Restoring of Interhemispheric Symmetry in Patients With Stroke Following Bilateral or Unilateral Robot-Assisted Upper-Limb Rehabilitation: A Pilot Randomized Controlled Trial

M. C. Mauro, A. Fasano, M. Germanotta, L. Cortellini, S. Insalaco, A. Pavan,
A. Comanducci, E. Guglielmelli, *Senior Member, IEEE*, and I. G. Aprile

***Abstract*—Bilateral robotic rehabilitation has proven helpful in the recovery of upper limb motor function in patients with stroke, but its effects on the cortical reorganization mechanisms underlying recovery are still unclear. This pilot Randomized Controlled Trial (RCT) aimed to evaluate the effects on the interhemispheric balance of unilateral or bilateral robotic treatments in patients with subacute stroke, using Quantitative Electroencephalography (qEEG). 19 patients with ischemic stroke underwent a 30-session upper limb neurorehabilitation intervention using a bilateral upper limb exoskeleton. Each patient was randomly assigned to the bilateral (BG, n=10) or unilateral treatment group (UG, n=9). EEG evaluations were performed before (T0) and right after (T0+) the first treatment session, after 30 treatment sessions (T1), and at 1-week follow-up (T2), in both eyes open and eyes closed conditions. From the acquired EEG data, the pairwise-derived Brain Symmetry Index (pdBSI) was computed. In addition, clinical evaluation was performed at T0 and T1 with validated clinical scales. After the treatment, a significant improvement in clinical and EEG evaluations was observed for both groups, but only the BG showed reduced pdBSI in delta and theta bands. In the cluster of sensorimotor channels, there was no significant difference between groups. The observed changes were not maintained at follow-up. No significant changes were observed in the pdBSI after a single rehabilitation session. Results suggest that balancing of interhemispheric symmetry comes along with a clinical improvement in the upper extremity and that the pdBSI can be used to investigate the mechanisms of neuronal plasticity involved in robotic rehabilitation after stroke.**

***Index Terms*—Stroke, quantitative electroencephalography (qEEG), robotics, rehabilitation, interhemispheric balance, brain symmetry index (BSI).**

I. INTRODUCTION

STROKE is the world's second leading cause of death and the leading cause of disability in adults, responsible for approximately 11% of total deaths in 2019, as reported by the World Health Organization (WHO) [1]. It has been estimated that 15% to 30% of all stroke survivors are significantly disabled due to a neurological impairment involving force, motion, sensory perception, and sensory-motor integration [2]. Stroke causes severe motor deficits particularly in the upper limb (UL), resulting in the loss of independence and causing major deteriorations in the quality of life [3].

Many therapeutic interventions have been proposed in rehabilitation settings to promote functional recovery after stroke. Traditional treatment, such as voluntary exercises performed by the therapist, has been demonstrated to promote functional recovery by reorganizing the motor cortex [4].

Several studies have shown that the quantity, duration, and intensity of training sessions are key variables in relearning motor skills and modifying the underlying neural architecture [5]. In this view, the use of robot-mediated therapies is

---

Received 11 April 2024; revised 9 August 2024; accepted 10 September 2024. Date of publication 13 September 2024; date of current version 27 September 2024. This work was supported in part by Italian Ministry of Research, through the complementary actions to the National Recovery and Resilience Plan (NRRP) "Fit4MedRob-Fit for Medical Robotics" under Grant PNC0000007; and in part by #NEXTGENERATIONEU (NGEU) and funded by the Ministry of University and Research (MUR), NRRP, project MNESYS under Grant PE0000006—A Multiscale integrated approach to the study of the nervous system in health and disease (DN. 1553 11.10.2022). Clinical Trial Registration: NCT05176600. *(M. C. Mauro and A. Fasano are co-first authors.) (Corresponding author: A. Fasano.)*

This work involved human subjects or animals in its research. Approval of all ethical and experimental procedures and protocols was granted by the Committee of Lazio 1 (609/CE Lazio 1), and performed in line with the Declaration of Helsinki.

M. C. Mauro, A. Fasano, M. Germanotta, L. Cortellini, S. Insalaco, A. Pavan, and I. G. Aprile are with IRCCS Fondazione Don Carlo Gnocchi ONLUS, 50143 Florence, Italy (e-mail: afasano@dongnocchi.it).

A. Comanducci is with IRCCS Fondazione Don Carlo Gnocchi ONLUS, 20148 Milan, Italy.

E. Guglielmelli is with the Department of Engineering, Università Campus Bio-Medico di Roma, 00128 Rome, Italy.

This article has supplementary downloadable material available at https://doi.org/10.1109/TNSRE.2024.3460485, provided by the authors.

Digital Object Identifier 10.1109/TNSRE.2024.3460485

becoming increasingly popular since robotic systems allow to increase the amount and intensity of the therapy and to standardize the treatment [6]. Furthermore, the presence of sensory feedback, such as visual and auditory stimuli, and the repetition of movement stimulate processes of brain plasticity and improve the rehabilitation outcome [7].

Interestingly, post-stroke brain alterations affect the balance between the two cerebral hemispheres [8], whose interactions are crucial in the execution of unilateral and bilateral movements [9], [10]. After a stroke, patients show abnormally high, and severity-dependent, activation in the contralesional sensorimotor network during movement of the affected hand [11]. Motor recovery from stroke would involve a reversal trend toward the ipsilesional motor area through an increased cortical activation in the affected primary sensorimotor cortex and a decrement in the unaffected one [8]. This shift restores the correct balance in activations between the brain hemispheres.

Recent studies have shown promising results on the effectiveness of treatment involving both ULs (bilateral practice) in patients with stroke [12], allowing activation in both hemispheres and inducing reorganization of neural networks [12], [13], [14]. In particular, Cauraugh et al. [15] and Stinear et al. [16] suggested that bilateral practice with the paretic and non-paretic limbs facilitates activation of the damaged hemisphere through improved control of interhemispheric inhibition, which is associated with the control of bimanual task performances.

In this context, robotic therapy by means of devices such as bilateral exoskeletons or end-effectors (e.g., Bi-Manu-Track [17] and Driver SEAT [18]) provides the possibility of movements of both the paretic and non-paretic limbs with multiple motion patterns. Preliminary clinical results indicate that bilateral robotic rehabilitation in patients with stroke can improve the range of motion, strength, or physical function of the UL, but clinical evidence remains inconclusive [19].

Few studies have investigated the effects of bilateral robotic therapy on cortical reorganization in patients with stroke. Recently, Tang et al. [20] evaluated the effect of bilateral robot-assisted training on functional recovery in patients with stroke in terms of cortical activity and connectivity, comparing the bilateral robotic treatment with the conventional one. They showed that post-stroke bilateral robotic treatment increases functional connectivity in motor related cortical areas. However, to the best of our knowledge, there are no studies in the literature comparing the effects, in terms of brain reorganization, induced by the unilateral and bilateral UL treatments by employing the same robotic device for both approaches.

