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Short term priming effect of brain-actuated muscle stimulation using bimanual movements in stroke

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HIGHLIGHTS

- Bimanual and unimanual brain-computer interface triggered-functional electrical stimulation (BCI-FES) in people affected by stroke achieve similar accuracy.
- Bimanual movements do not supress event-related desynchronization activation of lesioned hemisphere.
- Bimanual and unimanual BCI-FES result in comparable short-term priming.

ABSTRACT

Objective: Brain-computer interface triggered-functional electrical stimulation (BCI-FES) is an emerging neurorehabilitation therapy post stroke, mostly for the affected hand. We explored the feasibility of a bimanual BCI-FES and its short-term priming effects, i.e. stimuli-induced behaviour change. We compared EEG parameters between unimanual and bimanual movements and differentiated the effect of age from the effect of stroke.

Methods: Ten participants with subacute stroke, ten age-matched older healthy adults, and ten younger healthy adults underwent unimanual and bimanual BCI-FES sessions. Delta alpha ratio (DAR) and brain symmetry index (BSI) were derived from the pre- and post- resting-state EEG. Event-related desynchronization (ERD) and laterality index were derived from movement- EEG.

Results: Participants were able to control bimanual BCI-FES. ERD was predominantly contralateral for unimanual movements and bilateral for bimanual movements. DAR and BSI only changed in healthy controls. Baseline values indicated that DAR was affected by stroke while BSI was affected by both age and stroke.

Conclusions: Bimanual BCI control offers a larger repertoire of movements, while causing the same short-term changes as unimanual BCI-FES. Prolonged practice may be required to achieve a measurable effect on DAR and BSI for stroke.

Significance: Bimanual BCI-FES is feasible in people affected by stroke.

1. Introduction

Stroke is the leading cause of long-term disability in developed countries, with 1.1 million survivors in the UK (King et al., 2020), a number that is expected to grow as the population ages and stroke survival rates continue to increase. With a significant decrease in post-stroke mortality over the last ten years, the number of ageing stroke survivors with a disability has been constantly increasing.

Recovery after stroke is due to rehabilitation, including physiotherapy such as exercise, constraint-induced movement therapy, mirror therapy, and bilateral movement training (Cauraugh et al., 2010), which can also be aided with technology, such as functional

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electrical stimulation (FES) and robotic devices (Weber et al., 2018). The outcomes of rehabilitation, however, are still limited and approximately 40% of survivors are left with chronic motor impairment, leading to reduced quality of life (Hatem et al., 2016) and increased socioeconomic burden (Rajsic et al., 2019).

Brain-computer interfaces (BCI) are devices that can use motor imagery or motor attempt related brain signals, typically measured by an electroencephalogram (EEG), to control an external device such as a wheelchair, cursor, orthosis, or FES. BCIs were designed for communication and control, however, they are increasingly being used for neurorehabilitation, especially for people with stroke (Silvoni et al., 2011). In the context of neurorehabilitation, triggering a BCI with attempted movements can re-establish a causal link between cortical and peripheral neural activation, causing motor relearning through Hebbian mechanisms (Muralidharan et al., 2011). A meta-analysis assessing the effects of BCI training following stroke showed a medium effect size favouring BCIs for the rehabilitation of upper extremity function (Bai et al., 2020). Furthermore, it found that using FES as a therapeutic device controlled by BCI was more effective than using exoskeleton, orthosis, or visual feedback and that using movement attempts for BCI control is more effective than using motor imagery (Bai et al., 2020) because the latter inevitably involves suppression of a voluntary motor action (Chen et al., 2021; Zulauf-Czaja et al., 2021).

In line with this, our recent study demonstrated that even the smallest amount of muscle activity during imagined or attempted movements create a distinguishable difference in movement-related cortical potential, both during motor planning and the deafferentation phase, which involves feedback from the proprioceptors (Sosnowska et al., 2021). For that reason, unlike motor imagery, a movement attempt has the potential to establish a closed sensorimotor loop, which may restore the normal timing order of motor preparation, execution, and movement proprioception (Muralidharan et al., 2011). Thus, motor attempt-controlled BCI is the most direct way to engage the motor system in stroke patients (Pichiorri and Mattia, 2020). Brain patterns in motor action based BCI are derived from changes in sensorimotor rhythms, alpha (8–12 Hz) and beta (12–30 Hz) (Jeunet et al., 2019), and the underlying mechanism of event-related desynchronisation/synchronisation (ERD/ERS)(Neuper and Pfurtscheller, 2001; Pfurtscheller and Lopes da Silva, 1999).

In neurologically intact individuals, most functional activities are accomplished by using both hands in a highly coordinated and efficient manner, the performance of these activities deteriorates and bilateral arm use is reduced post-stroke (Kantak et al., 2017). Despite this, most BCI-FES therapies for stroke target rehabilitation of the affected hand only. The main reason for unimanual training is that post-stroke, the healthy hemisphere is already more active and inhibits the affected hemisphere even for unilateral movements of the affected hand (Dodd et al., 2017). The contralateral inhibition mechanism of the motor program is preserved for the unaffected side but is compromised for the affected side (Casula et al., 2021).

There is, however, evidence that bilateral priming accelerates upper-limb motor recovery following stroke by rebalancing the corticomotor excitability and interhemispheric inhibition (Stinear et al., 2014). A systematic review comparing unilateral and bilateral arm-training in chronic stroke survivors found both therapies to be effective (Van Delden et al., 2012), whereas a relatively recent review (acute, sub-acute, and chronic stroke studies) found bilateral training to be more effective, as assessed by the Fugl Meyer assessment, but equal to unilateral when measuring functional performance (Chen et al., 2019). As a result of interlimb coupling in bimanual movements, cortical inhibition is decreased and intracortical facilitation is increased (Wolf et al., 2014). This indicates that, unlike unimanual training, bimanual training would not cause the imbalance of intracortical inhibition in people affected by stroke and would not have a detrimental effect on the training of the affected hemisphere.

Quantitative EEG measures are useful to characterize the brain status after stroke and predict neurological outcomes. These measures can be derived from resting-state EEG (power spectral density, Delta Alpha Ratio (DAR), and Brain Symmetry Index (BSI)) (Doerrfuss et al., 2020; Finnigan and van Putten, 2013; Sheorajpanday et al., 2011) or during motor action (ERD, laterality index) (Sebastián-Romagosa et al., 2020; Stępień et al., 2011). While studies have been looking at EEG oscillatory indices of unimanual training in people affected by stroke, studies comparing the EEG measured neuronal activity between unimanual and bimanual training are lacking.

Quantitative EEG measures have been extensively used in previous studies to check the long-term efficiency of BCI rehabilitation therapy (Ang et al., 2015a; Sebastián-Romagosa et al., 2020; Zhang et al., 2018). In contrast, the short-term effect of BCI therapy on quantitative EEG parameters following a single BCI session has been insufficiently explored. Understanding this effect would elucidate the mechanism of BCI-FES beyond the general hypothesis of motor priming (Stoykov and Madhavan, 2015) and Hebbian learning (Guger et al., 2016).

EEG activity is age dependant (Scally et al., 2018). Despite this, most published studies developing BCI-FES technology only test the system on young volunteers. Knowing that stroke affects mostly elderly people, decoupling the effect of stroke and age is imperative. This would not only aid the improvement of therapies following a stroke, but could also provide evidence of BCI as a preventive treatment for motor control in an ageing population.

In light of this, we tested the feasibility of a bimanual BCI-FES system by validating the system design and comparing it with a commonly used unimanual BCI-FES system. Our first hypothesis is that it is possible to control a BCI-FES using bimanual movement attempts, however, it might be more difficult than its unimanual counterpart. Secondly, we check the effects of short-term BCI-FES priming using quantitative EEG. Our second hypothesis is that both sessions would lead to changes in quantitative resting-state EEG measures such as DAR and BSI. Thirdly, we compare movement-related EEG parameters (ERD intensity and its lateralisation) between unimanual and bimanual movements, as well as between hemispheres to indirectly assess interhemispheric inhibition. Our third hypothesis is that ERD and lateralisation patterns will be different between unimanual and bimanual movements. Lastly, we aim to compare the aforementioned measures between stroke, younger healthy, and older healthy groups. Our fourth hypothesis is that these measures will be affected by both age and brain lesion.

