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Assessment of the Efficacy of EEG-based MI-BCI with Visual Feedback and EEG Correlates of Mental Fatigue for Upper-Limb Stroke Rehabilitation

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***Abstract*— *Objective:* This single-arm multisite trial investigates the efficacy of the Neurostyle Brain Exercise Therapy Towards Enhanced Recovery (nBETTER) system, an Electroencephalogram (EEG)-based Motor Imagery Brain-Computer Interface (MI-BCI) employing visual feedback, for upper-limb stroke rehabilitation, and the presence of EEG correlates of mental fatigue during BCI usage. *Methods:* Thirteen recruited stroke patients underwent thrice-weekly nBETTER therapy coupled with standard arm therapy over 6 weeks. Upper-extremity Fugl-Meyer Motor Assessment (FMA) scores were measured at baseline (Week 0), post-intervention (Week 6) and follow-ups (Weeks 12 and 24). In total, 11/13 patients (mean age 55.2 years old, mean post-stroke duration 333.7 days, mean baseline FMA 35.5) completed the study. R*esults:* Significant FMA gains relative to baseline were observed at Weeks 6 and 24. Retrospectively comparing to the standard arm therapy (SAT) control group and BCI with haptic knob (BCI-HK) intervention group from a previous similar study, the SAT group had no significant gains whereas the BCI-HK group had significant gains at Weeks 6, 12 and 24. EEG analysis revealed significant positive correlations between relative beta power and BCI performance in the frontal and central brain regions, suggesting that mental fatigue may contribute to poorer BCI performance. *Conclusion:* nBETTER, an EEG-based MI-BCI employing only visual feedback, helps stroke survivors sustain short-term FMA improvement. Analysis of EEG relative beta power indicates that mental fatigue may be present. *Significance:* This study adds nBETTER to the growing literature of safe and effective stroke rehabilitation MI-BCI, and suggests an additional fatigue-monitoring role in future such BCI.**

***Index Terms*—Brain Computer Interface, EEG, Fatigue, FMA, Motor Imagery, Stroke Rehabilitation**

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I. Introduction

STROKE is a major cause of mortality and neuro-disability [2]. It causes much economic and social burden, and is exacerbated by aging population, globalization and urbanization [3]. In Singapore, stroke is the 4th leading cause of death and among the top causes of hospitalization [4]. Nearly half of the stroke survivors remain permanently disabled and have a poorer quality of life. Current interventions for stroke survivors range from traditional physical therapy, neuropharmacology, robotic aided therapies, and virtual reality enabled therapies, to use of technology such as Brain-Computer Interface (BCI) [5]. Preliminary studies have shown that stroke patients are able to operate non-invasive Electroencephalogram (EEG)-based Motor Imagery (MI) BCI as effectively as healthy subjects [6], [7], [8]. MI, the mental practice of movements, has been shown to activate similar cortical patterns as actual movements [9], [10] and is a potential facilitator of neuroplasticity [11], [12], [13]. MI-BCI may also be used for patients with severely compromised motor control or residual motor abilities [14], [15]. MI-BCI is not complete without a form of feedback for the user to regulate their brain activity; feedback can be visual or kinesthetic [16].

While many studies have employed MI-BCI with an orthosis attachment for kinesthetic feedback, few have studied the effect of MI-BCI with just visual feedback. Thus far, Prasad *et al.* [17] and Pichorri *et al.* [18] have shown positive results in this area. It is hence worthwhile to continue this research, in order to understand the effects of using BCI without the confounding effects of physical therapy from orthosis attachments [19].

Another caveat of using MI-BCI that has largely been unexplored in the stroke rehabilitation setting, is the mental fatigue that is induced due to performing mental tasks

repetitively [20]. Mental fatigue can be detected in EEG [21], but as far as we know, no study has investigated EEG for the presence of mental fatigue induced in stroke survivors during EEG-based MI-BCI therapy. An EEG-based MI-BCI system that detects or predicts mental fatigue objectively from EEG will be beneficial to stroke survivors, as the rehabilitation can then be personalized to their current state of mind for greater effectiveness.

The objective of this study is two-fold; firstly, to investigate the efficacy of using the Neurostyle Brain Exercise Therapy Towards Enhanced Recovery (nBETTER) system together with standard occupational therapy for upper-limb rehabilitation of subacute and chronic hemiparetic stroke survivors. The nBETTER is a non-invasive EEG-based MI-BCI employing visual feedback intervention. Efficacy is measured by the Fugl-Meyer Motor Assessment (FMA) score [22] as it is the primary outcome measure of this study and a reliable assessment of stroke patients' upper extremity strength [23]. Also, a retrospective comparison will be done with an intervention and control group from Ang *et al.*'s study [1] which has similar protocol. Secondly, we aim to investigate the EEG correlates of mental fatigue present in this EEG-based MI-BCI stroke rehabilitation intervention and the impact on BCI performance.

II. Related Works

A. Clinical Trials on EEG-based MI-BCI Interventions for Upper-Limb Rehabilitation

A number of randomized controlled trials (RCT) involving various EEG-based MI-BCI systems have been conducted in recent years (their details are tabulated in Supplementary Material Section I) [1], [24], [25], [26], [27], [18], [28], [29], [30]. These BCI systems are coupled with other interventions such as orthosis and stimulations. Few investigate the effect from the BCI component with just visual feedback. Prasad *et al.* first showed that for 5 chronic stroke patients, EEG-based BCI visual neurofeedback with physical practice was able to help improve functional outcome measures [17]. Subsequently, Pichiorri *et al.* showed that for 1 chronic and 13 subacute stroke patients at post-intervention, BCI-supported MI training resulted in significantly better outcomes than performing MI without BCI support [18]. Both studies lacked follow-up assessment though it would be interesting to see if there were any differences in motor scores as time passed. Hence it is worthwhile to investigate the effects of MI-BCI with engaging visual feedback post-intervention and at follow-ups.