To fill this gap, our study aimed to analyze the clinical and neurophysiological outcomes, in terms of interhemispheric balance measured using quantitative electroencephalography (qEEG) metrics, of unilateral and bilateral robotic treatments in patients with stroke. Our main hypothesis was that robotic upper limb treatment, whether unilateral or bilateral, would lead to significant improvement in the interhemispheric symmetry, as measured by the Brain Symmetry Index. Our exploratory hypothesis was that different robotic treatments (unilateral and bilateral) would lead to different effects in terms of interhemispheric balancing, along with different clinical improvements.

II. MATERIALS AND METHODS

A. Study Design and Participants

The study is a pilot randomized controlled trial (RCT), aimed to compare bilateral and unilateral upper limb robotic rehabilitation in patients with stroke. Patients were enrolled at the Santa Maria Della Provvidenza Centre of Fondazione Don Carlo Gnocchi ONLUS, in Rome between January 2022 and November 2022.

We recruited consecutive subjects with stroke (verified by MRI or CT). Eligibility criteria included: (1) age between 18 and 85 years; (2) ischemic type lesion; (3) first cortical and supratentorial event; (4) moderate upper extremity motor deficit (evaluated by Fugl-Meyer Assessment for Upper Extremity score between 29 and 42) [22]; (5) time since the acute events between 1 month and 6 months; (6) Trunk Control Test score greater than or equal to 48. Exclusion criteria were: (1) significant medical comorbidity (severe neurological disease, cardiovascular disease, diabetes/unstable hypertension); (2) cognitive impairment that prevents comprehension of administered exercises; (3) inability or unwillingness to provide informed consent.

The trial was approved by the Ethics Committee of Lazio 1 (609/CE Lazio 1) and registered at ClinicalTrials.gov with identifier number NCT05176600. All participants gave their written informed consent according to the Declaration of Helsinki.

B. Intervention

Eligible subjects underwent a 30-session upper-limb neurorehabilitation program, using the Arm Light Exoskeleton Rehab Station (ALEx RS, Wearable Robotics Srl). Each rehabilitation session lasted 45 minutes, with a frequency of 5 times a week. Each patient was randomly assigned to either the unilateral treatment group (UG) or the bilateral treatment group (BG).

For all patients, the schedule of the treatment session included: the first 5 minutes and the last 5 minutes of the training dedicated to exercises of shoulder abduction-adduction, shoulder intra-rotation and extra-rotation, shoulder flexion-extension, and elbow flexion-extension (60 repetitions in the first 5 minutes and 60 repetitions in the final 5 minutes of each session); 30 minutes during which the patient engaged in goal-oriented tasks through the system's exergames, with task duration dependent on the functional aim of the exergame and on the patient's performance; a total of 5 minutes allocated for the set-up and closure of the system. Regarding the initial and final mobilization exercises, in the UG, the sequence of movements was performed passively by the patient under the full guidance of the physical therapist. In the BG, the patient used the unaffected limb to perform the movements, replicating the movements of the therapist that was in front of him/her. These movements were detected by the machine's built-in sensors and reproduced in real time on the affected limb.

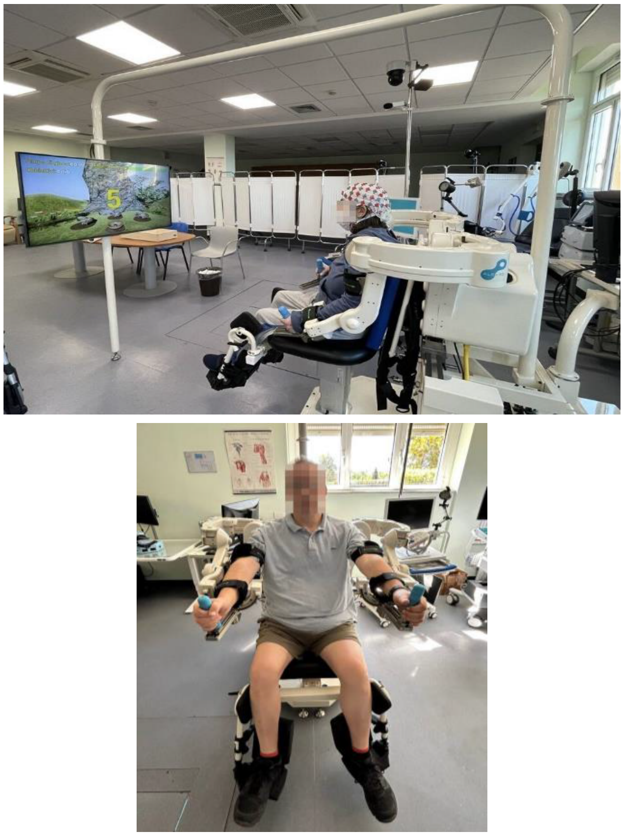

Fig. 1. Arm Light Exoskeleton Rehab Station (ALEx RS). Lateral (top) and frontal view (bottom).

In addition to the UL robotic rehabilitation session according to the allocated group, all subjects underwent conventional rehabilitation sessions (6 times/week), lasting 45 minutes, focused on lower limbs, sitting and standing training, balance, and walking. Subjects underwent occupational and speech therapy, if needed.

The randomization sequence was generated by using the R (version 3.3.0, R Core Team, Vienna, Austria) package *blockrand*, with random block sizes ranging from 2 to 8. Randomization was stratified according to age (younger, $<$ 65 years; older, $\geq$ 65 years), to ensure that the subjects' numbers and characteristics in each group were closely matched. The randomization list was prepared by an investigator with no clinical role in the study. Due to the nature of the interventions, it was not possible to blind participants or treating therapists to treatment allocation.

C. Robotic Treatment

The robotic sessions were performed with the UL exoskeleton ALEx RS (Fig. 1), consisting of two independent and symmetrical exoskeletons, one for the right UL and the other for the left UL. The two exoskeletons can be used simultaneously (bilateral configuration) or individually (unilateral configuration), depending on the treatment to be administered to the specific patient. The device provides several exergames in Virtual Reality (VR) that can be selected by the operator according to the needs of the patient. The exercises are of various types and are intended to stimulate the patient's concentration, thus helping the patient carry out cognitive as well as motor rehabilitation. Exercises include reaching, moving objects, coordination, reflex speed, association, concentration and attention, and trajectory tracking.

