More subjects attained further FMMA gains at week 12 from BCI-MANUS (7/11, 63.6%) than MANUS (5/14, 35.7%). A negative correlation was found between the rBSI and FMMA score improvements (P=0.026). The BCI-MANUS therapy was well tolerated and not associated with adverse events.

The BCI-MANUS therapy is effective and safe for arm rehabilitation following severe post-stroke hemiparesis. Motor gains were comparable to intensive robotic therapy (1040 repetitions/session) despite reduced arm exercise repetitions using EEG-based MI triggered robotic feedback (136 repetitions/session). The rBSI correlates with the motor improvements suggests that the rBSI can be used as a prognostic measure for BCI-based stroke rehabilitation.

Introduction

Brain-computer interface (BCI) systems using non-invasive electroencephalogram (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] Non-invasive BCI systems based on sensorimotor rhythms were able to achieve movement restoration in single cases with spinal cord lesions and chronic stroke for reaching and grasping.[3-5] There is now sufficient evidence that motor imagery (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 following stroke.[6,7]

As 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 (8-12 Hz) and beta (18-26 Hz) bands. Modulation of these frequency bands is similarly observed during actual as well as mentally rehearsed or imagined movements. Another example is the distinct phenomena such as event-related desynchronization or event-related synchronization (ERD/ERS) that are detectable from EEG during MI in healthy subjects.[4,10-13] Recent studies have also revealed that the ERD/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 non-invasive BCIs on chronic stroke patients.[16,17] Tan et al. described successful BCI-

triggered neuromuscular electrical stimulation (NMES) of wrist and finger extensors in 4 out of 6 stroke survivors with moderate to severe degrees of hand motor paresis.[18] Due to long latency periods to trigger one BCI-activated NMES (42 seconds), fatigue was evident after about 1 hour of BCI practice. Do et al. described a BCI-functional electrical system to trigger foot dorsiflexion in healthy subjects.[19] Buch et al. described 6 out of 8 chronic stroke patients >1 year poststroke with severe finger extensor paralysis who successfully learned to operate a Magnetoencephalography-based (MEG)-BCI device linked to a hand-opening/closing orthotic system.[20] Kaiser et al. measured the event-related desynchronization or synchronization in 29 stroke patients, and found 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 the motor functions as a result of BCI-based intervention.

A case study on MEG-based BCI followed by EEG-based BCI combined with physiotherapy had reported significant clinical outcomes in FMMA scores (+84%).[22] Positive functional Magnetic Resonance Imaging (MRI) and Diffusion Tensor Imaging (DTI) results from the case study suggested possible short-term BCI-induced cortical and ipsilesional corticospinal tract neuroplasticity. Mihara et al. recently presented the results of a Randomized Control Trial (RCT) on 10 stroke patients who received Near-Infrared Spectroscopy-based BCI with visual feedback versus 10 stroke patients who received NIRS-based BCI with irrelevant feedback.[23] The results showed that the patients who received BCI visual feedback showed significantly greater motor improvements measured using FMMA compared to the sham group. In addition, Ramos-Murguialday et

al. recently presented the results of a RCT on 16 chronic stroke patients who received BCI with hand and arm orthoses feedback versus 14 chronic stroke patients who received random orthoses feeback not linked to BCI.[24] Both groups received physiotherapy following either intervention. The results showed that the patients who received BCI orthoses feedback showed significantly greater motor improvement measure using combined hand and modified arm FMMA.

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

Rationale

As 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). 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 study had the following hypothesis: the safety and efficacy of the BCI-MANUS compared to the MANUS therapy for chronic stroke subjects with upper limb hemiparesis. We describe the set up of an integrated BCI-MANUS system, and a randomized controlled trial comparing the BCI-MANUS system to MANUS robot for moderate to severe chronic poststroke upper limb hemiparesis.

Methods

Ethics Statement

Ethics Committee approval was obtained from the institution's Domain Specific Review Board, National Healthcare Group, Singapore. The trial was registered in ClinicalTrials.gov (NCT00955838).

Study Design

The randomized controlled trial was conducted over ~two and a half years period from 1 April 2007 to 30 October 2009 involving subjects who had completed inpatient rehabilitation at the Tan Tock Seng Hospital, Singapore.