2. Materials and methods

2.1. Participants

The study included 3 groups of participants. The first group was comprised of ten right-handed sub-acute participants affected by ischemic stroke (9 male, mean ± std age 60.2 ± 10.4). They had moderate to severe motor impairment (Fugl Motor Assessment Upper-Extremity score 14–60) and could understand and attempt a motor task. All except two participants had a single stroke. People with severe decompensation of vital organs, shoulder subluxation, or comorbid neurological disease were excluded. The participant details are summarised in Table 1.

The second group was comprised of ten right-handed older healthy volunteers (4 male, mean ± std age 59.6 ± 2.4) with no known neurological conditions. The third group was comprised

Table 1
Characteristics of Group-1 comprising participants with stroke.

No	Lesion site	Lesion side	Age	Time since stroke (months)	FMA UE score	ARAT score	Barthel Index score	Mini-mental state exam.
1	C & S	L	66	3.5	52	31	90	25
2	C & S	R	67	1.6	53	43	90	27
3	P	R	63	1.3	59	57	95	28
4	S	R	65	2	14	3	40	27
5	C & S	L	55	1	60	57	60	28
6	C & S	R	67	1.4	60	54	95	29
7	S	L	70	1.1	57	51	95	29
8	S	R	59	1.4	57	49	60	28
9	S	R	58	5.6	60	57	90	30
10	C & S	R	32	1.2	15	3	25	29
Mean ± SD			60.2 ± 10.4	2.01 ± 1.4	48.7 ± 17.3	40.5 ± 20.2	74 ± 24.6	28 ± 1.4

C: cortical, S: subcortical, P: parasagittal, L: left hemisphere, R: right hemisphere, FMA UE: Fugl-Meyer assessment upper extremity, ARAT: Action research arm test.

of ten right-handed able-bodied young adults with no known neurological conditions (6 male, mean ± std age 26.6 ± 3.9).

The study was conducted at different centres for people affected by stroke and healthy volunteers, however, the same principal researcher used the same portable EEG and FES devices. Ethical approval was obtained from the Ethical Committee of Clinic for Rehabilitation, Dr Miroslav Zotović, Belgrade, Serbia for the stroke group, and from the Ethical Committee for the College of Science and Engineering, University of Glasgow, Glasgow, UK for younger and older healthy groups. The study was conducted according to the Declaration of Helsinki. All participants provided signed informed consent.

2.2. Experimental setup

The experimental setup is shown in Fig. 1. OpenBCI (OpenBCI, U.S.A, https://openbci.com/) biosensing hardware was used to record EEG data at a sampling rate of 200 Hz(. It is a low-cost EEG amplifier providing EEG recordings of comparable quality to medical-grade systems and is popular for BCI use (Frey, 2016; Peterson et al., 2020). Four Ag/AgCl EEG electrodes were placed on the scalp (FC3 and CP3 on the left side, and FC4 and CP4 on the right side, following the 10–10 standard EEG electrode placement system (Nuwer, 2018)) to record EEG in a bipolar configuration, effectively giving two channels (FC3-CP3 and FC4-CP4). The ground electrode was placed on the forehead, close to the active and reference electrodes. The reference electrode was placed on the left mastoid for participants doing an intervention on the right hand, and on the right mastoid for participants doing an intervention on the left hand in the unimanual session. In this way, the distance between the contralateral electrode and the reference electrode was minimal and the same for both right- and left-hand sessions, to minimise the volume conduction effect (Hu et al., 2018). Furthermore, by using the electrodes in a bipolar configuration,

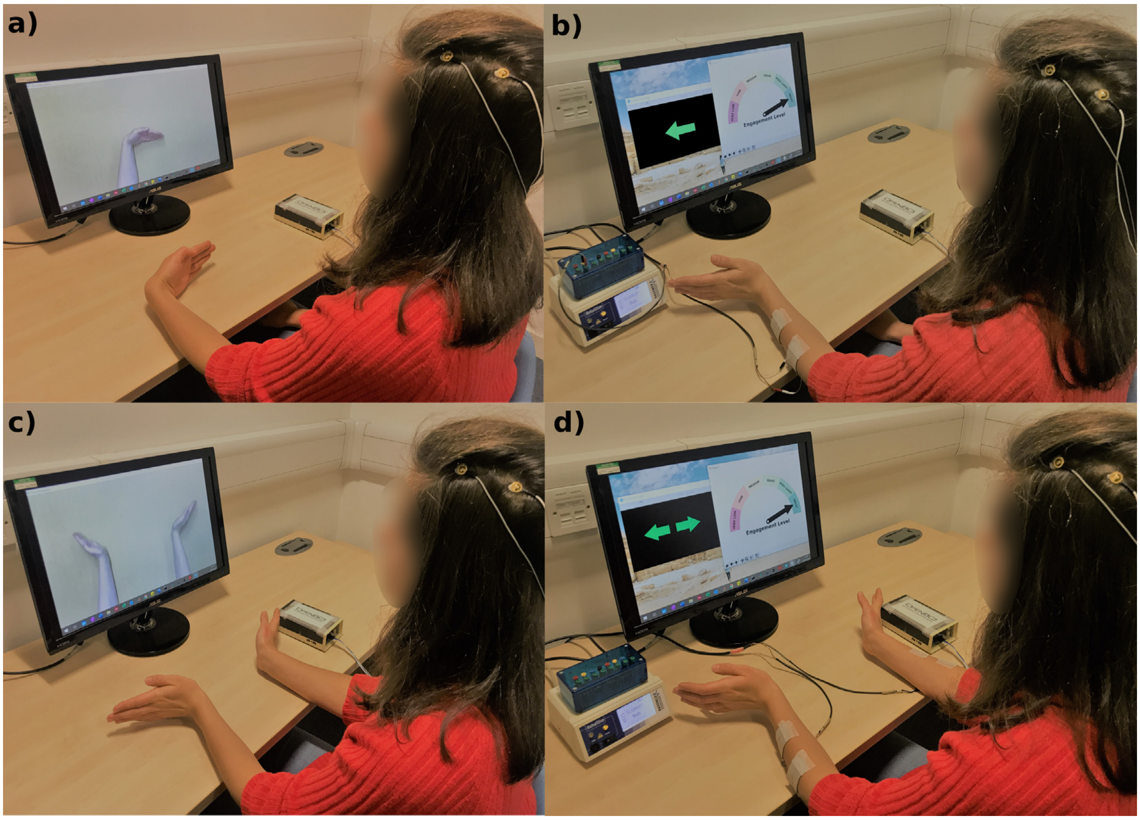

Fig. 1. Experimental setup for (a) unimanual calibration phase, (b) unimanual online phase, (c) bimanual calibration phase and (d) bimanual online phase. Photo taken with participants permission.

the effect of the original reference was cancelled. The reference electrode for the bimanual session had the same location as that of the corresponding unimanual session.

A multichannel medical-grade FES device, *Hasomed RehaStim* (Hasomed, Germany), was used to administer FES. Bipolar FES electrodes were placed over the extensor muscles in the forearm. The stimulation pulses were biphasic, delivered at a stimulation frequency of 33 Hz, with the pulse width set to 200 μs. For the stroke participants, the pulse intensity was adjusted for affected and healthy hands separately to trigger wrist extension without causing discomfort (Irimia et al., 2018; Sebastián-Romagosa et al., 2020). This ranged from 12 to 22 mA for the affected hand and 8–14 mA for the healthy hand within the stroke group. For healthy participants, pulse duration ranged from 12 to 16 mA for the younger group and 8–20 mA for the older group. In healthy participants who executed movement, FES intensity was adjusted to produce a near symmetric response on both hands for bilateral movements and was set to produce visible contractions without causing sensory discomfort.

2.3. Experimental protocol

Participants sat on a chair approximately 1.5 m from a computer screen with their hands resting on the table. There were two BCI-FES sessions carried out on separate days, within a week of one another: first unimanual followed by bimanual. During unimanual sessions, the stroke (ST) group used the affected hand, which was the left hand for 7 participants and the right hand for 3 participants. The first seven participants in the older healthy (OH) and younger healthy (YH) group used their left hand while the last 3 participants used right-hand to match with these numbers in the ST group. Each session consisted of four stages: 2 min resting-state EEG pre-intervention, an offline calibration stage to extract EEG parameters corresponding to the movement, an on-line BCI control stage using the same parameters to trigger FES, and 2 min resting-state EEG post-intervention. Resting-state data were recorded in the eyes open (EO) and eyes closed (EC) state pre and post-intervention. The NASA task load index (Hart, 2006) was used to assess the workload at the end of each session. At the end of the second session, participants were also asked which session (unimanual or bimanual) was easier for them.