The therapist can select, through the machine's graphical interface, different parameters to customize each rehabilitative session according to the patient's characteristics. Among these, the "arm weight compensation" is the level of weight relief (total or partial) of the patient's arm attached to the exoskeleton. When activated by the operator on the graphical interface, the exoskeleton applies additional constant vertical forces on the patient's arm suitable for supporting the patient. Arm weight compensation allows for a greater range of active movements that the patient can achieve during treatment, and a reduction of pain during movements. Moreover, the device is a robotic system provided with an automatic support that assists the patient in reaching the target in case he/she is unable to perform or complete the movement in a given time. The parameter of "assistance level" (minimum, medium, maximum) was adjusted by the therapist via the graphical interface whenever the patient had limited mobility in the initial sessions of the training. The level of arm compensation and movement assistance were modulated, for both treatment groups, on the severity of the patient's motor deficit and progressively reduced based on the progress made.

Both groups performed rehabilitation treatments in the presence of a physical therapist and an engineer.

D. Unilateral Treatment

With reference to the unilateral treatment group, the exergames used in the different sessions involved:

- Exergames with 3D-reaching tasks on the frontal and sagittal plane. The exercise consists of reaching the targets appearing on the screen randomly or in a predetermined order.
- Exergames involving both reaching and pick-and-lift tasks on the frontal and horizontal plane. During the task, the patient receives visual feedback on the movement performed, represented by a marker on the screen following the patient's movements.
- Exergames involving tracking tasks on the frontal plane. During the task, the patient is required to perform a coordinated and precise movement to follow trajectories with different shapes appearing on the screen.

The goal of these exergames was to focus treatment on the affected limb, improving proprioception and visual-motor abilities, specifically targeting visual-spatial exploration, oculo-manual coordination and memory. Several options were used to customize the treatment: (i) difficulty levels, i.e., number of objects to be moved or the available time to complete the required task; (ii) arm weight compensation, as defined above; (iii) movement amplification scale, i.e., the ability of the system to amplify the movement excursion of the patient in the virtual environment; (iv) object grip level, i.e., the force required to grab the object and hold it; (v) interaction force, i.e., the weight of each object being moved; (vi) movement assistance level, as defined above. More details about the exergames and treatment protocol in the UG can be found in the supplementary material (Appendix "*Treatment Protocol*").

E. Bilateral Treatment

The bilateral treatment consisted of bimanual tasks where both limbs perform the same movements (symmetrical exergames) or different movements (asymmetrical exergames). The bilateral exercises included:

- Exergames of 3D-reaching tasks with visual feedback on the frontal and sagittal plane that are asymmetrical and asynchronous and do not involve the simultaneous use of both limbs (e.g., reach a glowing circle when it lights up, by moving the limb whose associated marker's color corresponds to the color of the target circle).
- Exergames requiring synchronous movements of both limbs of symmetrical type (e.g., move and position a virtual tray) or asymmetrical type (e.g., navigation in a labyrinth).
- Complex tasks with asymmetrical and asynchronous movement sequences (e.g., cooking or archery) administered at the end of treatment. These exercises are the most complex in terms of both motor and cognitive aspects.

The goal of these exergames, beyond the proprioception, visual-motor abilities, visual-spatial exploration, oculo-manual coordination and memory, was to focus on enhancing upper limbs cooperation ability, thereby improving coordination and procedural memory in performing bimanual tasks. As in the UG, to customize these exercises, the difficulty level, movement amplification scale, assistance level and arm weight compensation parameters were modulated by therapists. More details about the exergames and treatment protocol in the BG can be found in the supplementary material (Appendix "*Treatment Protocol*").

F. EEG Assessment

Both groups of patients underwent a high-density EEG (HD-EEG) recording. The EEG data were collected using a 64-channel HD-EEG system (HD TruScan EEG; DEYMED Diagnostic) with a sampling frequency of 3 kHz. The signals were acquired using a cap with 64 Ag/AgCl scalp monopolar electrodes placed according to the International 10/20 montage. Contact impedance was kept below 5KΩ. Data was exported in EDF format for further analysis.

Recordings were executed at the following time points: before (T0) and right after (T0+) the beginning of the first rehabilitation session, the day after the end of 30 treatment sessions (T1), and 1-week follow-up (T2). The neurophysiological assessment right after the beginning of the first rehabilitation session (T0+) was conducted to evaluate the short-term effects of treatment, i.e., to investigate possible immediate brain changes underlying the motor recovery processes. The neurophysiological assessment at 1-week follow-up (T2) was conducted to investigate whether the neurophysiological changes remained stable over a short-term period of one week.

Resting state EEG recordings were performed for 10 minutes with eyes open and 10 minutes with eyes closed, with the subject relaxed and in a comfortable supine position.

1) EEG Signal Processing:

Signal processing and analyses were performed offline using MATLAB (Mathworks, Natick, MA, USA) with custom scripts based on the EEGLAB toolbox [23]. Sampled EEG data were imported into the software from EDF format with acquisition reference and additional information regarding the channel location was added to the EEG structure. Single bad channels were removed by visual inspection and successively interpolated (nearest neighbor). Data were resampled at 1 kHz and filtered with an IIR high-pass (5th order Butterworth filter with a 0.5 Hz cut-off) and a notch filter centered at 50 Hz. Data were then re-referenced to average reference. Independent Component Analysis (ICA) [24] was performed using the logistic infomax ICA algorithm, implemented in EEGLAB, to discriminate non-cerebral signal sources. The ICA decomposition was guided by automated rejection methods and supervised by an expert user via visual inspection. Indeed, only components with clear ocular and muscle artifacts were rejected by visual inspection of the component's topography, time-frequency, and time series. Spectral power for each channel's signal was calculated by Fast Fourier Transform (FFT) over the 1–25 Hz frequency range. Power Spectral Density (PSD) was computed using Welch's method (2 s window, 50% overlap).

Data analysis was performed by an investigator with no clinical role in the study and blinded to the randomization groups.

2) Brain Symmetry Index:

Subsequently, the pairwise-derived Brain Symmetry Index (pdBSI) was estimated for each processed EEG channel. This index estimates the asymmetry along homologous channel pairs (right and left), ranging from zero (perfect symmetry for all channels) to one (maximal asymmetry) [25]. Previous studies have shown that its value is closer to zero in healthy people and higher in people affected by stroke [26]. The pdBSI was defined as the absolute value of the relative difference of the average spectral density of the right and left hemispheres in the frequency range from 1 to 25 Hz [21], [27]:

$$\mathrm{pdBSI} = \frac{1}{\mathrm{NM}} \sum_{\mathrm{j=1}}^{\mathrm{M}} \sum_{\mathrm{i=1}}^{\mathrm{N}} \left| \frac{\mathrm{R_{ij}} - \mathrm{L_{ij}}}{\mathrm{R_{ij}} + \mathrm{L_{ij}}} \right| \tag{1}$$

With R_{ij} and L_{ij} being the FFT-based PSD obtained from a right and, respectively, left channel of a homologous channel pair (with $\mathrm{i} = 1, 2, \ldots, \mathrm{M}$, with M the number of channel pairs, i.e., M=32) at frequency j (with $\mathrm{j} = 1, 2, \ldots, \mathrm{N}$, with N the number of FFT coefficients). pdBSI was calculated for all the timepoints of evaluation (T0, T0+, T1, T2) in the frequency ranges (N): 1-4 Hz (delta), 4-8 Hz (theta), 8-12.5 Hz (alpha), 12.5-25 Hz (beta), 1-25 Hz.