B. Gap in MI- BCI Stroke Rehabilitation

A recent interest in BCI research but not in stroke rehabilitation is the detection of mental states. When healthy subjects use BCI, they seldom maintain the same mental state throughout. Fatigue, frustration and attention are a few of the mental states that were reported to be closely related to BCI performance [20]. BCI systems should therefore be psychologically adaptive in order to perform well even when the subjects' mental states change [20]. In the case of stroke rehabilitation, it is all the more important to detect such mental states, as stroke survivors are less likely to be able to maintain the same mental state throughout the session. Specifically, fatigue is a mental state that cannot be ignored for stroke patients. An anecdotal example is in Frolov *et al.*'s study where inter-trial or inter-session intervals were increased due to the patient's fatigue [30]. An EEG-based MI-BCI that adapts to fatigue as detected from the patient's EEG can provide a better rehabilitation experience, by customizing break-times accordingly for example [30]. However, most BCI stroke rehabilitation studies do not investigate or report the effect of fatigue on their subjects. One study that did so used the visual analog scale (VAS) to assess fatigue in the patients subjectively and reported the trend that greater VAS fatigue scores seemed to correspond with larger BCI performance variability [17]. Another study reported that though patients experienced fatigue after 20-30 minutes of training, they attributed it to concentration of attention and took it positively instead of dropping out [30]. An earlier study made passing remarks that there might be a link between fatigue and a session's cross-validation results based on the subjects' subjective qualitative report of being fatigued [31].

C. EEG Correlates of Mental Fatigue

Studies have found that there are EEG correlates of mental fatigue, as evidenced by their correlation with behavioral indicators of fatigue, such as Perclos (percentage of eyelid closure) in a mental task experiment [32], reaction time to driving simulation events [33] and driving error in a simulated driving experiment [34]. Increases in theta activity [33] and decreases in beta activity [35], [36], [37], [38] have been reported as indicators of the presence of fatigue but the changes in alpha activity are not consistently reported [21]. For instance, Zhao *et al.* found an increase in alpha rhythm [35] whereas Jap *et al.* reported that alpha activity decreased [36], though both studies involved a similar monotonous driving simulation to induce fatigue. Lal and Craig described instead an anteriorization of alpha activity; a decrease in alpha rhythm in the occipital and parietal regions accompanied by an increase in the frontal area [39]. The role of theta rhythm is also in question as it may reflect compensatory mechanisms that one undertakes when undergoing a fatiguing task [40]. Instead, it is generally agreed that beta activity is associated with the brain arousal level, and thus when fatigued, the arousal level is lowered as indicated by decreasing beta rhythms [35], [36], [37], [38].

III. Materials and Methods

A. Ethics Statement

This study obtained ethics approval from the Institution's Domain Specific Review Board, National Healthcare Group, Singapore. The trial is registered under NCT02765334 in ClinicalTrials.gov. Before study enrollment, participants gave their informed consent.

B. *Subject Inclusion and Exclusion Criteria*

This study included subjects aged 21-80 years old with first-ever clinical stroke, either ischaemic or haemorrhagic, diagnosed on CT or MRI brain imaging, stroke duration of 3 to 24 months, a FMA score of 10–50 for their affected upper limb, and the ability to pay attention and maintain supported sitting for 1.5 hours continuously. Subjects also had to be able to give their own consent and understand simple instructions. Finally, subjects were to achieve a BCI accuracy above the chance level of 57.5% in the screening MI-BCI experiment [1]. The chance level was calculated based on the inverse binomial cumulative distribution with a 95% confidence estimate [7]. The screening session is further described later in Section III.G.

Subjects were excluded if they had recurrent clinical stroke, or other conditions that were likely to affect their participation in the experiment such as severe aphasia or inattention; unresolved sepsis; postural hypotension; end stage renal failure; a life expectancy of less than a year due to malignancy or neurodegenerative disorder; and a history of epilepsy, severe depression or active psychiatric disorder and hemispatial neglect, or visual impairment. Other exclusion criteria included contraindications to transcranial magnetic stimulation (TMS) such as pregnancy, orthodontics, cardiac pacemakers, metal implants, cranial surgery; repetitive arm training contraindications such as severe spasticity with modified Ashworth scale (MAS) [41] >2 in any region, pain with visual analog scale (VAS) [42] > 4/10, fixed joint contractures; and poor skin conditions. Subjects were also excluded if they had skull defects or prior cranial surgery affecting the fit of the EEG cap.

C. *Clinical Protocol*

This study's clinical protocol is designed closely to that of Ang *et al.*'s study [1], as it is an extension of that work. Thus, similar to the BCI with haptic knob (BCI-HK) intervention group in Ang *et al.*'s study, there are 60 minutes of BCI intervention and 30 minutes of standard arm therapy per session. Furthermore, Ang *et al.*'s control group, called the standard arm therapy (SAT) group, which underwent 90 minutes of standard arm therapy per session, is used as a historical control group for this single-arm study.

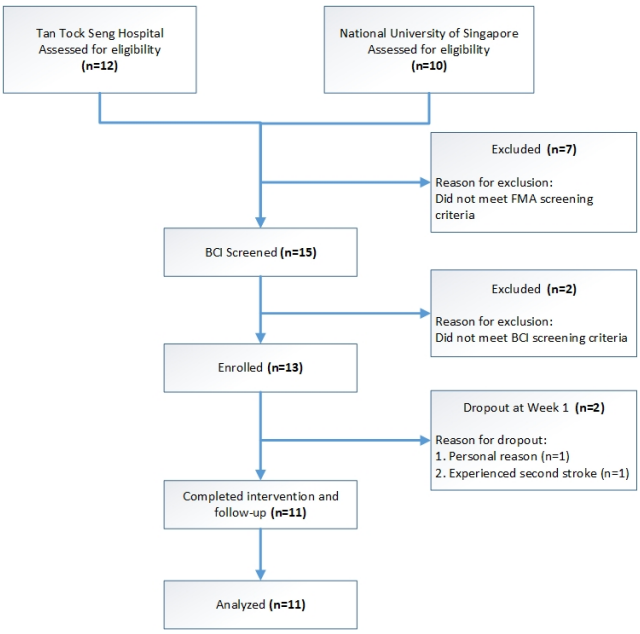


Fig. 1. CONSORT diagram showing the flow of the study from enrollment to analysis.