Figure 1 shows a flow chart of the trial. Subjects were first assessed for eligibility. Eligibility criteria included first-ever clinical ischaemic or hemorrhagic stroke diagnosed by Computed tomography (CT) or MRI brain imaging within 3 hours from the event, poststroke duration of > 3 months, age between 21 to 65 years, FMMA score of the affected upper limb from 0-45.[26] In addition, subjects were required to understand simple instructions, have >6/10 on the Abbreviated Mental Test (AMT) score. Exclusion criteria included: transient ischaemic 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, hemi spatial neglect or severe visual impairment, craniotomy skull defects compromising EEG cap fit, upper limb spasticity with the Modified Ashworth Scale (MAS) [27] >2 in any shoulder, elbow or wrist/finger regions in order to avoid robotic interruptions, and shoulder pain

(Visual analogue scale (VAS 0-10) >4/10), fixed joint contractures and skin conditions which could be worsened by robotic exoskeletal or EEG cap contact. Eligible subjects were then screened for their ability to operate EEG-based MI-BCI. Details on the BCI screening procedure were reported by Ang et al.[28] Subjects with >60% MI-EEG classification accuracy, based on previous local experience of healthy subjects and BCI-naïve 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 either one of the interventions:

(1) BCI-MANUS which consisted of EEG-based MI-BCI with MANUS robotic feedback, [28] or

(2) MANUS which consisted of MIT Manus robotic protocol guided shoulder and elbow reaching exercises with computer screen visual feedback using the clock face game.[29]

The randomization allocation sequence was 1:1, generated using STATA software version 10.2 (Stata Corp, College Station, TX, USA) and sealed envelopes method. Enrollment and assignment of participants was provided by KSGC. As subject blinding was not feasible, all outcome assessments for this study were performed by occupational therapist JL, who was blinded to allocation. There were no protocol deviations.

Both groups received total 18 hours of intervention each, delivered over 4 weeks (1.5 hours each, 3 times per week) in the presence of an occupational therapist CWKK and

engineer KSP. This included 20 minutes required for initial set up and rest breaks. A shorter 4 week intervention protocol was employed in an attempt to reduce subject fatigue and non-compliance. Subject involvement including follow up totaled ~ 4 months. Standard physical therapy was not carried out in combination with BCI-MANUS or MANUS intervention, and concurrent rehabilitation therapies and medications of the patients were maintained during the study period because of ethical reasons. Discontinuation criteria for recruited patients include, new neurological or serious adverse events, increase in arm pain or spasticity of greater than 30% from baseline or severe fatigue related to BCI interventions.

MANUS Intervention

MANUS intervention consisted of 12 therapy sessions of robotic guided protocol with 2 degrees of freedom, involving planar non-resistive, horizontal elbow and forearm reaching exercises within the robotic exoskeletal shell while using an 8-point clock face drawing interactive video game (Figure 2(a)).[29] During the study intervention, 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 individually predetermined prior to training. The 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 centre towards the target displayed on the screen and back along a pre-determined robotic trajectory. The small yellow circle displayed the current position of the robotic arm that held the patient's stroke-affected arm, and the big red circle displayed the target

position. The subjects were instructed to move their stroke-affected arm from the centre to the target position and then back to the centre position. This to-and-fro movement was considered as a single voluntary movement trial. Subsequently, the big red circle was then displayed onto the next target position in a clockwise manner. Robotic 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 towards the target.[29] The timing for a single movement trial averaged 3 to 5 s as it was self-paced by the subjects. A therapy session consisted 3 robot-assisted runs of 320 trials interspersed with 5 non-assisted runs of 16 trials. This amounts to 1040 trials that lasted ~1.5 hours inclusive of breaks for each therapy session.

BCI-MANUS Intervention

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 2(b)). During the calibration session, EEG data were first collected from subjects who performed kinaesthetic MI of the stroke-affected hand while strapped to the MANUS robotic exoskeleton. The subjects were specifically instructed to imagine moving their stroke-affected arm and hand forward in order to reach for an imagery target in front of them and to reach the clock face target. During the period required to perform MI, voluntary movements were restricted by locking the mobility of the exoskeletal arm of the MANUS robot. Any voluntary movements by the subjects during this period were countered with static resistance by the MANUS robot and such voluntary movements

were sensed by the MANUS robot and recorded. The calibration session consisted of 4 runs of 40 trials each for a total of 160 trials, and an inter-run break of at least 2 minutes was also given after each run. Each run comprised of 20 trials of MI and 20 trials of idle condition. Figure 3(a) shows the timing for a single trial. Each trial lasted ~12 s and each run lasted ~8 minutes. The calibration session lasted ~1 hour inclusive of EEG setup time. The calibration session only collected EEG data to train a subject-specific MI detection model, thus no 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 the specific subject.[28]