An additional analysis was conducted to investigate the effect of the robotic treatments in the sensorimotor area. The pdBSI was computed in the sensorimotor cluster of channels: (i) C4, CP4, P4, C2, CP2, P2 (for the right hemisphere); (ii) C3, CP3, P3, C1, CP1, P1 (for the left hemisphere). In particular, this analysis was performed computing the pdBSI in the range 1-25 Hz as well as in the individual frequency bands.

G. Clinical Assessment

Clinical evaluations were performed by a physical therapist at baseline (T0) and after 30 sessions of treatment (T1) using the following scales: (i) the Fugl-Meyer Assessment for upper extremity (FMA-UE) [22]; (ii) the Action Research Arm Test (ARAT) [28]; (iii) the Motricity Index (MI) [29]; (iv) the Modified Ashworth Scale (MAS) [30]; (v) the Wolf Motor Function Test (WMFT) [31]. The evaluators who performed the clinical assessment were blinded to the treatment assignment.

The FMA is a stroke-specific, performance-based impairment scale, belonging to the body function domain of the ICF model. In this study, the motor and the sensation domains of the upper extremity subsection were administered (FMA-UE motor, range: 0-66, 66 = no motor deficits; FMA-UE sensation, range: 0-12, 12 = no light touch and position deficits). The ARAT assesses UL function using observational methods and consists of 19 items organized in 4 sections: Grasp, Grip, Pinch, and Gross movements. The performance of each task is scored on a 4-point ordinal scale (0 = unable to complete any part of the task, 1 = the task is only partially completed, 2 = the task is completed but with great difficulty and/or in an abnormally long time, and 3 = the movement is performed normally). The maximum ARAT score is 57 points, which means a normal UL function. The MI of the upper extremity was performed in order to provide information on the upper limb strength. The test includes shoulder abduction, elbow flexion, pinch grip and the final score ranges from 0 (no movement) to 100 (normal strength). The MAS is an ordinal scale used for grading the resistance encountered during passive muscle stretching, ranging from 0 (normal muscle tone) up to 4 (limb rigid in flexion or extension). In this study, shoulder (abduction and intrarotation), elbow, and wrist joints were assessed. The WMFT quantifies the upper extremity motor ability through timed and functional tasks. It uses a 6-point ordinal scale ("0" = "does not attempt with the involved arm", to "5" = "arm does participate; movement appears to be normal"). The maximum score is 75; lower scores are indicative of lower functioning levels.

H. Subjective Evaluations

The subjective evaluation of device usability was assessed by administering at the end of the 30-session upper-limb neurorehabilitation program the System Usability Scale [32], which is a questionnaire consisting of 10 questions whose answers are structured on a Likert scale with five response options (from strongly agree to strongly disagree), and a total score ranging from 0 to 100. Satisfaction with the treatment was assessed by asking patients to score on a 0-10 Likert scale the question: "Overall, how satisfied are you with the robotic treatment performed?".

I. Statistical Analysis

The statistical analysis was performed to evaluate the changes in motor performance and brain interhemispheric symmetry induced by the rehabilitation treatment.

Normal data distribution was confirmed by means of Q-Q plot visual inspection.

To compare pdBSI values at T0 between treatment groups, independent samples Student's t-test was performed in eyes open and eyes closed conditions, separately.

To compare neurophysiological data, a mixed Analysis of Variance (ANOVA) test was conducted, considering time (3 levels: T0 vs. T1 vs. T2) as a within-group factor (with Bonferroni correction for multiple comparisons), and group (2 levels: unilateral vs. bilateral) as a between-group factor. This analysis was conducted to compare pdBSI values: (i) in the 1-25 Hz frequency range, for all channel pairs; (ii) in each frequency band separately, for all channel pairs; (iii) in the 1-25 Hz frequency range, for the sensorimotor clusters; (iv) in each frequency band separately, for the sensorimotor clusters.

The analysis was performed considering eyes open (EO) and eyes closed (EC) conditions, separately. Mauchly's test was used to confirm sphericity, while homoscedasticity was assessed through the Levene's test.

With respect to clinical data, a mixed ANOVA test was conducted, considering the time (2 levels: T0 vs. T1) as a within-group factor, and group (2 levels: unilateral vs. bilateral) as a between-group factor. Moreover, an explorative analysis was conducted to evaluate the short-term effects of treatment, i.e., after one 45 minutes-session, by means of a mixed ANOVA test performed on the pdBSI in the range 1-25 Hz, considering the time (2 levels: T0 vs. T0+) as a within-group factor, and group (2 levels: unilateral vs. bilateral) as a between-group factor. Finally, subjective evaluation of usability and satisfaction were compared between the two groups, by means of the Mann-Whitney U test.

For all the analyses, a p-value lower than 0.05 was considered as significant. Statistical analysis was performed using the SPSS Statistics software (version 28, IBM Corp., Armonk, NY, USA). Statistical analysis was performed by an investigator with no clinical role in the study and blinded to the randomization groups.

III. RESULT

A. Sample

87 patients were assessed for eligibility. Of them, 64 were excluded because of the inclusion criteria, 1 declined to participate and 3 for other reasons not related to the study. 19 patients, who matched the inclusion criteria and signed informed consent, were then randomized to the UG (n=10) or BG (n=9) treatment groups. Of those, one patient of the UG performed less than 30 treatment sessions for reasons unrelated to the study and did not undergo the T1 and T2 evaluations. Therefore, 18 patients (UG, n=9; BG, n=9) were evaluated at T1 and T2 and considered for the analysis. Fig. 2 shows the flowchart of the trial (CONSORT diagram). The baseline characteristics of the two treatment groups (UG vs. BG) are summarized in TABLE I. The baseline values were compared between groups by means of Mann-Whitney U test and Chi-squared test, respectively for numeric and categorical variables. The two groups were comparable in terms of age, sex, time from onset to randomization, index stroke location, affected side, dominant side and clinical scores.