In this study, subjects who fulfilled the clinical inclusion criteria, detailed in Section III.B, underwent the 40-minute MI-BCI screening session, and those who achieved a BCI accuracy above 57.5% were recruited into the study. They then completed a 40-minute MI-BCI calibration session that was identical to the screening session. This was followed by 6 weeks of intervention. The intervention consisted of thrice-weekly rehabilitation sessions supervised by an occupational therapist and bioengineer. Each of the 18 rehabilitation sessions consisted of a 60-minute nBETTER supervised and therapy session, and a 30-minute standard arm therapy session with appropriate rest breaks. The details of all these MI-BCI sessions are covered in Section III.G. No therapy is conducted after Week 6.

As the FMA score is commonly used to measure clinical efficacy, it is measured at 4 time points: at baseline (Week 0), post-intervention (Week 6), and also at follow-up weeks (Week 12 and Week 24). There were secondary outcomes measured at the same time points as well: the total Action Research Arm Test (ARAT) score [43], Frenchay Arm Test of Function (FAT) score [44], and grip strength [45].

D. *Patient Enrollment*

The multisite clinical trial was conducted over ~1.5 year period from February 2016 to September 2017, involving stroke survivors from Tan Tock Seng Hospital and National University Hospital. Fig. 1 shows a flow chart of the trial. In total, 13 stroke patients were recruited, 7 from Tan Tock Seng Hospital, and 6 from National University of Singapore. Out of the 13 recruited subjects, 2 dropped out and 11 completed the study. A subject dropped out due to social reasons prior to starting the study interventions, and the other dropped out due to a second stroke occurring 2 days after his 5th nBETTER training session (Fig. 1). This was deemed not to be directly related to the nBETTER MI-BCI training. Thus, a total of 11 subjects underwent the calibration session and the nBETTER sessions.

The demographics and baseline characteristics of the stroke survivors are tabulated in Table I, along with the BCI-HK and SAT groups in Ang *et al.*'s study [1], with the latter's cohorts used for retrospective comparison. All groups underwent MI-BCI screening. The nBETTER and BCI-HK group then performed MI-BCI calibration before undergoing 18 sessions of nBETTER and BCI-HK intervention respectively over 6 weeks. The SAT group did not perform MI-BCI calibration but had 18 sessions of SAT intervention over 6 weeks. In each session, the BCI intervention groups used the BCI systems for an hour, followed by 30 minutes of arm therapy. On the other hand, the SAT group had 90 minutes of arm therapy in each session. These similarities and differences are reflected in Table 1 as well.

TABLE I
DEMOGRAPHICS, BASELINE CHARACTERISTICS AND INTERVENTION OF PARTICIPANTS

	nBETTER Group	**SAT Group** [1]	**BCI-HK Group** [1]
N	11	7	6
Age (years)	55.2 ± 11.0	58.0 ± 19.3	54.0 ± 8.9
Gender, N (%)			
Male	6 (54.5%)	4 (57.1%)	4 (66.7%)
Female	5 (45.5%)	3 (42.9%)	2 (33.3%)
Stroke Type, N (%)			
Infarction	8 (72.7%)	5 (71.4%)	2 (33.3%)
Hemorrhagic	3 (27.3%)	2 (28.6%)	4 (66.7%)
Paresis Side, N (%)			
Right	8 (72.7%)	3 (42.9%)	4 (66.7%)
Left	3 (27.3%)	4 (57.1%)	2 (33.3%)
Stroke Nature, N (%)			
Cortical	3 (27.3%)	3 (42.9%)	1 (16.7%)
Subcortical	8 (72.7%)	4 (57.1%)	5 (83.3%)
Stroke Period, N (%)			
Subacute (1-6 months post-stroke)	2 (18.2%)	0 (0.0%)	0 (0.0%)
Chronic (>6 months post-stroke)	9 (81.8%)	7 (100.0%)	6 (100.0%)
Post-stroke duration (days)	333.7 ± 179.6	455.4 ± 109.6	285.7 ± 64.0
Baseline Characteristics (Week 0)			
FMA	35.5 ± 12.6	23.4 ± 14.0	30.7 ± 17.2
ARAT	13.4 ± 17.7	6.6 ± 6.5	22.2 ± 21.1
FAT	0.4 ± 0.9	0.6 ± 1.0	2.2 ± 2.1
Grip strength	6.2 ± 2.6	6.6 ± 2.9	6.8 ± 1.6
Pre-Intervention			
MI-BCI Screening	√	√	√
MI-BCI Calibration	√	-	√
Intervention Session			
Session frequency	3 sessions per 6 consecutive weeks		
Classifier adaptation	√	-	-
60 minutes of intervention	nBETTER: 160 MI trials with visual feedback	SAT: repetitive task training	BCI-HK: 120 MI trials with haptic feedback
30 minutes of physical therapy	Therapist-assisted arm mobilization		

Using one-way ANOVA, no significant intergroup differences in the demographics and baseline characteristics were found: age ($F_{(2,21)} = 0.16$, $p = 0.86$), gender ($F_{(2,21)} = 0.11$, $p = 0.90$), stroke type ($F_{(2,21)} = 1.45$, $p = 0.26$), paresis side ($F_{(2,21)} = 0.79$, $p = 0.47$), stroke nature ($F_{(2,21)} = 0.51$, $p = 0.61$), stroke period ($F_{(2,21)} = 1.26$, $p = 0.30$), post-stroke duration ($F_{(2,21)} = 2.64$, $p = 0.10$), FMA score ($F_{(2,21)} = 1.61$, $p = 0.22$), ARAT score ($F_{(2,21)} = 2.09$, $p = 0.15$), FAT score ($F_{(2,21)} = 1.30$, $p = 0.29$), and grip strength ($F_{(2,21)} = 0.19$, $p = 0.83$).