During the BCI-MANUS therapy sessions, the subjects performed single-trial kinaesthetic MI of the stroke-affected hand with on-line MANUS robotic feedback. The modified clock face exercise from the MANUS robotic protocol was employed during these BCI-MANUS therapy sessions (Figure 2(b)). During the period cued to perform MI, the subjects were instructed to imagine moving their stroke-affected hand towards the target indicated on the 8-point clock face video game. Voluntary movements during this period were restricted by locking the mobility of the MANUS robot. Subjects were instructed to minimize voluntary head and body movements during this period and any small voluntary arm movements were countered with resistance by the MANUS robot, and such voluntary movements were sensed by the MANUS robot and recorded. If MI was successfully detected, visual and movement feedback was provided by the MANUS robot through passive movement of the paretic arm from the centre towards the target displayed on the screen and back to the target along a pre-determined robotic trajectory.[29] The BCI-MANUS therapy session consisted of 4 runs of 40 trials each for a total of 160

trials, and an inter-run break of 3-5 minutes was also given after each run. Figure 3(b) shows the timing for a single trial. Each trial lasted ~17-19 s and each run lasted ~13 minutes. Each BCI-MANUS therapy session lasted ~1.5 hours inclusive of 20 minutes set up time required for scalp EEG recordings. Although there were a total of 160 trials, there were trials whereby MI were not detected and robotic feedback was not provided (~15% of total number of trials estimated from the median online MI detection rate across subjects). Thus on average, there were about 136 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 (http://www.neuroscan.com) 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 are bandpass 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 inter-subject variability with respect to the brain signal characteristics.[30] Hence this study employed the filter bank common spatial pattern (FBCSP) algorithm [31] to construct a subject-specific MI detection model from the calibration session in order 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 employs a filter bank that decomposes the EEG into multiple frequency pass bands using a total of 9 band-pass

filters, namely, 4-8 Hz, 8-12 Hz, 12-16 Hz, 16-20 Hz, 20-24 Hz, 24-28 Hz, 28-32 Hz, 32-36 Hz, and 36-40 Hz.

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

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

where $\mathbf{E}_{b,i} \in \mathbb{R}^{c \times t}$ denotes the single trial EEG from the b^{th} band-pass filter of the i^{th} 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 ^{T} denotes 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 b^{th} band-pass filtered EEG is given by

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

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

The FBCSP feature vector for the i^{th} trial is formed using $\mathbf{v}_i = \left[\mathbf{v}_{1,i}, \mathbf{v}_{2,i}, \ldots, \mathbf{v}_{9,i}\right]$ such that the FBCSP feature matrix from training data is $\mathbf{V} = \left[\mathbf{v}_1^T \quad \mathbf{v}_2^T \quad \cdots \quad \mathbf{v}_n^T\right]^T$ 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 **V** for the subject's task using the Mutual Information-based Best Individual Feature (MIBIF) algorithm to select k=4 best features from a total of 9*2m features.[33] Since CSP features are paired, the corresponding features that are paired with the selected k features are included. The training data after feature selection is 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; d=8 if all 4 features selected are from 4 pairs of CSP features, since their corresponding pair is included.

The fourth stage employs the Naïve Bayesian Parzen Window (NBPW) classification algorithm to model and classify the selected CSP features. Given that $\mathbf{x} = \left[x_1, x_2, \ldots x_d\right]$ denotes a random evaluation trial, the NBPW 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

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

Outcomes

Outcomes were measured at 4 time points during the study: at baseline (Week 0), at week 2, on completion of training (Week 4); and finally at 8 weeks follow-up (Week 12). All

assessments were performed by blinded occupational therapist JL not involved in training. The primary outcome was the total FMMA scale scores (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

The EEG data collected during the BCI-MANUS therapy sessions were also analyzed using the following revised Brain Symmetry Index (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 4-40 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 s from the MI time segment of 2.5 to 4.5 s with duration T=2 s from all 12 BCI-MANUS therapy sessions were computed using a routine implemented in MatLab (The Matworks Inc).

Sample Size

Assuming 15% gain in total FMMA for BCI-MANUS group compared to MANUS group (standard deviation 8%), 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 software V1.0.