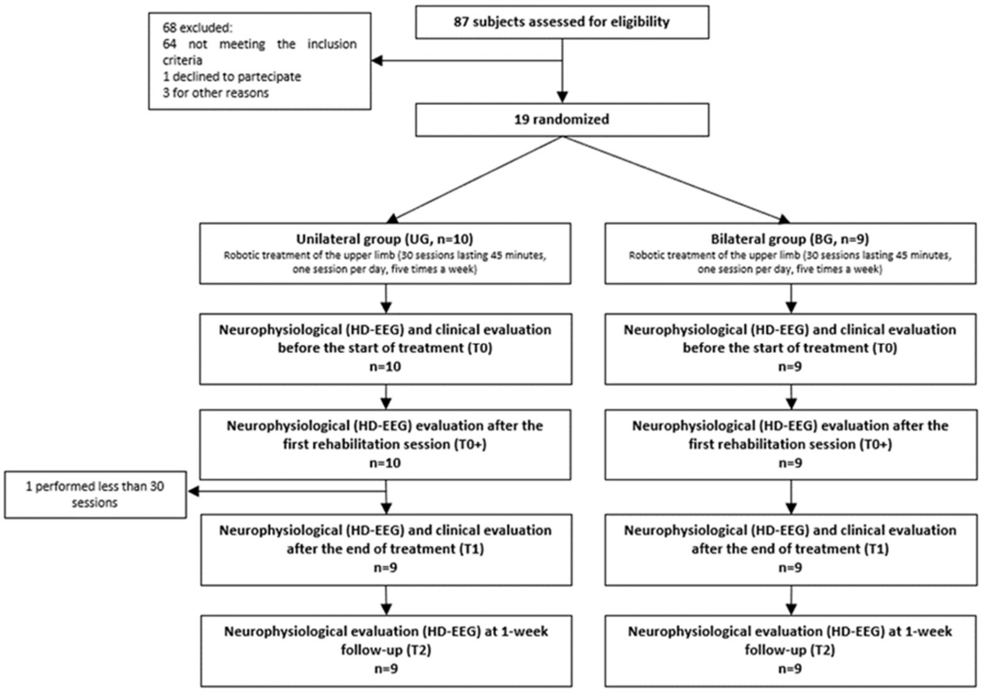

Fig. 2. CONSORT diagram.

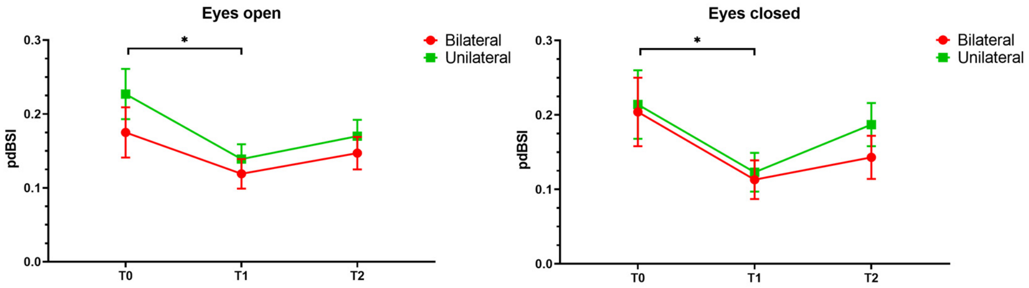

Fig. 3. Pairwise-derived Brain Symmetry Index (pdBSI) in the two conditions (eyes open and eyes closed), at enrolment (T0), at the end of 30 treatment sessions (T1) and follow-up (T2) for the two groups, separately, along with the results of statistical analysis (*: $P<0.05$).

Mauchly's tests indicated that the assumption of sphericity has been confirmed for all the data samples, except for the pdBSI computed in the sensorimotor cluster for the 1-25 Hz range, in the eyes closed condition, for which the correction of Greenhouse-Geisser has been considered. Levene's tests indicated that the assumption of homogeneity of variances has been met for all the data samples.

B. Neurophysiological Evaluation

The independent samples Student's t-test showed that the pdBSI at baseline (T0) was not significantly different between UG and BG (EO: $P = 0.303$; EC: $P = 0.879$).

1) pdBSI in 1-25 Hz for All Channel Pairs: With respect to the pdBSI computed in the 1-25 Hz range for all channel pairs, the results of the mixed ANOVA test showed that the interaction factor *timeXgroup* was always not significant. The main effect time was statistically significant in both EC ($P = 0.014$) and EO ($P = 0.018$) conditions. The post-hoc tests showed that in both conditions the pdBSI at T1 was statistically different from the pdBSI at T0 (EC: $P = 0.010$, EO: $P = 0.006$), also after Bonferroni correction for multiple comparisons (EC: $P = 0.030$, EO: $P = 0.017$). On the contrary, no differences between the T2 evaluation and the other time points were detected. Data are also depicted in Fig. 3.

In the explorative analysis (TABLE II), performed to investigate the short-term effect of the robotic treatment on brain activity, i.e., right after the first rehabilitation session, we found that neither the interaction factor nor the main effect time were statistically significant in the two analyzed conditions, EC ($P = 0.08$) and EO ($P = 0.167$).

2) pdBSI in Frequency Bands for All Channel Pairs: With respect to the pdBSI evaluated in the delta frequency band for all channel pairs, the results of the mixed ANOVA test showed that the interaction factor *timeXgroup* was significant in EC condition ($P = 0.003$), but not in EO condition. The main effect time was statistically significant, in EC condition ($P = 0.001$), but not in EO condition. The post-hoc tests showed that in EC condition, the pdBSI at T1 was statistically different from the pdBSI at T0 in the BG ($P = 0.023$, after Bonferroni correction for multiple comparisons), the pdBSI

TABLE I

BASELINE CHARACTERISTIC OF THE SAMPLE. DATA ARE MEAN (SD) OR N (%). P-VALUES REFER TO MANN-WHITNEY U TEST AND CHI-SQUARED

Characteristics	**Unilateral group (n=10)**	**Bilateral group (n=9)**	***p-value***
Age, years	*68.9 (14.7)*	*70.2 (4.9)*	*0.447*
Sex			*0.498*
Men	*6 (60%)*	*4 (44.4%)*	
Women	*4 (40%)*	*5 (55.5%)*	
Index stroke location (ischemic stroke)			*0.449*
Lacunar stroke	*0 (0.0%)*	*1 (11.1%)*	
Partial anterior circulation stroke	*8 (80%)*	*5 (55.5%)*	
Total anterior circulation stroke	*2 (20%)*	*2 (22.2%)*	
Posterior circulation stroke	*0 (0.0%)*	*1 (11.1%)*	
Affected side			*0.764*
Right	*6 (60%)*	*6 (66.6%)*	
Left	*4 (40%)*	*3 (33.3%)*	
Dominant side			
Right	*9 (90%)*	*9 (100%)*	*0.329*
Left	*1 (10%)*	*0 (0%)*	
Days from index stroke to enrolment	*107.6 (49.3)*	*93.5 (42.6)*	*0.604*
Body function			*1.000*
Fugl-Meyer Upper Extremity Motor Function Score (0-66)	*35.2 (22.6)*	*36.3 (13.9)*	
Fugl-Meyer Sensory Function	*7.7 (3.9)*	*8.4 (3.9)*	
Motricity Index Upper Limb (0-100)	*56.2 (31.1)*	*64.6 (16.7)*	*0.604*
Modified Ashworth Scale (0-4)			
Shoulder abduction	*0.6 (1.0)*	*0.6 (0.7)*	*0.842*
Shoulder intrarotation	*0.8 (1.0)*	*0.7 (0.7)*	*1.000*
Elbow	*1.2 (0.9)*	*1.2 (0.8)*	*0.968*
Wrist	*0.7 (0.8)*	*0.8 (0.6)*	*0.720*
Action Research Arm Test (0-45)	*24 (24)*	*25 (23)*	*0.905*
WOLF Motor Function test	*37 (32)*	*41 (22)*	*0.968*

at T2 was statistically different from the pdBSI at T1 in the UG ($P = 0.008$, after Bonferroni correction for multiple comparisons), and the pdBSI at T2 was statistically different from the pdBSI at T0 in the UG ($P = 0.022$, after Bonferroni correction for multiple comparisons).