Calibration: The calibration trial schematic is shown in Fig. 1 a. It involved 2 runs, each involving 10 repetitions of a 16 s “follow-along” video. The first 8 seconds showed the trial number and the participants rested, avoiding any movements. The next 8 seconds showed one hand wrist extension and flexion for the unimanual session and both hands wrist extension and flexion for the bimanual session. The calibration schematic is shown in Fig. 2. The ST group had a varying range of motion depending on stroke severity, so they attempted movement alongside action observation (AO), while participants in OH and YH groups executed movement alongside AO. Further in the text, both attempted and executed movements will be referred to as movement (MOV) for consistency.

On-line BCI control: The participants were asked to move the pointer of a gauge (shown in Fig. 3) in the clockwise direction via MOV. There were 30 trials completed in a minimum of 3 runs. One BCI run was subdivided into 10 trials. Within one trial, the user was cued to attempt/execute the movement of their hand. They had a minimum of 1 s and a maximum of 10 s to activate the FES. The minimum time was introduced to avoid unintentional FES activation, due to natural EEG fluctuation, before a person had a chance to perform a movement. Successful trials were rewarded by a 5 s FES followed by a 15 s rest period. Unsuccessful trials were followed by a rest period of 8 s before the next trial started. Breaks between runs were provided as needed. The on-line BCI control trial schematic is shown in Fig. 1b–c.

NASA task load index: After each session, the participants rated their perceived workload on six aspects: mental demand, physical demand, temporal demand, performance, effort, and frustration on a 21-point scale (Hart, 2006). A lower rating represented less workload.

The ratings were added across these subsections and averaged for each group.

2.4. BCI-FES session

The BCI software was developed in an open-source software platform Open Vibe (Arrouët et al., 2005) by incorporating addi-

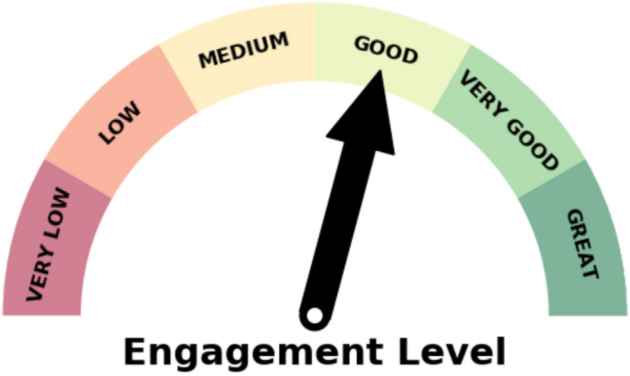

Fig. 3. Gauge used to provide neurofeedback.

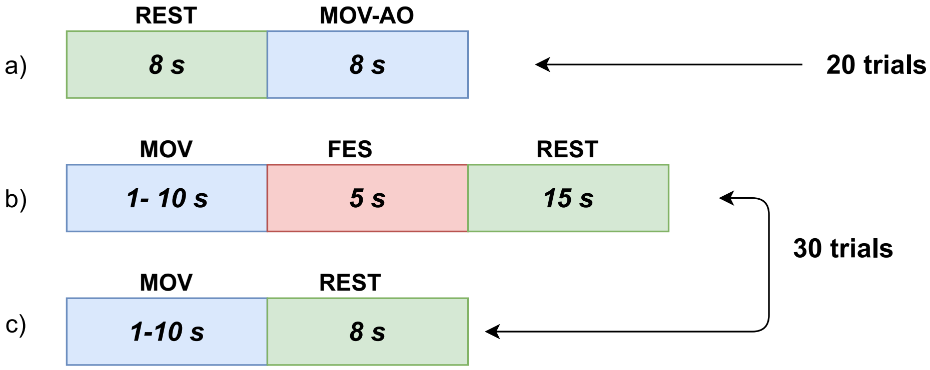

Fig. 2. Schematic of (a) calibration trial, (b) successful on-line BCI control trial and, (c) unsuccessful on-line BCI control trial (c). MOV refers to attempted or executed movement and AO refers to action observation. BCI and FES refer to brain-computer interface and functional electrical stimulation respectively.

tional features using an open-source programming language Python. The GUI contained cues for different tasks i.e., movement and rest, as well as a gauge for providing on-line feedback on brain activity. The raw data was filtered with a Butterworth bandstop filter (48–52 Hz) followed by a Butterworth bandpass filter (2–40 Hz) for both calibration and on-line BCI control stages.

On-line BCI control: The fast Fourier transform (FFT) power was evaluated in the selected frequency band. The BCI-FES control was based on a time-controlled threshold switch (Vučković et al., 2015), where power in the "selected frequency band" has to be below "the power threshold" for a certain time for FES to be triggered. This time is called "threshold time". The power threshold was defined as a percentage of the calibration power Pc, set in a range of 80–100% in steps of 5%, and was fixed for a run. The "selected frequency band" and "calibration power" are obtained from calibration data. The threshold time was set between 1 s and 1.6 s in steps of 0.2 s and was also fixed for a run. The parameters were set individually for each participant with the main criteria being to avoid mental fatigue and unintentional activation of FES; for the exact procedure see publications by our group (Vuckovic et al., 2015; Zulauf-Czaja et al., 2021). For the unimanual session, contralateral power had to be below a certain percentage of the contralateral threshold, while for the bimanual session, both C3 and C4 powers had to be below a certain percentage of the respective thresholds to activate FES.

The "selected frequency band" and "calibration power" were calculated from the rest and movement trials of the calibration data. The baseline was taken from an 8 s resting period between trials, skipping first 2 s to avoid the transition effect. The movement was taken 0.5 s after the movement video began as ERD starts around that time for motor observation as well as execution (Duann et al., 2016). The FFT power spectrum was obtained in 0.1–100 Hz and averaged over movement and rest trials to obtain the movement power spectrum (Pm) and the rest power spectrum (Pr), which were used to calculate the movement-related decrease in power, i.e. event-related desynchronization (ERD), as follows:

$$\boldsymbol{ERD} = \frac{\boldsymbol{Pr} - \boldsymbol{Pm}}{\boldsymbol{Pr}} \tag{1}$$

The frequency bands for movement-related activation are highly variable between subjects (Suk and Lee, 2011). For this reason, the band with the highest ERD among 10 frequency bands: 8–12, 12–16, 16–20, 16–24, 8–16, 10–16, 18–24, 8–14, 20–30 and, 12–30 Hz was chosen for on-line BCI control, referred to as the "selected frequency band". This method of choosing a subject-specific frequency band using ERD has also been previously applied in studies involving people with stroke (Ray et al., 2020).

To calculate the calibration power (P_c), a 6 s EEG epoch extracted from a movement trial by dividing it into 1 s long Hanning windows with 0.2 s overlap. The FFT power was then evaluated in the "selected frequency band" to calculate P_c. For a bimanual session, the signal was processed in the same way as a unimanual one, but the selected frequency band was kept the same as in the corresponding unimanual session and the calibration power was obtained for both sides to give P_c C3 and P_c C4. The epoch duration and analysis were chosen to mimic power calculation during the on-line BCI control.

Visual feedback: The feedback on brain activity was provided every 0.2 s via a gauge where the pointer moved according to the on-line power (1 s window) expressed as a percentage of the calibration power P_c. The gauge is shown in Fig. 3. The middle of the gauge represented 100% P_c. The clockwise side represented the on-line power being less than the calibration power, i.e. stronger ERD compared to calibration. The anticlockwise side represented the on-line power being more than the calibration power (note that anticlockwise control may still reflect ERD). Decreasing the on-line power resulted in clockwise gauge movement, such that an on-line power value that is 66–100%, 33–66% and less than 33% of P_c is classified as "good", " very good" and "great" respectively. Since the threshold was always between 80% and 100% of P_c, i.e. in the range of "good", the gradation was simply for visualisation. For the bimanual session, the gauge pointer moved to the clockwise side only when both C3 and C4 on-line powers were less than their respective P_c, with the segment indicated by the gauge representing the weaker ERD of the two sides. For example, if the power of C3 was less than 33% of P_c C3 ("good") and the power of C4 was between 33% and 66% of P_c C4 ("very good"), the gauge would point to "good". If either side was above the calibration power, the gauge moved to the anticlockwise side.