Statistical methods

Data was collected using Statistical Package for Social Sciences (SPSS version 14) and analyzed using STATA (Stata Corp). Due to the small sample size, non parametric tests were used for univariate analyses and multivariate analyses. For continuous outcome measures, we used the Analysis of Covariance (ANCOVA) model to examine differences in mean values at each follow-up period, between the two groups, after adjusting for baseline differences. Data analysis was performed in STATA VII (Stata Corp, College Station, TX, USA) and the level of significance was set at 5%.

Results

Patient enrollment

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

Altogether, there were 15 males, 11 females. (mean age of 50.5 years and mean stroke duration of 313.9 days). In the MANUS group, 6 subjects had cortical strokes involving the frontal or temporal-parietal regions, 9 had subcortical strokes involving the corona radiata, basal ganglia and thalamus. In BCI-MANUS group, 2 subjects had cortical strokes involving mainly the temporal-parietal regions and 9 had subcortical strokes involving the basal ganglia. None had brainstem involvement. There were no significant baseline differences between the 2 groups in terms of demographic, 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 when compared with baseline FMMA with mean total FMMA gains of +6.3 (+23.7%) for the MANUS group and +4.5 (+17.1%) for the BCI-MANUS group ($P < 0.05$). However there were no significant inter-group differences at all time points during the study ($P>0.05$) (Table 2).

Positive gains in FMMA scores from week 0 to week 4 for the MANUS group were observed in 11/14 (78.6%) subjects. For the non responders, their baseline FMMA scores were 4-13/66. For the BCI-MANUS group, 7/11 (63.6%) demonstrated positive gains in FMMA scores week 0 to week 4. Their baseline FMMA scores were slightly higher at 2-19/66.

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

EEG quantification

The averaged rBSI from all 12 sessions for the 11 subjects in the BCI-MANUS group were analyzed for correlation with the FMMA score improvements (Figure 5). A negative correlation was found (r=-0.616, P=0.044).

Adverse events

There were no reported serious adverse events or deaths related to study interventions during the 4 month study duration. All subjects, except for 1 dropout in 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 out of 15 (33.3%) subjects in the MANUS group complained of transient, mild arm fatigue while 2 out of 11 (18.2%) subjects in the BCI-MANUS group complained of 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 mental concentration and lower limb strength during the 4 week training duration. In general, there was a high degree of subject acceptability (80%) to both interventions and willingness for further similar related interventions.

Discussion

This study presents 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, quoted gains after 36 hours of MANUS shoulder-elbow robotic therapy ~+2.17 FMMA points after 12 weeks of training and ~+2.88 points after 36 weeks.[35] This study yielded FMMA gains of ~+6.3 points for subjects in the MANUS group and +4.5 points for subjects in the BCI-MANUS with a 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 12-36 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 achieved majority of their gains in FMMA in the first 2 weeks of training compared with BCI-MANUS group who gained during weeks 2-4. Both groups achieved similar FMMA scores at week 4, and further gains were observed in more subjects from the BCI-MANUS compared with the MANUS group. Generalization of proximal shoulder and elbow training effects were observed in the positive gains from the wrist-hand FMMA sub scores. This is likely due to the reproducible effects related to arm robotic training, concomitant outpatient rehabilitation therapies, andincreased 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 scores) between the 2 groups at each of the 4 time points. At completion of training (week 4), subjects in the BCI-MANUS group (+4.5 FMMA points) faired slightly worse than MANUS group

(+6.3 FMMA points, P=0.51) This could be due to the reduced training intensity for BCI-MANUS group (136 repetitions/hour) due to latencies in the BCI-MANUS system compared to MANUS group (1040 repetitions/hour). However, the subjects in the BCI-MANUS group received higher training intensity compared to local standard therapy whereby ~100 human-based repetitions are possible per treatment. Yet with only 13% of repetitions in the BCI-MANUS group, their gains were comparable to those in the MANUS group. Although the current stroke rehabilitation strategies to improve motor function is focused on high-intensity, repetitive, and task-specific practice,[39,40] the result suggests that BCI-induced functional recovery[10,12,17,41] could be another promising strategy.