E. EEG Data Acquisition

In this study, EEG data was collected using the Neurostyle acquisition hardware[1] with 24 unipolar Ag/AgCl channels placed in the international 10-20 system positioning: F3, F4, FC3, FC4, C3, C4, CP3, CP4, P3, P4, FT7, FT8, T3, T4, TP7, TP8, Fz, Oz, FCz, Cz, CPz, Pz, A1 and A2. The EEG was digitally sampled at 256Hz with a resolution of 24 bits for voltage ranges of ±300mV. The impedance level was ensured to be below 5 kΩ before proceeding with the experiment.

[1] Neurostyle Ptd Ltd, http://neuro-style.com/

F. The nBETTER System

The nBETTER system is a portable, internet-connected device that detects the imagination of movement of the stroke-affected limb. It is an EEG-based MI-BCI that provides visually engaging feedback for exercising the brain towards better recovery after stroke. Fig. 2a shows a subject using the nBETTER application. A more detailed description and images are in the Supplementary Material Section II.

G. MI-BCI Sessions

For all MI-BCI sessions, for MI trials, subjects were instructed to perform upper-arm kinesthetic MI of their affected side; they were to "imagine to move" the stroke-affected arm and hand forward to repeatedly reach for an imaginary target in front of them. They were also advised to keep still and minimize any body movements. If the Idle task was to be performed, the subjects were instructed to relax, keep still and stare straight at the computer screen.

The MI brain signals were detected using the Filter Bank Common Spatial Pattern (FBCSP) algorithm, described in detail in [46]. In brief, it band passes the EEG signal into several frequency bands within 4 to 40 Hz. This removes eye artifacts which are maximal at frequencies below 4 Hz [47]. The common spatial pattern (CSP) algorithm is used to detect the event-related desynchronization/synchronization that occurs when MI is performed. Subsequently, m pairs of the computed CSP features for each frequency band are used in the next step. The best k CSP features with their corresponding pairs are then selected by mutual information methods to build a subject-specific model. As in [46], $m = 2$ and $k = 4$ are used. Finally, a fisher linear discriminant classifier is used to obtain the accuracy of model. The BCI accuracy is thus the classification accuracy output of the FBCSP in detecting MI.

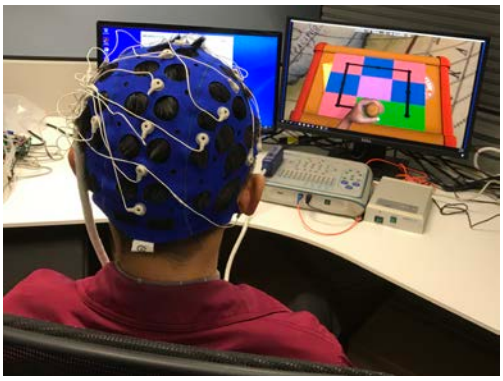
The various MI-BCI sessions and standard arm therapy sessions in the clinical protocol are detailed below:

1) MI-BCI screening and calibration sessions

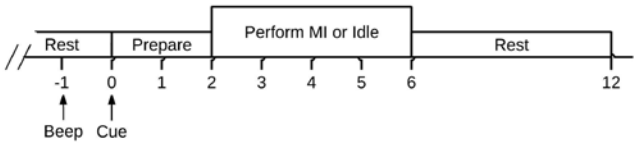
The screening and calibration sessions are identical. Subjects performed MI and Idle tasks as cued by the screen. In each session, subjects completed a total of 4 runs, each consisting of 20 MI trials and 20 Idle trials. Each trial lasted about 12s (Fig. 2b). Accuracies of these sessions are obtained via a 10 by 10-fold cross validation. The purpose of the screening session was to ensure that the subject was able to perform kinesthetic MI that the system was able to detect. Thus, as per Ang *et al.*'s study [1], only those whose accuracies were above chance level of 57.5% were recruited. The calibration session was then used by the system to train a subject-specific model for subsequent sessions, to detect the subject performing MI.

2) nBETTER supervised session

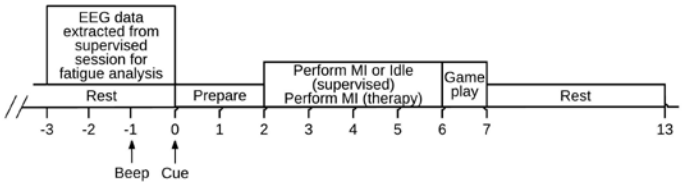
In the nBETTER supervised session, subjects performed both the MI and Idle tasks but with the nBETTER interface which provided visually engaging feedback; as subjects successfully performed MI, a picture was slowly revealed. In this session, subjects completed 1 run consisting of 20 MI and 20 Idle trials. Each trial lasted about 13s, including 1s of game play providing engaging visual feedback (Fig. 2c). The