With respect to the pdBSI evaluated in the theta frequency band for all channel pairs, the results of the mixed ANOVA test showed that the interaction factor *timeXgroup* was significant in EC condition ($P = 0.042$), but not in EO condition. The main effect time was not statistically significant in both EC and EO conditions. The post-hoc tests showed that in EC condition, the pdBSI at T1 was statistically different from the pdBSI at T0 in the BG ($P = 0.022$, after Bonferroni correction for multiple comparisons).

With respect to the pdBSI evaluated in the alpha frequency band for all channel pairs, the results of the mixed ANOVA test showed that the interaction factor *timeXgroup* was not significant. The main effect time was statistically significant in EC condition ($P = 0.018$), but not in EO condition. The post-hoc tests showed that in EC condition, the pdBSI at T1 was statistically different from the pdBSI at T0 ($P = 0.016$, after Bonferroni correction for multiple comparisons).

With respect to the pdBSI evaluated in the beta frequency band for all channel pairs, the results of the mixed ANOVA test showed that both the interaction factor *timeXgroup* and main effect time were not significant in both EC and EO conditions. Data referred to the pdBSI evaluated in the frequency bands are depicted in Fig. 4.

3) pdBSI in 1-25 Hz for the Sensorimotor Clusters: With respect to the pdBSI evaluated in the sensorimotor clusters, the results of the mixed ANOVA test showed that the interaction factor *timeXgroup* was not significant. The main effect time was statistically significant in EC condition ($P = 0.045$), but not in EO condition. The post-hoc tests showed that in EC condition, the pdBSI at T1 was statistically different from the pdBSI at T0 ($P = 0.047$, after Bonferroni correction for multiple comparisons). Data referred to the pdBSI (1-25 Hz) evaluated in the sensorimotor clusters are depicted in Fig. 5.

4) pdBSI in Frequency Bands for the Sensorimotor Clusters: With respect to the pdBSI evaluated in the frequency bands for the sensorimotor clusters, the results of the mixed ANOVA tests showed that the interaction factor *timeXgroup* was always not significant, while the main effect time was not statistically significant only in the delta band, in EC condition ($P < 0.001$), but not in the EO condition. The post-hoc test showed that, in EC condition, the pdBSI in the delta band at T1 was statistically different from the pdBSI in the delta band at T0 ($P < 0.001$), and the pdBSI in the delta band at T2 was statistically different from the pdBSI in the delta band at T1 ($P = 0.001$), after Bonferroni correction for multiple comparisons. Data referred to the pdBSI evaluated in the frequency bands for the sensorimotor clusters are depicted in Fig. 6.

C. Clinical Evaluation

The results of the mixed ANOVA test related to clinical evaluation are shown in TABLE III. The interaction factor (*timeXgroup*) was always found to be statistically non-significant, thus indicating no different behavior in the two treatment groups (UG vs. BG). With respect to the main effect time, it was statistically significant in the following

TABLE II

PAIRWISE-DERIVED BRAIN SYMMETRY INDEX (PDBSI) IN THE TWO CONDITIONS EYES OPEN (EYES OPEN, EO) AND EYES CLOSED (EYES CLOSED, EC) AT ENROLMENT (T0) AND AT THE END OF THE FIRST SESSION (T0+) FOR THE TWO GROUPS, SEPARATELY, ALONG WITH THE RESULTS OF STATISTICAL ANALYSIS. BI = BILATERAL; UNI = UNILATERAL

		t	group	Mean	SD	SE	timeXgroup	time	Group
pdBSI	EC	T0	bi	0.204	0.144	0.048	0.759	0.08	0.726
			uni	0.214	0.134	0.045			
		T0+	bi	0.152	0.090	0.030			
			uni	0.177	0.089	0.030			
	EO	T0	bi	0.175	0.131	0.044	0.132	0.167	0.592
			uni	0.227	0.063	0.021			
		T0+	bi	0.178	0.116	0.039			
			uni	0.172	0.058	0.019			

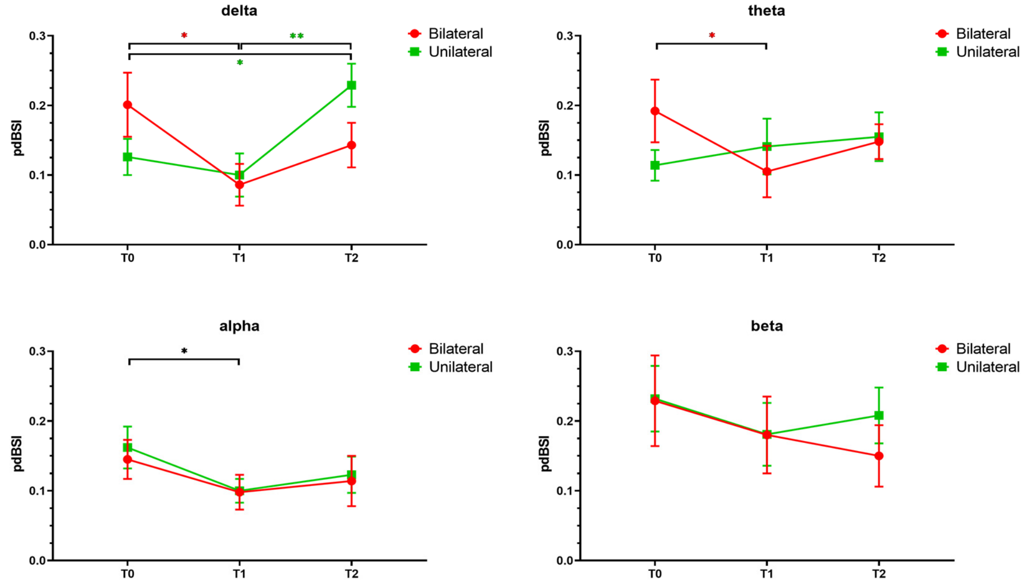

Fig. 4. Pairwise-derived Brain Symmetry Index (pdBSI) in frequency bands, in the eyes closed condition, at enrolment (T0), at the end of 30 treatment sessions (T1) and follow-up (T2) for the two groups, separately, along with the results of statistical analysis (*: $P<0.05$; **: $P<0.01$).