2.5. Off-line signal analysis

The off-line processing and data analysis was done in MATLAB (Mathworks, U.S.A) version R2019b.

2.5.1. Pre-processing

EEGLAB (Delorme et al., 2011) was used for processing EEG data from the on-line phase by applying a high pass filter (cut-off 3 Hz, order 198, Hamming, non-causal) followed by a notch filter (48–52, order 15, FIR least squares, non-causal). The continuous data were epoched into 16 s epochs (8 s rest, followed by 8 s MOV-AO EEG recording) for calibration trials and 10 s epochs (2 s MOV followed by 5 s FES and 3 s rest EEG recording) for the on-line BCI control trials. Noisy trials were removed by visual inspection. On average six trials out of 30 were removed. Resting-state data was processed using a Butterworth bandstop filter (48–52 Hz, order 40) followed by a Butterworth bandpass filter (0.5–40 Hz, order 5). Noisy segments were removed manually after visually inspecting EEG for eyeblinks, muscle artifacts, sharp peaks, bursts, etc.

2.5.2. Normalised on-line powers and activation rate

The average on-line power of successful trials was plotted to demonstrate the use of a threshold switch for FES control. For each subject and session, the normalised on-line power (Pn) was derived using Eq. (2), where P_{RT} and P_c refer to on-line power in the selected frequency band and calibration power, respectively.

$$\boldsymbol{Pn} = \frac{\boldsymbol{P_{RT}}}{\boldsymbol{P_c}} \times 100\% \tag{2}$$

A 1.4 s period of MOV before FES activation was chosen for the purpose of visualisation. The Pn was averaged over all successful runs and across subjects. The activation rate (AR) was calculated as shown in Eq. (3), where N_s and N_T refer to the number of successful trials and total trials, respectively. We did not have any false positives as attempted or executed movement could be observed in each trial and we never saw the FES being activated without a movement.

$$\boldsymbol{AR} = \frac{\boldsymbol{N_S}}{\boldsymbol{N_T}} \times 100\% \tag{3}$$

2.5.3. Event-related desynchronization

An increase of amplitude with respect to baseline is called event-related synchronization (ERS) and a decrease of amplitude is called event-related desynchronization (ERD). Event-related spectral perturbation (ERSP) plots were used to present ERS/ERD simultaneously in different frequencies. The EEGLAB toolbox was used to calculate ERSP (Delorme and Makeig, 2004) using the sinusoidal wavelet method. The baseline period was taken from the rest period between trials at t = 6000 ms to t = 6500 ms. The number of wavelet cycles at the lowest frequency was set to 3, the window size was set to 200 (1 s) and the number of bootstrap repetitions was set to 200. The frequency range used was 2–35 Hz and the bootstrap significance level was set to 0.05.

To visualize time–frequency spectral changes at specific frequencies, values from ERSP plots were averaged in the selected frequency band, giving the ERS/ERD time-series. To quantify ERD during movement for each participant, ERSP values were summed up over the selected frequency band and time (2 s of MOV before FES activation for on-line trials). Positive values, corresponding to ERS were set to 0 (Ang et al., 2015b).

2.5.4. Laterality index

The laterality index (LI) was used to compare which brain hemisphere dominates during a given task in terms of the EEG parameter being considered. The LI for the unimanual (and bimanual) movement was calculated based on subject-level ERD in the selected band, in accordance with Romagosta et al. (Sebastián-Romagosa et al., 2019), as shown by Eq. (4). Symbols C and I refer to the contralateral and ipsilateral hemispheres respectively. The LI spans from -1 to 1, representing complete lateralization towards the ipsilateral or contralateral hemispheres respectively (Belfatto et al., 2018), for the unimanual movements. For bimanual movement, by default the left side (C4) was considered contralateral and the right side (C3) ipsilateral. A review conducted by Seghier (2008) outlined the standard threshold value for concluding contralateral or ipsilateral dominance as 0.2 and -0.2 respectively. The values between 0.2 and -0.2 represented no lateralisation.

$$LI = \frac{ERD_C - ERD_I}{ERD_I + ERD_I} \tag{4}$$

2.5.5. Resting-state EEG analysis

Quantitative EEG measures such as relative power, brain symmetry index, and delta alpha ratio were derived from the resting-state EEG data. The relative power in delta (1–4 Hz), theta (4–7.5 Hz), alpha (7.5–12.5 Hz), and beta (12.5–30 Hz) bands were obtained during the resting state EEG in different states (eyes open (EO) state pre-intervention, EO post-intervention, eyes closed (EC) state pre-intervention and EC state post-intervention) through a Welch periodogram in MATLAB with 2 s window and 50% overlap (Mane et al., 2018).

Brain Symmetry Index (BSI) is a localized measure of asymmetry quantifying the activation imbalance between homologous channel pairs (left vs right) (Mane et al., 2019). It is calculated in the 1–25 Hz frequency band as shown in equation (5).

$$\boldsymbol{BSI} = \frac{1}{25}\sum_{\boldsymbol{i}=1}^{25}\left|\frac{\boldsymbol{C4_i} - \boldsymbol{C3_i}}{\boldsymbol{C4_i} + \boldsymbol{C3_i}}\right| \tag{5}$$

Here, $C4_i$ and $C3_i$ represent the trial averaged PSD from C4 and C3 channels respectively at frequency i = 1,2,…,25. The BSI ranges from 0 to 1, with 0 being defined as perfect symmetry and 1 as maximal asymmetry. Previous studies showed that the BSI value is closer to 0 in healthy people and higher in people affected by stroke (Sebastián-Romagosa et al., 2020).

Delta alpha ratio (DAR) is the ratio of delta (δ) to alpha (α) activity absolute power:

$$\boldsymbol{DAR} = \frac{\delta}{\alpha} \tag{6}$$

To derive DAR, the absolute powers were obtained during the resting state EEG conditions through a Welch periodogram using a 2 s window with 50% overlap. DAR is expected to be higher in people affected by stroke compared to healthy adults (Van Kaam et al., 2018) and in older people compared to younger people (Ishii et al., 2018).

2.5.6. Statistical methods

Owing to the relatively small sample size in each group, most of the variables were not normally distributed, as confirmed by the Shapiro-Wilk test. Therefore, a non-parametric Wilcoxon sign-rank test was used to compare data within each group. For comparing data between groups, a non-parametric Kruskal Wallis Test was used. The significance level was set to p = 0.05 for all tests and the Holm-Bonferroni method was used to correct for multiple comparisons. To facilitate comparison, most parameters were calculated with respect to baseline or normalised.

Effect sizes of significant results were evaluated using Cohen's d, based on Lakens et al., for unpaired and paired t-tests (Lakens, 2013). The effect sizes were interpreted as originally suggested by Cohen and expanded on by Sawilowsky et al.: d (0.01) = very small, d (0.2) = small, d (0.5) = medium, d (0.8) = large, d (1.2) = very large, and d (2.0) = huge (Sawilowsky, 2009). The statistical methods were performed in MATLAB.

3. Results

This section is organised with reference to research hypotheses 1–3, namely differences between uni- and bi-manual movements on (i) BCI-FES control, (ii) short-term priming of resting-state EEG parameters, and (iii) movement-related EEG parameters. The fourth hypothesis, exploring the influence of age and stroke on the aforementioned parameters, will be addressed for each of the first three hypotheses separately.

3.1. Validation of the BCI-FES system

Selected frequency band: The frequency band chosen for on-line BCI control varied between participants. Alpha (8–12) band was chosen in 3/10 participants in ST group, 3/10 in OH group, and 4/10 in YH group. Beta (12–30) band was chosen in 1/10 participants in ST group, 4/10 in OH group, and 3/10 in YH group. The rest of the participants were trained in bands spanning both alpha and beta frequencies.

On-line power: The normalised on-line power in the selected band for unimanual and bimanual tasks during the on-line trials are shown in Fig. 4. The minimum values of power occur during the period just before FES, and remain relatively low during FES, compared to early periods of relaxation. Thus, both sessions have desynchronization during the movement period before FES activation, which is predominantly contralateral for unimanual movements and to the same degree on both sides for bimanual movements.

Activation rates: The unimanual mean ± std activation rates for ST, OH and YH groups were 78.7 ± 12.4%, 76.8 ± 12.1% and 86.7 ± 11.3% respectively, while bimanual activation rates were 71.2 ± 22.1%, 83.5 ± 12.3% and 90 ± 7.4% respectively. The activation rates were not compared between groups as the parameters for control, such as threshold level and threshold time, vary between participants.