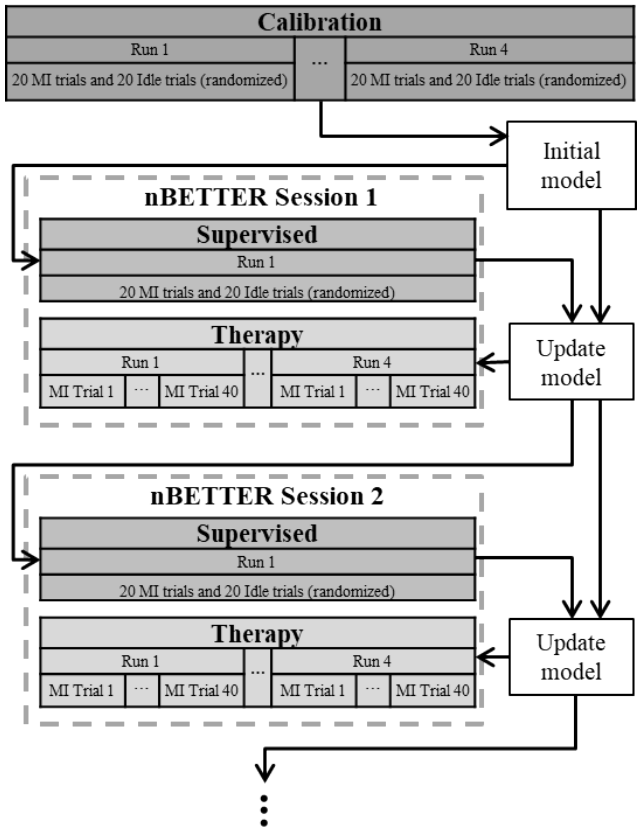
(a) A subject undergoing nBETTER intervention



(b) A trial in the MI-BCI screening and calibration sessions. In each of these sessions, 4 runs, each consisting of 20 MI and 20 Idle trials, are performed.



(c) A trial in the nBETTER supervised and therapy sessions. In each supervised session, 1 run of 20 MI and 20 Idle trials are performed. In each therapy session, 4 runs of 40 MI trials each are performed.



(d) Illustration of the subject-specific model update process, where the model is updated after every supervised session and used for the same day's therapy session, and the subsequent supervised session.

Fig. 2. Subject using the nBETTER system, performing trials in the MI-BCI screening and calibration sessions, and in the nBETTER supervised and therapy sessions, with classifier updates after each nBETTER supervised session.

purpose of the supervised session was to tune the subject-specific model built during the calibration session. Fig. 2d illustrates how the model is updated for each subject; after each supervised session, the model is retrained with all collected data from that supervised session as well as previous sessions. Further details and analysis of this adapted model can be found in Zhang *et al.*'s paper [48]. An analysis of the features selected each time the model is adapted is included in Section III of the Supplementary Material.

3) nBETTER therapy session

The nBETTER therapy session is similar to the nBETTER supervised session, except that subjects performed only the MI trials, and completed a total of 4 runs, each consisting of 40 MI trials. The purpose of the nBETTER therapy session was to encourage neuroplasticity in the brain towards recovery of movement on the affected side.

4) Standard arm therapy session

The standard arm therapy session was modelled along neurodevelopmental techniques and included passive and active-assisted mobilization, abnormal tone management, functional reach and grasp-release training, and arm ergometer exercise.

H. EEG Fatigue Correlates

As mentioned in Section II.C, from the literature, beta activity decreases with fatigue [35], [36], [37], [38]. To understand how fatigue, if present, affected the BCI performance, 3-second pre-cue EEG relative beta power was correlated with the nBETTER supervised sessions' accuracies.

Before computing EEG beta activity, the raw EEG was pre-processed to reduce muscle noise contamination in the EEG [49]. As Laplacian was not able to address muscle contamination at the circumferential electrodes adequately [50], other muscle artifact removal methods were used [51]. First, the EEG was processed channel-wise with Wang *et al.*'s fast ensemble empirical mode decomposition method [52] with noise level 0.4, 10 ensembles and 8 intrinsic mode functions, followed by canonical correlation analysis implemented with publicly available code [53] with default parameters (https://github.com/germangh/eeglab_plugin_aar). This is followed by a next-nearest neighbor Laplacian [50], [54] with the available channels.

The beta activity was then computed as such: A 3-second pre-cue EEG segment (see Fig. 2c) was extracted from each trial. The beta frequency (12-30Hz) band power was calculated for each trial and normalized by its total power in 4-50Hz. The total power in 4-50Hz is chosen as it removes

artifacts in the low and high frequency range. This relative beta power is thereafter expressed in decibels.

Relative beta power was then averaged among the channels in each brain region [frontal (F3, Fz, F4), central (C3, Cz, C4), and parietal-occipital (P3, Pz, P4, Oz)]. To analyze the correlation between the relative beta power and BCI performance with consideration to each subject having 18 supervised sessions, a repeated measures correlation [55] was computed for each brain region.

I. Sample Size Statistical Analysis

To estimate the sample size required for a statistical power of 80%, the mean and standard deviation gain in total FMA score from a previous study was used. Based on Ang *et al.*'s three-armed study SAT group, which had similar study inclusion criteria [1], the FMA score improved with a mean and standard deviation of 4.9 and 4.1 respectively. Using MATLAB® function *sampsizepwr* with a z-test and p-value of 5%, the sample size required is calculated to be 6.

J. Statistical Methods

To test the normality of each group's FMA scores, the Shapiro-Wilk test [56] is used. Öner and Deveci Kocakoç's MATLAB® codes [57] were utilized.

As all groups' FMA scores tested normal, a two-way mixed-design ANOVA was conducted to analyze the effects due to intervention and over time. Intervention was the between-subject factor with 3 levels (nBETTER, SAT, BCI-HK), and time was the within-subject repeated measure factor with 4 levels (Weeks 0, 6 , 12 and 24). Subsequently, we performed post-hoc analysis for the time effect, on each group's FMA score at time-points of Weeks 6, 12 and 24 against that at baseline (Week 0). As the FMA scores were normal and this was a within-group comparison, one-sample paired t-tests with Bonferroni correction for multiple comparisons were used for the post-hoc analysis. These statistical tests were carried out in MATLAB®.