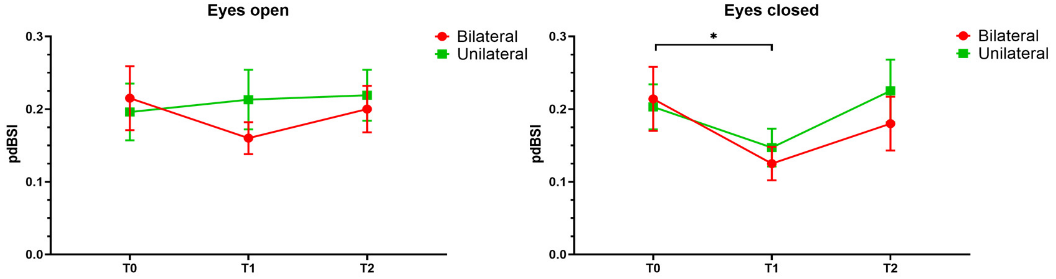

Fig. 5. Pairwise-derived Brain Symmetry Index (pdBSI) in the sensorimotor clusters, in the two conditions (eyes open and eyes closed), at enrolment (T0), at the end of 30 treatment sessions (T1) and follow-up (T2) for the two groups, separately, along with the results of statistical analysis (*: $P<0.05$).

clinical scales: FMA-UE motor function ($P = 0.001$), ARAT ($P = 0.015$), WMFT ($P = 0.007$), and MI ($P = 0.025$). In contrast, it was not statistically significant for the MAS (shoulder $P = 0.415$; elbow $P = 0.867$; wrist $P = 0.412$) and the FMA-UE sensation ($P = 0.471$).

D. Subjective Evaluation of Usability and Satisfaction

Patients in both groups rated positively the usability of the device (bilateral group: 76.9±11.0; unilateral group: 74.4±7.6) and were satisfied with the rehabilitation treatment (bilateral group: 8.3±2.2; unilateral group: 8.6±1.3). There

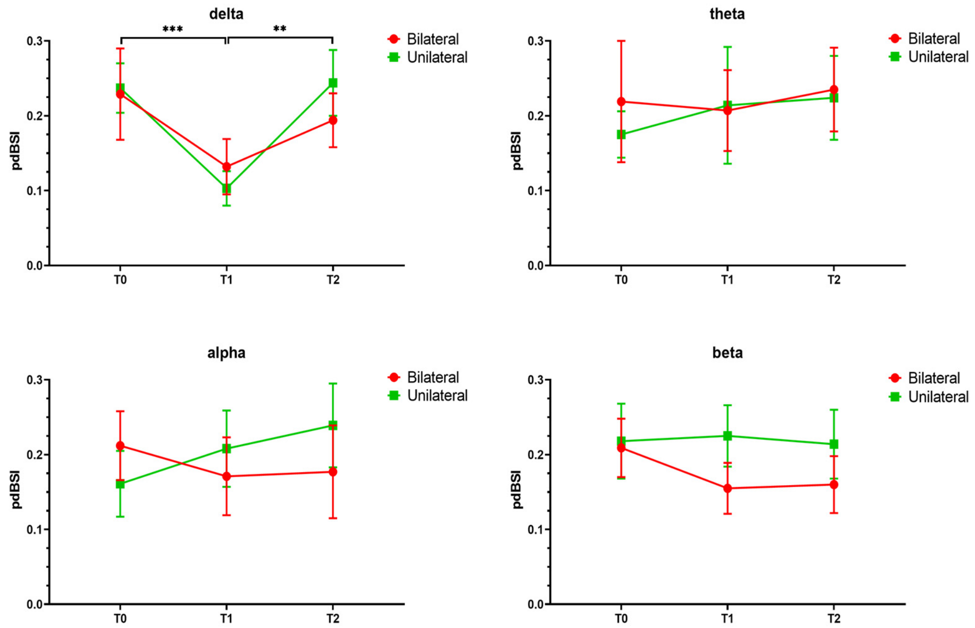

Fig. 6. Pairwise-derived Brain Symmetry Index (pdBSI) in sensorimotor clusters and in frequency bands, in the eyes closed condition, at enrolment (T0), at the end of 30 treatment sessions (T1) and follow-up (T2) for the two groups, separately, along with the results of statistical analysis (**: $P<0.01$; ***: $P<0.001$).

were no statistically significant differences between the two groups in the subjective assessment of the treatment (SUS: $P = 0.248$; Likert: $P = 0.878$).

IV. Discussion

This pilot RCT aimed to evaluate the effects on the interhemispheric balance of unilateral and bilateral robotic treatments in patients with subacute stroke, using qEEG.

Results demonstrated improvement in both neurophysiological and clinical outcomes in response to both robotic interventions for the rehabilitation of the UL. In particular, the primary finding from our research is the increase of the interhemispheric balance observed in both treatment groups after robot-assisted rehabilitation intervention. This phenomenon refers to the functional balance between the brain hemisphere affected by the stroke and the unaffected one, evaluated here through the pdBSI derived from resting-state EEG signals.

We specifically observed a decrease in the pdBSI after 30 treatment sessions (T1) performed with an exoskeleton for the UL, demonstrating the occurrence of neurophysiological changes induced by this robotic rehabilitation protocol. Lower pdBSI values reflect less power asymmetry over the cerebral hemispheres, indicating an increase of the interhemispheric balance in EEG activity [33] and thus a positive effect on the brain plasticity post-stroke. The rebalancing was also confirmed when computing the pdBSI in the cluster of channels covering sensorimotor areas, across the entire frequency range (1-25 Hz). This confirmation of pdBSI improvement in the sensorimotor cluster is particularly significant because it is directly related to motor and sensory processing, which are critical functions targeted by robotic rehabilitation.

The detailed analysis in individual frequency bands, for all channels, showed two markedly different results. In the higher frequency bands (alpha and beta), the trend was similar to the one observed over the total frequency range, but a significant rehabilitation effect on the symmetry index was seen only in the alpha band, regardless of the treatment group. In the lower frequency bands (theta and delta), the two groups behaved differently in time. In the delta band, only the bilateral group showed a significant decrease in interhemispheric asymmetry following treatment (T1). Conversely, the unilateral group did not show a significant improvement post-treatment (T1), but exhibited a significant worsening one week after the end of rehabilitation (T2). In the theta band, the bilateral group showed a significant improvement after treatment (T1), while the unilateral group displayed minimal variation in pdBSI with rehabilitation in this band. It is important to note, however, that in the delta and theta bands the two groups seemed to differ in their baseline pdBSI values (T0), although this difference was not statistically significant.