***NASA task load index*:** On average, the unimanual session was found to be less mentally demanding than bimanual, although this difference was not statistically significant (ST: p = 0.1367, OH: p = 0.7422 and YH: p = 0.4727). For the ST group, 6 participants reported the bimanual session more difficult than unimanual, while others rated it the same as unimanual. For the OH group, 2 participants reported the unimanual session easier than bimanual, 4 found the bimanual session to be easier and 4 considered both to be the same. In the YH group, 5 participants found the unimanual session easier than bimanual, 1 found bimanual easier and 4 considered both to be the same.

3.2. Effects of short-term BCI-FES priming

Delta alpha ratio: The DAR in different baseline conditions is shown in Fig. 5. In EO state for the unimanual session, DAR

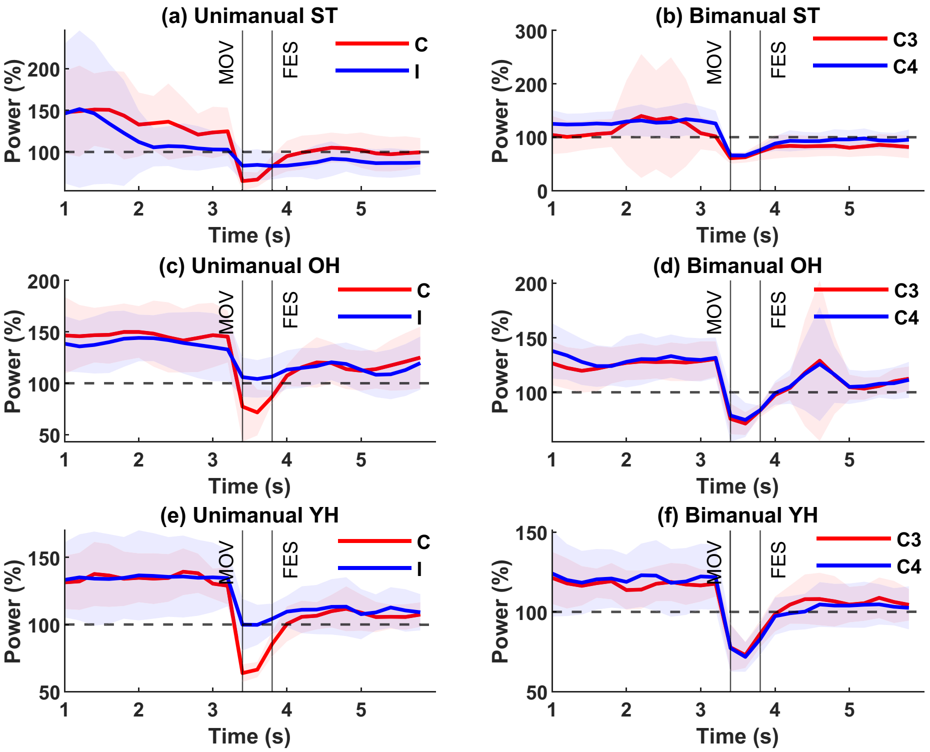

Fig. 4. On-line power from the On-line phase averaged across subjects in a group. ST, OH and YH refer to stroke, older healthy and younger healthy groups. C and I refer to contralateral and ipsilateral sides (lesioned and healthy in ST group). MOV and FES refer to movement and functional electrical stimulation, respectively.

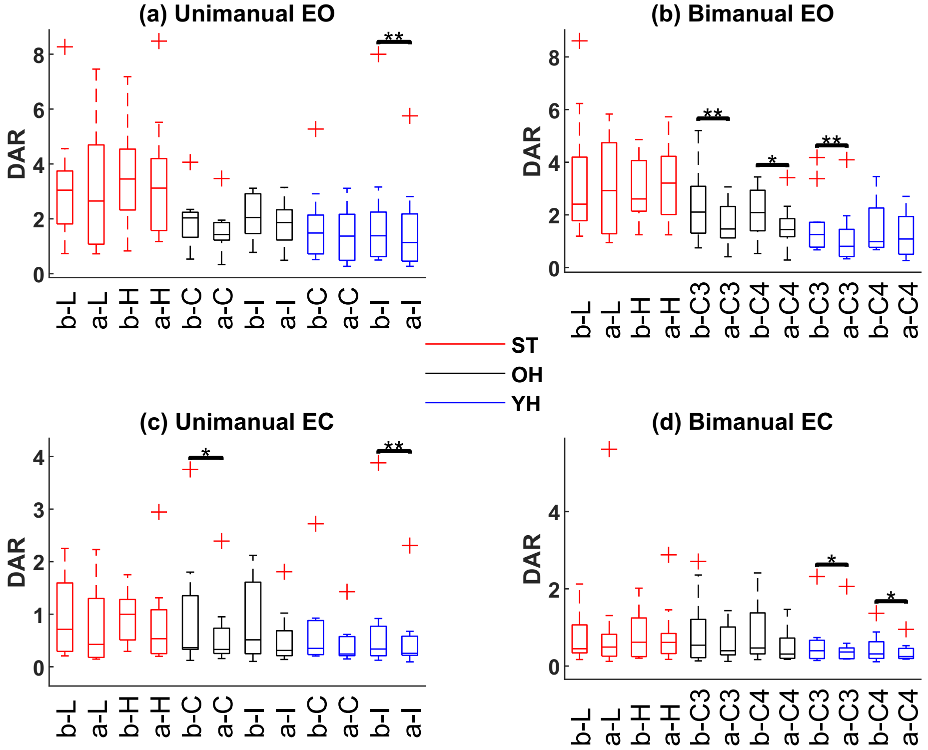

Fig. 5. Resting state delta alpha ratio (DAR) before and after BCI-FES session in eyes open (EO) and eyes closed (EC) state. ST, OH and YH refer to stroke, older healthy and younger healthy groups. L and H stand for lesioned and healthy side for the ST group. C and I stand for contralateral and ipsilateral side in unimanual session for the OH and YH groups. 'b' and 'a' refer to before and after BCI-FES session. * represents $p \leq 0.05$, ** represents $p \leq 0.01$. BCI and FES refer to brain computer interface and functional electrical stimulation, respectively.

decreased post-intervention on the contralateral side ($p = 0.0371$, $d = 0.73$, medium) for OH group, and the contralateral ($p = 0.0273$, $d = 0.53$, medium) and ipsilateral ($p = 0.002$, $d = 0.64$, medium) sides for YH group. After correcting for multiple comparisons, only the DAR change on the ipsilateral side in the YH group was significant. In EC state for the unimanual session, DAR decreased post-intervention on the contralateral (p = 0.0137, d = 0.69, medium) and ipsilateral (p = 0.0371, d = 0.77, medium) sides in OH group as well as the contralateral (p = 0.0273, d = 0.66, medium) and ipsilateral (p = 0.0098, d = 0.53, medium) sides in YH group. After correcting for multiple comparisons, the DAR change on the contralateral side in the OH group and the ipsilateral side in the YH group were significant.

In EO state for the bimanual session, DAR decreased post-intervention at C3 (p = 0.0059, d = 0.87, large) and C4 (p = 0.0371, d = 0.82, large) for OH group, and at C3 (p = 0.002, d = 1.08, large) for YH group. In EC state for the bimanual session, DAR decreased post-intervention at C3 (p = 0.0195, d = 0.80, large) and C4 (p = 0.0176, d = 0.66, medium) for YH group. All results for the bimanual session were significant after correcting for multiple comparisons. The DAR decreased in half of the ST participants.

The changes in delta, theta, alpha, and beta relative powers are shown in Appendix A, Figs. A1–A2 for reference. It is evident that the DAR changes are driven by a decrease in delta and an increase in alpha.

Comparison of DAR between groups: The pre-intervention DAR from both unimanual and bimanual sessions was pooled within each group. Statistical analysis showed no statistically significant difference in DAR between lesioned and healthy sides for the ST group, with p = 0.9679 and p = 0.7782 for EO and EC state respectively. Similarly, no statistically significant difference was found between C3 and C4 in OH (EO: p = 0.5755, EC: p = 0.7089) and YH (EO: p = 0.3905, EC: p = 0.8373) groups. Therefore, the data from hemispheres were pooled within each group and compared using the Kruskal Wallis test. A statistically significant difference was found between groups in EO condition (p = 2.13e-05) and post-hoc tests revealed that DAR was significantly higher for the ST group than the OH (p = 0.0243, d = 1.54, very large) and YH (p = 1.09e-05, d = 1.74, very large) groups. These results were significant after correcting for multiple comparisons.