Broetz had reported +84% gains in FMMA arm scores and functional gains in gait speed in a single chronic stroke subject 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.[42] Similar clinical benefits and increases in fMRI ipsilesional corticospinal tract plasticity and post training 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 ERDS/ERS changes in 2/5 subjects, all showed gains which approached minimally clinically important differences in ARAT and grip strength after 6 weeks (12 sessions) of

EEG-based BCI paired with physical practice.[43] Further support of BCI-induced cortical reorganization was reported in an uncontrolled clinical trial of 8 chronic stroke subjects, whereby low intensity BCI training over 4-7 months (12-20 sessions) coupled with mechanical hand opening orthotic training resulted in new voluntary severe finger flexor extensor activity detected by EMG activity in all 8 trained subjects, with 5/8 demonstrating gains in ARAT. Short term increased cortical excitability over the lesioned hemisphere was measured by transcranial magnetic stimulation in 4/8 subjects within 1 week of training.[44]

The results from the EEG analysis on MI from the BCI-MANUS group showed a negative correlation between rBSI and FMMA. The rBSI captures the asymmetry in spectral power between the two cerebral hemispheres, and is normalized between 0 for perfect symmetry and 1 for maximal asymmetry.[45] The results hence showed that patients with higher asymmetry in the EEG tend to gain less motor improvements. Studies had shown that bilateral changes in the hemispheric reorganization had been observed chronically after unilateral stroke.[46,47] The results in this study are consistent with the recent findings that found activity dependent competition between the lesioned and non-lesioned corticospinal systems resulted in persisting asymmetry and associated with poor recovery.[48] Since EEG was not monitored for the MANUS group, the use of rBSI as a predictor for motor response could not be commented upon. Nevertheless, the result suggests a promising direction to use 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 neuro-feedback training sessions of >1.5-2 hours.[18,43] Fatigue was not a major problem in our study, likely related to frequent brief rest periods during the 1.5 hour training programme, 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 in our study are its small sample size, heterogeneity within subjects and training repetitions between the 2 intervention groups, lack of functional neuroimaging outcomes, and multiple factors contributed to the functional gain in both groups. The gain in FMMA score of the BCI-MANUS group as a result of BCI-based intervention cannot be discerned in this study since 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 MANUS and BCI-MANUS system could not be minimized, hence underpinning the ongoing limitations for BCI as a tool for intensive upper extremity training.

Subject pre-requisites for BCI include sustained attention, active participation and upright postural tolerance for 1.5-2 hours hence it may not be a suitable for acute stroke patients. However it is noteworthy that Tan et al. reported partial successes in a small cohort of acute and subacute strokes.[17] While the AMT was used to screen for cognitive deficits,

tests for specific attention processing, relevant in MI-BCI could be more ideal. Due to current heterogeneity of clinical BCI protocols, suitable candidates for MI-BCI , dosing, duration, intensity and predictors of outcomes and appropriate pairing with arm rehabilitation needs further study.[16]

Currently, EEG-based MI-BCI robotic rehabilitation is not without its drawbacks; requiring a set up time, latency in the performance and detection of MI, specialized staff and hair washing are needed after each session due to wet EEG electrodes, adding to the paretic subjects' and caregivers' burdens. Although the EEG-based MI-BCI system is portable, the MANUS robot is not portable. 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 future, suitable BCI tools for rehabilitation may involve portable EEG-based systems with dry electrodes with visual feedback. Finally, pre and post-functional neuroimaging is important to identify suitable neural substrates for MI-BCI practice and objectively quantify the nature of BCI-related neuroplasticity.

Conclusions

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

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Figure 1 CONSORT Flow Diagram. The diagram shows a flow from recruitment through follow-up and analysis for the subjects.