IV. Results

A. Clinical Efficacy – FMA Score Gain

A retrospective comparison was done with the SAT and BCI-HK groups in Ang *et al.*'s three-arm study [1]. All groups' FMA scores at all time points were tested to be normal. The mean and standard deviation of each group's FMA score gains relative to Week 0 are tabulated in Table II and the boxplot is displayed in Fig. 3. From the boxplot in Fig. 3, the nBETTER and BCI-HK groups are shown to have an increasing FMA improvement median over the time points while the SAT group's decreases. The nBETTER and BCI-HK groups also had smaller variance in FMA score improvement compared to the SAT group.

Using a two-way mixed-design ANOVA, we found no significant interaction effect ($F_{(6,63)} = 1.59$, $p = 0.17$). There is also no significant intervention effect between groups ($F_{(2,21)} = 1.89$, $p = 0.18$). However, there is a significant main effect within groups ($F_{(3,63)} = 20.25$, $p = 2.64\text{x}10^{-9}$), i.e. over time. Thus, we performed separate post-hoc analysis within each group with one-sample paired t-tests for time points Weeks 6, 12 and 24 compared to Week 0. We used Bonferroni correction for the multiple comparisons. Relative to Week 0, the nBETTER group demonstrated significant FMA score gains at Week 6 [($M = 4.4$, $SD = 3.6$), $t_{(10)} = -4.07$, $p = 0.0068$)] and Week 24 [($M = 5.8$, $SD = 5.6$), $t_{(10)} = -3.46$, $p = 0.019$] but not Week 12 [($M = 3.5$, $SD = 6.7$), $t_{(10)} = -1.72$, $p = 0.35$]. Relative to Week 0, the SAT group did not achieve significant FMA score gains at Week 6 [($M = 4.9$, $SD = 4.1$), $t_{(6)} = -3.10$, $p = 0.063$], Week 12 [($M = 3.6$, $SD = 5.5$), $t_{(6)} = -1.71$, $p = 0.42$] and Week 24 [($M = 3.6$, $SD = 5.9$), $t_{(6)} = -1.60$, $p = 0.48$]. The BCI-HK group attained significant FMA score gains at Week 6 [($M = 7.2$, $SD = 2.3$), $t_{(5)} = -7.58$, $p = 0.0019$], Week 12 [($M = 8.2$, $SD = 2.9$), $t_{(5)} = -6.83$, $p = 0.0031$] and Week 24 [($M = 9.7$, $SD = 2.9$), $t_{(5)} = -6.83$, $p = 0.0014$]. All t-test p-values reported above are Bonferroni-corrected.

Performing the same two-way mixed-design ANOVA analysis on the secondary outcomes measures yielded also no significant interaction effect (ARAT: $F_{(6,63)} = 0.88$, $p = 0.52$, FAT: $F_{(6,63)} = 1.77$, $p = 0.12$, grip strength: $F_{(6,63)} = 1.16$, $p = 0.34$) and no significant intervention effect between groups (ARAT: $F_{(2,21)} = 2.24$, $p = 0.13$, FAT: $F_{(2,21)} = 1.74$, $p = 0.20$, grip strength: $F_{(2,21)} = 0.18$, $p = 0.83$). There is a significant main effect within groups, i.e. over time (ARAT: $F_{(3,63)} = 18.57$, $p = 9.64\text{x}10^{-9}$, FAT: $F_{(3,63)} = 6.31$, $p = 8.18\text{x}10^{-4}$, grip

TABLE II
IMPROVEMENT IN FMA SCORE

Group	Baseline FMA (Week 0)	Improvement in FMA score relative to Week 0		
		Week 6	Week 12	Week 24
nBETTER	35.5 ± 12.6	4.4 ± 3.6*	3.5 ± 6.7	5.8 ± 5.6*
SAT	23.4 ± 14.0	4.9 ± 4.1	3.6 ± 5.5	3.6 ± 5.9
BCI-HK	33.0 ± 16.2	7.2 ± 2.3*	8.2 ± 2.9*	9.7 ± 2.9*

*significant improvement, $p<0.05$

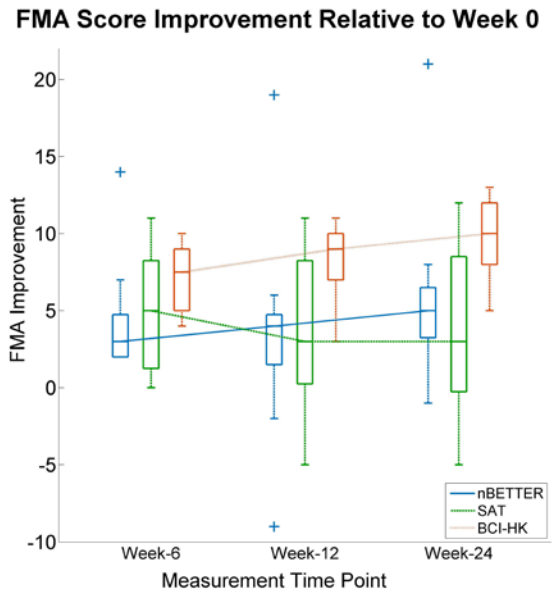


Fig. 3. Boxplot showing the improvement in FMA scores at post-intervention (Week 6) and follow-ups (Week 12 and 24) for the nBETTER, SAT and BCI-HK groups.

strength: $F_{(3,63)} = 4.60$, $p = 0.0056$). However, upon conducting post-hoc tests with Bonferroni correction, most secondary outcomes for the groups did not yield significant results over time (as reported in Section IV of the Supplementary Material).