Brain symmetry index: The BSI in different baseline conditions is shown in Fig. 6. BSI increased post-intervention for unimanual sessions in EC condition (p = 0.0371, d = 0.72, medium), while it decreased for bimanual sessions in EC condition (p = 0.0195, d = 0.84, large) for the OH group. There were no statistically significant changes in BSI in other groups. Although not significant, BSI also decreased in post-bimanual session for the YH group. All BSI results were significant after correcting for multiple comparisons. The BSI decreased post-bimanual session in approximately half of the ST participants.

Comparison of BSI between groups: The pre-intervention BSI from sessions were pooled within each group and compared using the Kruskal Wallis test. A statistically significant difference was found between groups in EO condition (p = 0.0012) and post-hoc tests revealed that BSI was significantly higher in the ST group than the OH (p = 0.0115, d = 0.07, very small) and YH (p = 0.0018, d = 0.13, very small) groups. A statistically significant difference was also found between groups in EC condition (p = 0.0065) and post-hoc tests revealed that BSI was significantly higher in the ST group than the OH (p = 0.0227, d = 0.06, very small) and YH (p = 0.0116, d = 0.12, very small) groups.

3.3. Movement related brain activity during unimanual and bimanual movements

Comparison of ERD between hemispheres: The ERD of the contralateral/affected hemisphere was significantly stronger than the ipsilateral/healthy hemisphere in all groups (p = 0.002 for all) for unimanual movement. The results were significant after correcting for multiple comparisons. There were no statistically significant differences in ERD between affected and healthy hemispheres for bimanual movements in the ST group (p = 0.8457), or between C3 and C4 in OH (p = 0.6953) and YH (p = 0.3750) groups.

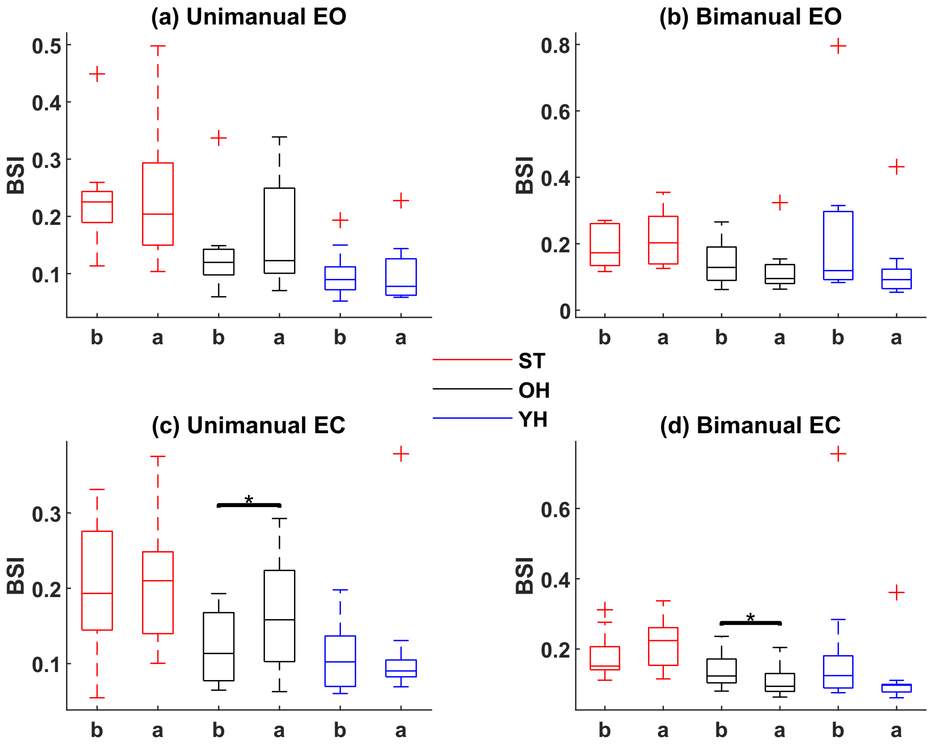

Fig. 6. Resting state brain symmetry index (BSI) before and after BCI-FES session in eyes open (EO) and eyes closed (EC) state. ST, OH and YH refer to stroke, older healthy and younger healthy groups. 'b' and 'a' refer to before and after BCI-FES session. * represents $p \leq 0.05$. BCI and FES refer to brain computer interface and functional electrical stimulation, respectively.

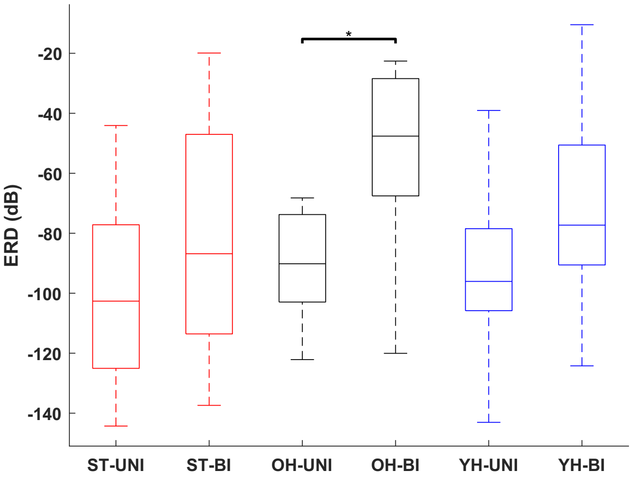

Fig. 7. Event-related desynchronization (ERD) during attempted movement in stroke (ST) and motor execution in older healthy (OH) and younger healthy (YH) group in Unimanual (UNI) and Bimanual (BI) session. * represents $p \leq 0.05$.

Comparison of ERD between movements: When unimanual and bimanual ERD during MOV were compared on the contralateral side (lesioned side for ST group) corresponding to the unimanual session, unimanual ERD was found to be greater for the OH group (p = 0.0137, effect-size = 1.09, large) in the selected band. For the ST and YH groups, there were no statistically significant differences between unimanual and bimanual ERD of the lesioned or contralateral side. ERD values during MOV are illustrated in Fig. 7.

Comparison of ERD between groups: There were no statistically significant differences in ERD between groups. When considering cortical (with subcortical) and subcortical stroke separately, there were still no differences. The p-values values have been provided in Appendix A, in Table A1.

Laterality Index during movement: The average LI values in different conditions and p-values comparing the absolute LI between unimanual and bimanual sessions are presented in Table 2. Unimanual LI shows lateralisation towards the contralateral side in the selected band for most subjects in all three groups. For bimanual sessions, the total ERD was not lateralised towards eitherside in most of the subjects in the selected band during MOV. The absolute value of unimanual LI was found to be significantly greater than bimanual LI in ST (p = 0.0488, d = 0.76, medium), OH (p = 0.0098, d = 1.12, large) and YH (p = 0.002, d = 1.58, very large) groups. These results were significant after correcting for multiple comparisons.

Comparison of laterality index between groups: There was no statistically significant difference in unimanual LI (p = 0.2542) or bimanual LI (p = 0.8103) between groups.

4. Discussion

Most of the BCI-FES systems for rehabilitation of people affected by stroke focus on FES activation of the affected hand only. For everyday functional tasks, however, bimanual movements are used more than unimanual movements (Wolf et al., 2014). By using bimanual BCI-FES post-stroke, bilateral neural coupling mechanisms can be used to enhance and harness the plasticity of the central nervous system (Sleimen-Malkoun et al., 2011). We tested the feasibility of a bimanual BCI-FES system and explored short-term indices of BCI-FES priming. We further compared EEG measured neuronal activity between unimanual and bimanual sessions, as well as between groups of different age and different neurological status.

Our first hypothesis was that it is possible to control a BCI-FES system using bimanual movements. We show that a dual bipolar channel BCI can achieve control of FES for both uni- and bimanual movements with at least a 70% true activation rate, a result comparable to unimanual BCI-FES reported in the literature (Vuckovic et al., 2015, Biasiucci et al., 2018; Frolov et al., 2017; Shu et al., 2018). Furthermore, according to the NASA task load index assessment, bimanual BCI-FES did not come with a significant additional task load and some participants found it easier than unimanual BCI-FES.