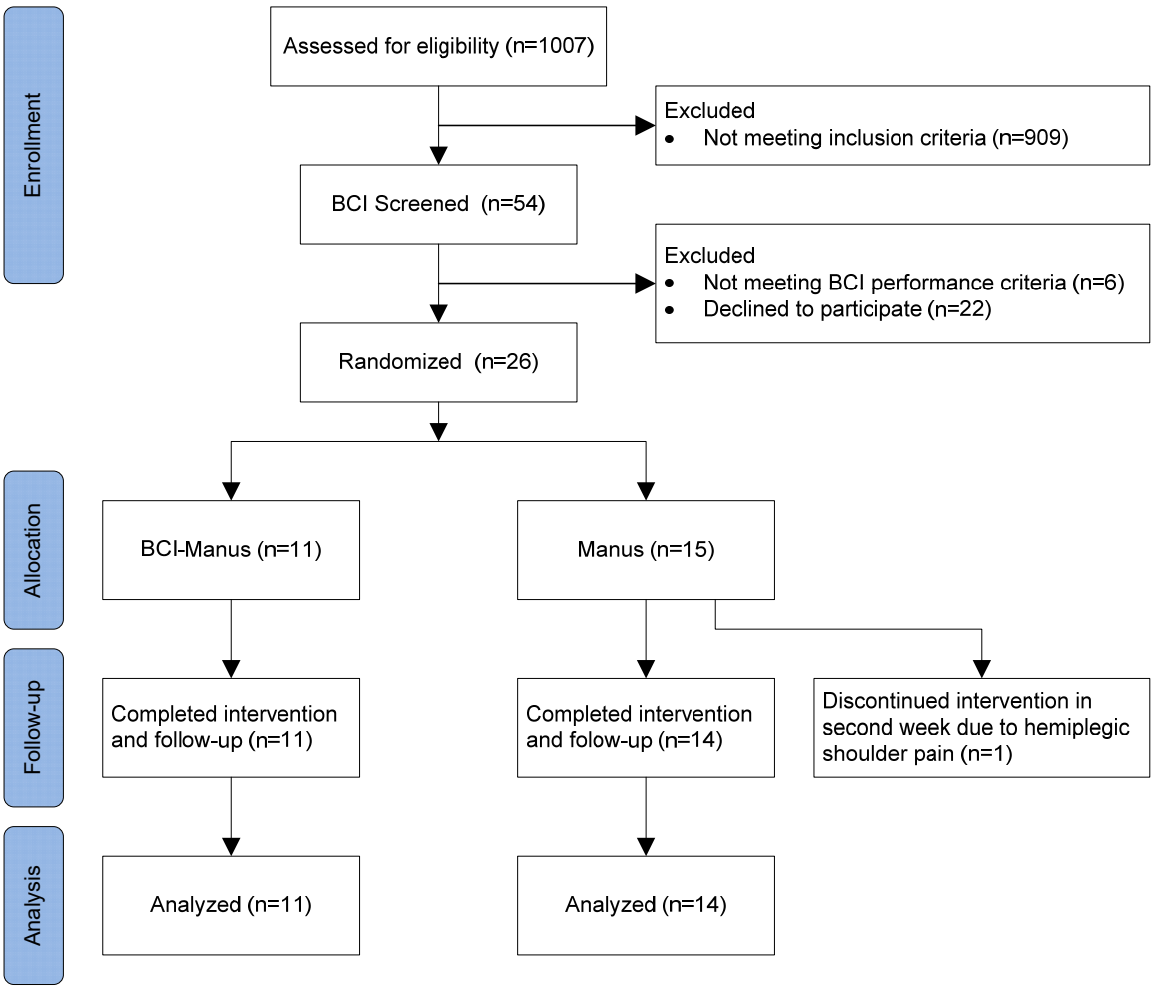
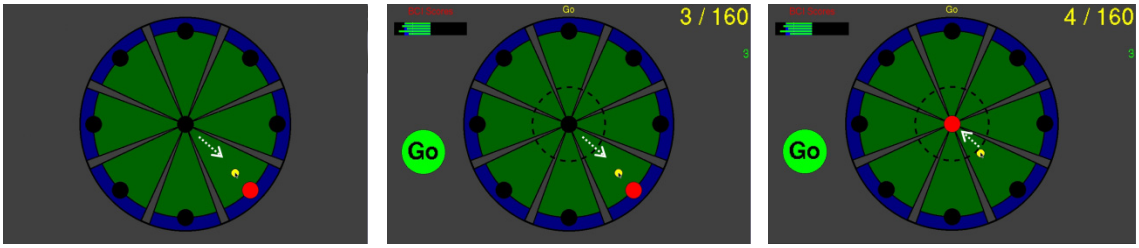
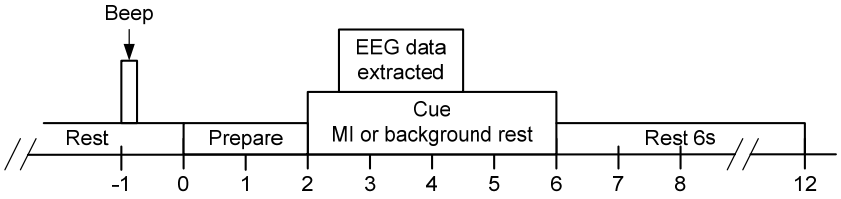


Figure 2 8-point clock face game for MANUS and BCI-MANUS interventions. (a) Original clock face game used in the MANUS intervention where the small yellow circle represents the current position of the robotic arm that holds the patient's stroke-affected arm, and the big red circle represents the target position. (b) Modified clock face game used in the BCI-MANUS intervention. If motor imagery is detected, the robotic arm will move the stroke-affected arm to the respective target and (c) back to the centre position. The physical distance between the centre and the target is approximately 0.15 m.