B. EEG Fatigue Correlates

Fig. 4 shows the repeated measures correlations between relative beta power and BCI performance accuracies of 18 supervised sessions per subject. Significant positive correlations were found in the frontal and central, but not parietal-occipital, brain regions [Frontal (F3, Fz, F4), $R = 0.251$, $p < 0.01$; Central (C3, Cz, C4), $R = 0.181$, $p < 0.05$; Parietal-Occipital (P3, Pz, P4, Oz), $R = 0.033$, $p > 0.05$].

V. Discussion

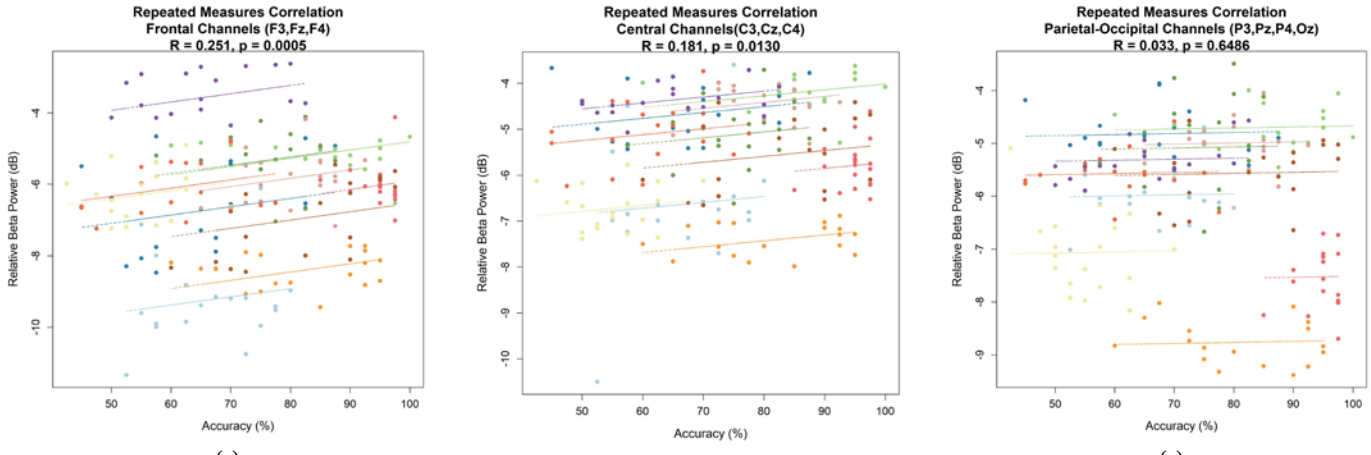
A. Clinical Efficacy of the nBETTER Intervention

This single-arm multisite clinical study has investigated the clinical efficacy, in terms of FMA score improvement, of using nBETTER, an EEG-based MI-BCI system, for stroke rehabilitation. This clinical trial is performed similarly to a previous three-arm RCT where significant improvement in FMA scores were achieved using BCI with a haptic knob robotic feedback (BCI-HK) as compared to just using a haptic knob or undergoing only standard arm therapy [1]. Thus we aimed to investigate the efficacy of a BCI intervention with engaging visual feedback, and retrospectively compare it to a group which had no BCI intervention (the SAT group) and a group which had BCI intervention with orthosis attachment (the BCI-HK group). To our knowledge, there has been no study which investigated the effects of EEG-based MI-BCI with purely visual feedback with an 18-week follow-up period for chronic patients. While Prasad *et al.* [17] and Pichiorri *et al.* [18] did investigate the effects of EEG-based MI-BCI with visual feedback, the former study was with a small sample size of 5 chronic patients, the latter study was mainly with subacute patients, and both studies were without follow-up assessments. In our study, we have taken thus this investigation further by conducting it with a game for a more visually engaging interface, with chronic stroke survivors to see how MI-BCI could aid their rehabilitation, and with follow-up assessments to better understand the short-term effects of MI-BCI intervention.

This preliminary explorative study showed that 18 sessions of therapist-supervised training over 6 weeks, using 60 minutes of nBETTER followed by 30 minutes of conventional therapy, achieved significant short-term gains in terms of improved FMA scores. Retrospectively comparing with the SAT and BCI-HK groups in a previous similar RCT by Ang *et al.* in 2014 [1], no significant interaction between intervention and time was found. No significant intervention effects were found either, meaning that all groups performed comparably. The SAT group had no significant FMA score gains at all time points, whereas the nBETTER group had significant FMA score gain in Week 6 and it was sustained at Week 24 though not at Week 12. The lack of significant gains in Week 12 may be due to larger standard deviation of 6.7 amongst the subjects (see Table II), which may possibly have been caused by the lack of therapy after Week 6. By Week 24, subjects were possibly more stabilized and therefore had significant FMA gains.

In Ang *et al.*'s BCI-HK group, there were significant FMA score improvement at Weeks 6, 12 and 24. The BCI-HK group had consistent and the greatest positive FMA score gains compared to the other two groups, and was the only group which reached the Minimal Clinically Important Difference (MCID) of 9-10 for subacute to chronic stroke [58] at Week 24. Thus, the nBETTER group's FMA scores had better sustainability than the SAT group, but lesser gains and consistency than the BCI-HK group.

As this study was designed closely to that of Ang *et al.*'s [1], similar to its BCI-HK group, this nBETTER group was also paired with standard arm therapy. In addition, as both studies were designed generally for chronic stroke patients, information on subjects' prior therapy regime was not collected. It might have been possible that prior therapy regimes or the standard arm therapy conducted in the BCI intervention groups (nBETTER and BCI-HK) influenced their FMA gains. However, the BCI intervention groups achieved superior and significant gains despite only having about 33%



(a) (b) (c)

Fig. 4. Plot of repeated measures correlation of relative band power against BCI performance accuracy. Significant positive correlation of relative beta power with accuracy in frontal and central, but not parietal-occipital, brain regions were found.

of the SAT group's conventional therapy duration. Thus, it is likely that the FMA gains are the result of the BCI interventions.