Previous studies on healthy volunteers have shown the short-term effects of uni- or bimanual training through changes in motor activity (Nierhaus et al., 2021; Smith and Staines, 2010). In this study, we looked at changes in quantitative resting-state EEG measures as indices of short-term priming. Our second hypothesis stated that both unimanual and bimanual single BCI-FES sessions would lead to short-term changes in the delta alpha ratio and brain symmetry index, both derived from resting-state EEG. We only found changes in these parameters for the healthy groups. The delta alpha ratio decreased after the BCI-FES session in both healthy groups,driven by both an increase in alpha and a decrease in delta band power. Brain symmetry index increased post-intervention for unimanual sessions, while it decreased for bimanual movement in the older healthy group. This is likely because unimanual control involves the contralateral side while bimanual control involves both, resulting in increased symmetry in the latter. Decreases in delta alpha ratio and brain symmetry index are associated with stroke recovery, hence these short-term changes indicate beneficial priming (Finnigan and van Putten, 2013). However, we did not find any significant changes in the stroke cohort for whom such changes would be beneficial, although the delta alpha ratio and brain symmetry index decreased in approximately half of the stroke subjects. It is possible that an injured brain might require longer sessions for inducing short-term changes or that gradual changes may occur based on a cumulative effect in long-term studies (Bentes et al., 2018; Finnigan and van Putten, 2013; Sheorajpanday et al., 2011; Trujillo et al., 2017). Nevertheless, our results indicate that bimanual BCI-FES could be used for conditioning the brain before conventional bimanual hand therapy, causing the desired effect of increased symmetry of cortical activation.

Our third hypothesis stated that movement-related brain activity would be different between unimanual and bimanual movements. In able-bodied people, the amplitude of ERD is stronger for the hemisphere contralateral to the moving limb, due to the intracortical inhibition of the ipsilateral side. This fast inhibition

Table 2
mean ± std of the absolute value of the Laterality Index in the selected frequency band and the number of subjects with lateralisation towards contralateral, ipsilateral, or neither side in unimanual session, and C3, C4 or none of the sides in bimanual session.

Group	UNI	C	I	N	BI	C3	C4	N	p-val
ST	0.46 ± 0.29	9	0	1	0.23 ± 0.20	1	3	6	0.048
OH	0.57 ± 0.26	10	0	0	0.16 ± 0.15	0	3	7	0.009
YH	0.62 ± 0.22	10	0	0	0.22 ± 0.28	0	4	6	0.002

UNI: Unimanual session, BI: Bimanual session, C: Contralateral, I: Ipsilateral, N: None, ST: Stroke, OH: older healthy, YH: younger healthy.

is necessary to suppress mirror movements in the passive hand (Beaulé et al., 2012; Mayston et al., 1999). The amplitude of ERD is of a comparable intensity on both hemispheres during bimanual movements (Deiber et al., 2001; Formaggio et al., 2013; Vuckovic et al., 2018). The amplitude of ERD is proportional to the activation of the corticospinal tract (Rau et al., 2003) or corticomotor excitability (Daly et al., 2018), and is attenuated on the affected side in people with stroke (Pfurtscheller et al., 1980; Stępień et al., 2011). In healthy people, unilateral hand movements are accompanied by a transient decrease in corticospinal excitability of neurons innervating the muscles of the opposite hand via the phenomena of interhemispheric inhibition (Duque et al., 2004). This inhibition is unbalanced in stroke as it decreases from the affected to the healthy hemisphere, but increases from the healthy to the affected hemisphere (Dodd et al., 2017). This reduces the corticomotor excitability of the affected side in stroke for movements involving the affected hand (Murase et al., 2004), ascertained via transcranial magnetic stimulation induced motor evoked potential measurements. However, since ERD is also a measurement of cortical activation (Pfurtscheller, 2003), we believe that ERD could serve as an indirect marker of interhemispheric inhibition.

The analysis of the ERD and laterality index shows that unimanual movements result in predominantly contralateral activity for healthy volunteers, as is expected. We did not find any attenuation of ERD in the stroke group, perhaps because attenuation is inversely related to motor impairment (Hsu et al., 2016; Rossiter et al., 2014), which was mild to moderate in this cohort. For bimanual movements, there were no differences between ERD of left and right hemispheres in healthy groups, or between affected and healthy hemispheres in people with stroke. Owing to increased interhemispheric inhibition in stroke, we would have expected ERD of the affected hemisphere to be reduced, as the healthy hand was also used in bimanual movements. In our stroke cohort, we did not see a reduction of ERD, perhaps because participants did not have a severe stroke and may have been in the process of recovery, which is associated with symmetrical activation during bimanual movements (Brunner et al., 2014).

Unimanual ERD was greater than bimanual ERD in healthy groups. In our previous study (Vučković́ et al., 2018), ERD was stronger during bimanual movements, but was detected by frontocentral electrodes which were not measured in this study. Deiber et al., also found stronger ERD in the alpha band for a bimanual task but attributed that to task difficulty, which was larger than in the current study (Deiber et al., 2001).

In summary, satisfactory performance of bimanual our/the BCI-FES system, changes in quantitative EEG measures in the desired direction, and the absence of ERD attenuation of the affected side during bimanual movements indicate that bimanual BCI-FES is feasible in stroke and could be used as an adjuvant to conventional therapy.

Our fourth hypothesis stated that there would be an effect of age and neurological injury on BCI-FES performance as well as on EEG activity. Chen et al. found that younger adults (18–23 years) have higher BCI accuracy than older healthy adults (56–83 years) (Chen et al., 2018). Activation of motor, sensory and cognitive regions (Goble et al., 2010) increases, and the laterality index decreases with age for imagined but not actual movements (Zich et al., 2015). Results from the literature are inconclusive, reporting stroke participants performing better (Irimia et al., 2018), worse (Ang et al., 2011), or the same (Shu et al., 2018) as healthy participants during unimanual BCI-FES. In this study, both healthy groups had comparable performance. The stroke group had a similar true positive rate as the healthy groups for unimanual BCI-FES, but had worse performance in bimanual control. The older healthy and stroke participants were of comparable age, thus the lower activation rate in stroke participants could be attributed to a decreased level of concentration and injury to the sensory-motor cortex. However, the manual adjustment of activation time and threshold level may have partly contributed to these findings.

The baseline EEG measures of the delta alpha ratio and brain symmetry index were different between groups. The brain symmetry index of the stroke group was significantly higher than the healthy groups. This is in line with previous research indicating higher asymmetry in brain activity occurs in people affected by stroke, with age not affecting brain symmetry index in healthy people (Agius Anastasi et al., 2017; Sebastián-Romagosa et al., 2020). Since bimanual BCI-FES led to a decrease in brain symmetry index, we hypothesise that it could be used in neurorehabilitation to reverse the effect of stroke-induced asymmetry. The delta alpha ratio for the stroke group was significantly higher than the delta alpha ratio of both healthy groups. This is expected as published literature reported increased delta concomitant with decreased alpha activity post-stroke (Doerrfuss et al., 2020; Finnigan et al., 2007), and a higher delta alpha ratio compared to healthy participants (Van Kaam et al., 2018). Although not significant, the older healthy group had a higher delta alpha ratio than the younger group. Therefore, the differences between the stroke and healthy groups could be partially attributed to age, as a reduction in the amplitude of alpha and a global increase of delta are characteristics of aging in very old participants (up to 90 years) (Babiloni et al., 2006; Hartikainen et al., 1992; Ishii et al., 2018). Nevertheless, bimanual and unimanual BCI-FES could be used by people affected by stroke and older populations as a neuromodulatory intervention to reverse an increase in the delta alpha ratio as a result of both ageing and stroke. Depending on the duration of intervention, BCI-FES can be used as a standalone therapy or as a form of priming before the primary therapy (Stoykov et al., 2017).

Future studies should include patients more severely affected by stroke and should explore control strategies that give more weight to affected hemisphere activation to encourage stronger activation of the motor cortex of the affected side.

5. Limitations

The study had a limited sample size per group (n = 10). Furthermore, the stroke cohort was non-homogeneous as the lesion side and location varied between participants, which may influence EEG response (Park et al., 2016). In addition, most of the stroke participants had a mild stroke, as measured by a large FMA score. Nevertheless, most effect sizes were large. The lack of significant short-term effects on resting-state EEG indices in the stroke group could be due to the injury requiring a longer time to prime the brain.