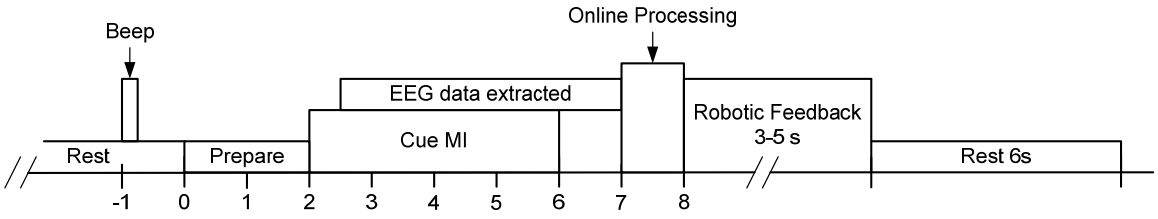


(a) (b) (c)

Figure 3 Acquisition of MI-EEG for BCI-MANUS system. (a) Timing of the kinaesthetic motor imagery of the stroke-affected hand or background rest tasks for the calibration session before commencement of the therapy; (b) Timing of the kinaesthetic motor imagery of the stroke-affected hand with on-line robotic feedback for the therapy session.



(a) Calibration session before commencement of the therapy



(b)Therapy session with BCI-MANUS system

Figure 4 Positions of EEG channel locations. The reference electrode is located on the Nasion. Channels on the left and right hemisphere are labelled blue and green respectively.

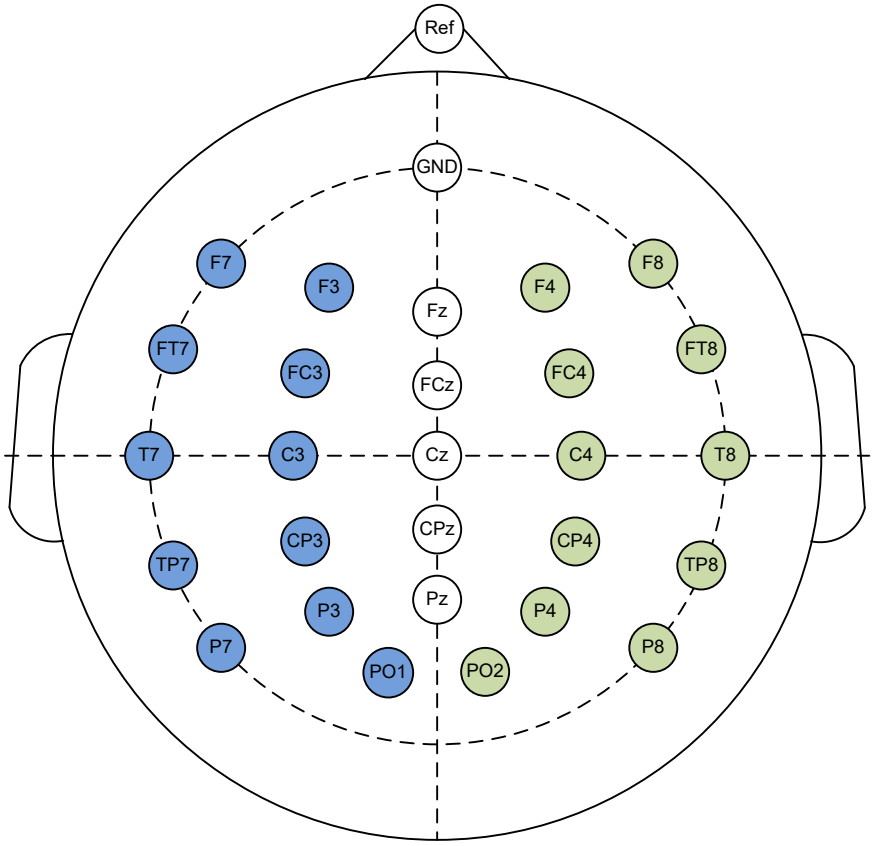


Figure 5 Plot of revised Brain Symmetry Index on motor imagery EEG against Fugl-Meyer Score Improvement of BCI-MANUS group (n=11)