The sustained FMA gains of the nBETTER group compared to the SAT group could imply brain priming through neuroplasticity driven processes occurring after mental imagery and visual feedback compared to limb practice. Varkuti *et al.*, in a small study of 9 subjects undergoing BCI with kinesthetic feedback training followed by functional Magnetic Resonance Imaging (fMRI), suggested that there were changes in resting brain states [11]. Thus, this hypothesis on the brain priming effects of MI-BCI with visual feedback needs further validation by non-invasive brain imaging.

It is also noted that the nBETTER group had similar intervention session duration as the BCI-HK group, but did not achieve greater FMA score gains. This is likely due to the lack of kinesthetic feedback in the nBETTER system compared to the BCI-HK system. This is in agreement with Ono *et al.*'s results that suggested kinesthetic feedback may be more effective than purely visual feedback [26], supporting our use of pairing nBETTER with arm therapy.

We also report the EEG spatial filters of the nBETTER group in the Supplementary Material Section V.

Overall, training on the nBETTER, an EEG-based MI-BCI with engaging visual feedback, with standard arm therapy, in stroke rehabilitation was effective and safe; there were no adverse events observed by research and medical personnel or self-reported by subjects. Further theoretical advantages of the nBETTER system include the possibility of treating stroke patients who may be excluded from robotic or intensive arm training protocols such as Constraint Induced Movement Therapy (CIMT) due to their lacking inherent minimal criteria in terms of postural or arm motor requirements and absence of significant pain and spasticity. Other advantages are that the nBETTER system is highly portable and accommodates a variety of supported postures.

B. Mental Fatigue in EEG-based MI-BCI

A major challenge in the use of EEG-based MI-BCI in stroke patients is the cognitive pre-requisite of sustained attention and potential fatigue induction during training, which may limit its suitability to the majority of stroke patients and reduce its efficacy. Thus in this study, we also aimed to investigate the presence of fatigue via an EEG correlate of fatigue, the relative beta power.

We computed the repeated measures correlation between relative beta power and the classification accuracies across the 18 supervised sessions for the frontal, central and parietal-occipital brain regions. We found that relative beta power was significantly positively correlated to the BCI performance in terms of the BCI accuracy, at the frontal and central areas. From the literature, a lower beta activity may suggest lower brain arousal and the presence of fatigue [35], [36], [37], [38]. Thus, our result indicated that fatigue might be present and a cause of poorer BCI performance. This suggests a disadvantage of EEG-based MI-BCI systems in inducing fatigue due to the monotony of performing MI.

In this study, a repeated measure correlation method was used in order to include within-subject effects. The analysis revealed, as shown in Fig. 4, that there was lower relative beta power in the frontal and central areas when subjects did not perform well in an nBETTER supervised session. However, while statistically significant, the correlation values are low. Furthermore, the parietal-occipital area does not show this correlation. Thus, it is not a strong indication of the presence of fatigue. This is a limitation of this study and thus, further investigation with larger number of subjects and trials per class per session is needed for more conclusive results. However, the preliminary analysis in this study presents the potential of BCI to play the additional role of fatigue or mental state monitoring to enhance the clinical efficacy and personalization of stroke rehabilitation for stroke survivors according to their detected or predicted fatigue or mental state.

VI. Study Limitations and Future Work

One limitation of this study is the small sample size. Though it was not underpowered, it may not be representative of the whole stroke population, since some patients may not be able to operate BCI effectively. A non-trivial estimate of 15-30% of BCI users are BCI-illiterate [59] and the value may be higher for stroke patients. Further research can be done for these BCI-illiterate users so that they too may benefit from the advantages of BCI interventions.

This study was also not a true RCT as the SAT and BCI-HK groups from a previous study were used for retrospective comparison. The small and unequal sizes of the groups also warrant that we interpret this paper's results with caution. For instance, the difference in the groups' stroke duration might have affected the FMA analysis as it shows a trend ($p = 0.1$), though it was not significant possibly due to the small and unequal group sizes. Thus moving forward, a larger and more balanced RCT will be conducted in order to verify the efficacy of the nBETTER system with and without robotic haptic feedback, to better understand the effects of both visual and haptic feedback in EEG-based MI-BCI stroke rehabilitation systems.

A limitation with this study's EEG analysis is that only the relative beta power was used as an EEG correlate of fatigue. However, the correlation found may be indicative of other mental states instead. Thus, moving forward, we will apply other EEG mental state features to further investigate the presence of fatigue or other mental states in stroke survivors during EEG-based MI-BCI stroke rehabilitation.

VII. Conclusion

We conducted a single-arm multisite clinical trial with the nBETTER system, a non-invasive EEG-based MI-BCI system that provides visual feedback for stroke rehabilitation. We had the two-fold aim to investigate the clinical efficacy of using nBETTER as well as relationship between EEG correlates of fatigue and the BCI performance during the intervention.

Clinical efficacy was measured using FMA score, and the results yielded significant improvements at Week 6 and Week

24 compared to baseline, though not reaching MCID. This suggested that the nBETTER intervention had positive short-term effects compared to a previous study's SAT group that did not yield any significant FMA score improvements at any time points, while not exceeding the consistent significant FMA gains of the BCI-HK group at Weeks 6, 12 and 24 [1]. The presence of fatigue was investigated via the EEG relative beta power correlate. A significant positive repeated measures correlation with the nBETTER supervised sessions' accuracies was found in the frontal and central areas.

This study demonstrated that nBETTER as an EEG-based MI-BCI, together with conventional therapy, was effective and safe for use in the subacute or chronic stroke population within a rehabilitation setting. Hence future larger clinical trials are warranted to verify its clinical efficacy and role in the rehabilitation milieu. The EEG fatigue analysis results also motivate further research to investigate and mitigate the effects of fatigue on EEG-based MI-BCI in stroke rehabilitation.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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