EEG was measured with only two bipolar EEG channels, to minimise discomfort of participants with stroke. While this is a trend in long-term BCI-FES applications for clinical use due to the simple setup (Jovanovic et al., 2021), and was sufficient for the proof of concept, future studies using multichannel EEG would enable source localisation and connectivity analysis to uncover the mechanism underlying short-term changes. The unimanual session used the left hand in 7 and right-hand in 3 participants; in effect, the study compared left hand BCI-FES and bimanual BCI-FES. Future studies should comprise an equal number of participants with left-side and right-side lesions as the lesion side also affects laterality parameters (Liew et al., 2018).

The study was performed in two different countries. While this inevitably makes the environmental noise characteristics different between stroke and healthy groups, the dominant noise in both cases comes from 50 Hz line noise. The same piece of equipment was used at both locations and RK was physically present at all experiments to make sure identical procedures were followed. Furthermore, all the measures derived from EEG were normalised with respect to baseline or ratios.

Another limitation of the study concerns the fixed order of sessions: unimanual followed by bimanual. This may have affected the NASA scores in the bimanual session, as participants already had some experience with controlling BCI. In addition, participants were asked only once, after secondsession, which session they found easier; as the bimanual experience was fresh in their mind, they might have responded in favour of it. The order of sessions was not randomised intentionally, so that participants were unfamiliar with bimanual strategy during unimanual sessions. This was done to avoid unimanual trials where the participant would try to use their unaffected hand to support the affected hand. The training carry-over effect was minimised by doing the bimanual session on a different day.

6. Conclusions

A brain-computer interface controlled by bimanual movement attempts is feasible. Both unimanual and bimanual movements are accompanied by ERD on both hemispheres, even in the lesioned hemisphere of the stroke group. Unimanual and bimanual BCI-FES sessions are accompanied by beneficial short-term priming, but these changes are significant only for healthy participants. A larger and more homogenous sample size is needed to evaluate these changes in people affected by stroke. Quantitative EEG parameters are affected by both age and stroke. We recommend using bimanual BCI-FES as an adjuvant or alternative to unimanual BCI-FES for people who find bimanual movements easier or more intuitive.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A:. Figures and tables

(See Figs. A1–A2 and Table A1).

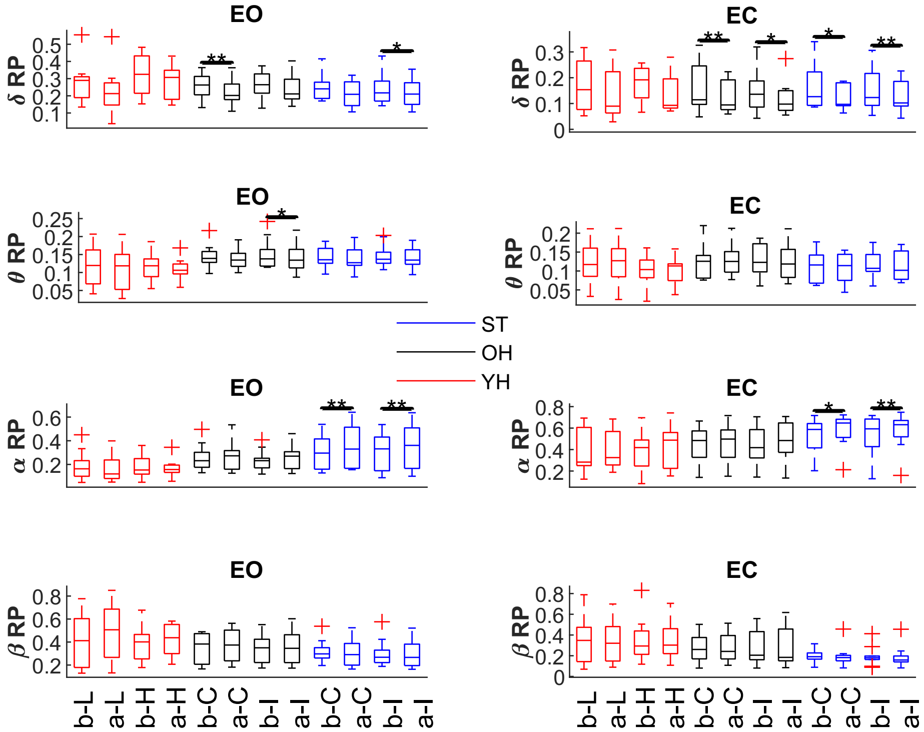

Fig. A1. Resting state relative powers before (b) and after (a) unimanual BCI-FES session in eyes open (EO) and eyes closed (EC) state. ST, OH and YH refer to stroke, older healthy and younger healthy groups. L and H stand for lesioned and healthy side for the ST group. C and I stand for contralateral and ipsilateral side in unimanual session for the OH and YH groups. The symbols δ, θ, α and β represent relative power (RP) in delta, theta, alpha and beta bands, respectively. BCI and FES refer to brain computer interface and functional electrical stimulation, respectively. * represents $p \le 0.05$, ** represents $p \le 0.01$. The p-values have not been corrected for multiple comparisons.

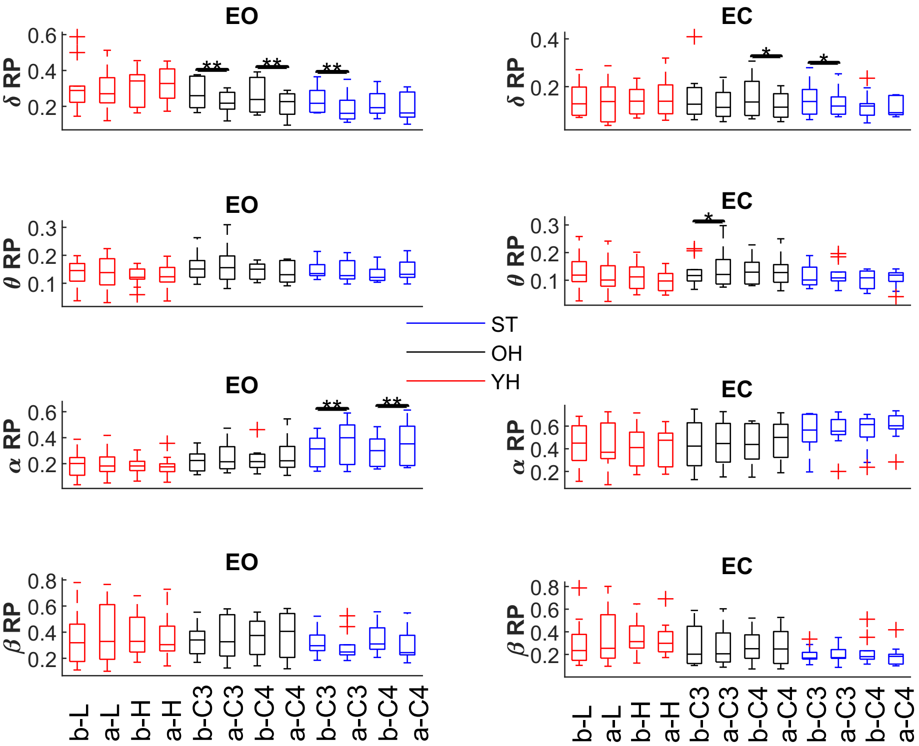

Fig. A2. Resting state relative powers before (b) and after (a) bimanual BCI-FES session in eyes open (EO) and eyes closed (EC) state. ST, OH and YH refer to stroke, older healthy and younger healthy groups. L and H stand for lesioned and healthy side for the ST group. The symbols δ, θ, α and β represent relative power (RP) in delta, theta, alpha and beta bands, respectively. BCI and FES refer to brain computer interface and functional electrical stimulation, respectively. * represents $p \leq 0.05$, ** represents $p \leq 0.01$. The p-values have not been corrected for multiple comparisons.

Table A1
p-values for comparison of event-related desynchronization (ERD) between groups. The column represents the sides that were compared, and the row represents whether the ERD data from the entire stroke cohort, only cortical stroke, or only subcortical stroke was used.

p-value	contralateral ST, OH, YH	lesioned ST, C3 OH, C3 YH	lesioned ST, C4 OH, C4 YH	healthy ST, C3 OH, C3 YH	healthy ST, C4 OH, C4 YH
All	0.5976	0.1935	0.3622	0.2498	0.3503
Cortical	0.5289	0.3530	0.4605	0.3787	0.4250
Subcortical	0.7047	0.5097	0.6730	0.6300	0.7047

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