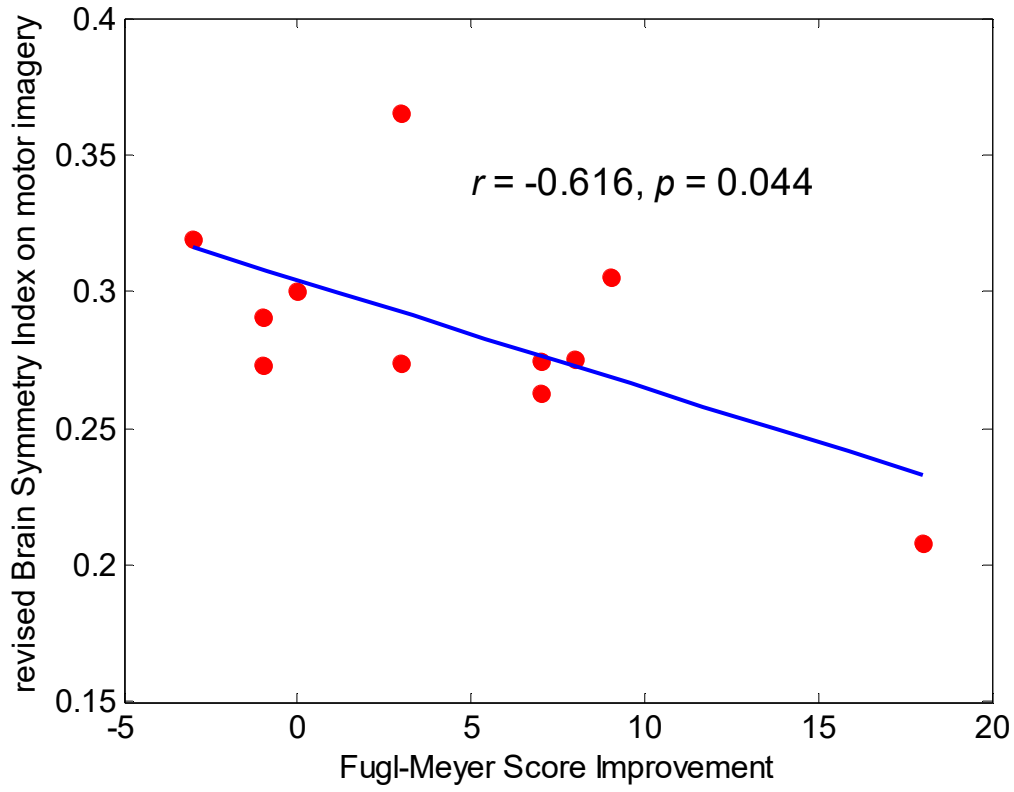


Table 1 Demographics and baseline characteristics of subjects by intervention

Variable	Total	Intervention	
		BCI-MANUS	MANUS
N	26	11	15
Age (years)	51.4±11.6	48.5±13.5	53.6±9.5
Gender N(%)			
Male	16 (61.5%)	9 (81.8%)	7 (46.7%)
Female	10 (38.5%)	2 (11.2%)	8 (53.3%)
Handedness N(%)			
Right	23 (88.5%)	10 (90.9%)	13 (86.7%)
Left	3 (11.5%)	1 (9.1%)	2 (13.3%)
Race N(%)			
Chinese	21 (80.8%)	9 (81.8%)	12 (80.0%)
Others	5 (19.2%)	2 (18.2%)	3 (20.0%)
Stroke type N(%)			
Infarction	10 (38.5%)	5 (45.5%)	5 (33.3%)
Haemorrhage	16 (61.5%)	6 (54.4%)	10 (66.7%)
Stroke nature N(%)			
Cortical	8 (30.8%)	3 (27.3%)	5 (33.3%)
Subcortical	18 (69.2%)	8 (72.7%)	10 (66.7%)
Affected limb N(%)			
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	26.4±14.8	26.3±10.3	26.5±18.2

CVA indicates Cerebrovascular accident; FMMA, Fugl-Meyer Motor Assessment

Table 2. Efficacy measures by FMMA scores for each intervention group (n=14 for MANUS, and 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