These results suggest that efficacy of bilateral versus unilateral robotic rehabilitation may be frequency-dependent and influenced by the underlying neurophysiological processes unique to each frequency band. Specifically, bilateral robotic rehabilitation may be more effective in promoting interhemispheric balance in lower frequency bands, delta and theta, which is particularly noteworthy given the role of these bands in brain injury and recovery mechanisms [34]. Indeed, increase of slow-frequency activity and relative decrease of fast-frequency activity are associated with reductions in brain metabolism in ischemic events [35], while with physical rehabilitation the delta-to-alpha power ratio usually decreases [36]. Furthermore, Saes and colleagues [37] showed that the BSI in delta and theta bands is a reliable predictor of the FMA-UE score at 26 weeks post-stroke.

TABLE III

Clinical Evaluation Before (T0) and After Treatment (T1) and Related Statistical Analysis (Mixed Anova Test). Bolded Are p-Values Less Than 0.05. FMA-UE Mf/s = Fugl–Meyer Assessment of Upper Extremity – Motor Function/ Sensation; ARAT = Action Research Arm Test; WMFT = Wolf Motor Function Test; MI = Motricity Index; MAS = Modified Ashworth Scale (Sh = Shoulder, el= Elbow, Wr = Wrist); Bi = Bilateral; Uni = Unilateral

	t	group	Mean	SD	SE	timeX group	time	group
FMA-UE *m.f.*	T0	bi	36.3	13.9	4.6	0.212	**0.001**	0.481
		uni	32.9	22.6	7.5			
	T1	bi	46.2	10.8	3.6			
		uni	37.9	21.0	7.0			
FMA-UE *s.*	T0	bi	8.4	3.9	1.3	0.951	0.471	0.851
		uni	8.1	4.2	1.5			
	T1	bi	8.9	4.0	1.3			
		uni	8.5	3.8	1.4			
ARAT	T0	bi	25.0	23.0	7.7	0.695	**0.015**	0.600
		uni	20.8	23.4	7.8			
	T1	bi	35.0	22.0	7.3			
		uni	28.2	22.9	7.6			
WMFT	T0	bi	41.2	22.0	7.3	0.844	**0.007**	0.465
		uni	33.3	31.6	10.5			
	T1	bi	53.2	21.8	7.3			
		uni	43.9	25.8	8.6			
MI	T0	bi	64.7	16.7	5.6	0.986	**0.025**	0.365
		uni	53.9	32.1	10.7			
	T1	bi	72.7	13.8	4.6			
		uni	61.8	33.4	11.1			
MAS *sh.*	T0	bi	0.6	0.7	0.2	0.784	0.415	0.849
		uni	0.7	1.0	0.3			
	T1	bi	0.4	0.5	0.2			
		uni	0.4	0.7	0.2			
MAS *el.*	T0	bi	1.2	0.8	0.3	0.867	0.867	0.937
		uni	1.2	0.9	0.3			
	T1	bi	1.2	0.3	0.1			
		uni	1.2	1.0	0.3			
MAS *wr.*	T0	bi	0.8	0.6	0.2	0.582	0.412	>0.999
		uni	0.7	0.9	0.3			
	T1	bi	0.8	0.7	0.2			
		uni	0.9	1.0	0.3			

When considering the sensorimotor channels' cluster only, the pdBSI maintained significance only in the delta band. In this band, irrespective of the treatment type, the pdBSI improved at T1 and worsened from the end of rehabilitation to the follow-up (T2). Therefore, the pdBSI in sensorimotor cortex appeared to be more sensitive to robotic rehabilitation at very slow frequencies; on the other hand, our sample size was likely not sufficient to observe a predominance of one treatment over the other in the interhemispheric balance of those areas.

Our findings add a valuable dimension to the existing body of knowledge, especially considering the limited exploration of the effects of robotic treatments on the interhemispheric balance in patients with stroke. To the best of our knowledge, no previous study investigated the changes in interhemispheric balance induced by a robotic rehabilitation treatment. Only the relationship between interhemispheric balance and motor performance was investigated. Trujillo et al.'s study [21] provided insights into the relationship between qEEG measures and motor recovery in patients with chronic stroke undergoing robot-assisted rehabilitation. In particular, the authors analyzed the correlation between the pdBSI at T0 and the outcome measures of rehabilitation (FMA-UL), in order to investigate the prognostic value of this index. Interestingly, they found no significant correlation between the pdBSI and the motor outcomes, contrary to Ang et al. [38], who employed a slightly different version of the BSI. However, there are notable differences in methodologies, patient populations, and set of outcome measures between our work and the one of Trujillo et al. that included ten patients with chronic stroke (with a time since the stroke event ranging from 1 to 14 years). The rehabilitation protocol consisted of fewer total amount of sessions and lower weekly frequency concerning our protocol. Importantly, Trujillo's work focused on unilateral treatments. In contrast, our study specifically delves into the comparative effects of unilateral and bilateral robotic treatments on interhemispheric balance in patients with stroke during the subacute phase. An investigation on bilateral robotic treatment in patients with subacute stroke was recently proposed by Tang et al. [20], who compared the effects of bilateral upper limb robot-assisted therapy with a conventional (i.e., non-robotic) treatment on the EEG rhythms and brain functional connectivity. The authors found that the functional connectivity of bilateral cerebral hemispheres increased in the bilateral robotic group. However, since the authors did not focus on the analysis of interhemispheric balance (BSI), their results are not comparable to ours.

Furthermore, both Tang et al. and Trujillo et al. proposed a robot-assisted rehabilitation program employing end-effector upper extremity robots. Instead, the current study involves robot-assisted rehabilitation with a different robotic system, an exoskeleton offering a broad range of bilateral complex movements, in goal-oriented tasks, exploring a wider workspace on different planes of movement for all the target joints, through a wider range of exergames.

Importantly, although the interhemispheric rebalancing after rehabilitation was evident in both treatment groups, its persistence was not maintained one week after the end of the rehabilitation protocol (T2). This transience could be attributed to several factors, primarily the limited sample and the individual variability in patients' recovery trajectories, but also the need for additional treatment sessions to consolidate neurophysiological changes. In fact, while neural reorganization is a critical driver of functional recovery post-stroke, it may not always result in lasting improvements [39], [40]. Given the time course of neuroplasticity, it is plausible that a longer consolidation period might be necessary for the observed changes to become enduring [41], [42]. Therefore, we cannot exclude that the 30-session protocol was not sufficient to induce lasting changes in interhemispheric balance. This underscores the importance of longer rehabilitation intervention but also extended post-rehabilitation monitoring [39], [43].

Concerning the explorative analysis, we found no statistically significant variation in the neurophysiological index after a 45-minute session (T0 vs T0+). This was an expected result, given the fact that the cerebral reorganization mechanisms related to motor recovery require longer training periods to occur. Other electroencephalographic measures could be employed to assess short-term effects related to attentional [44], cognitive [45], and memory processes [46]. Indeed, the EEG analysis of these individual processes may reveal patient-specific responsiveness to the interaction with virtual environments [47] and may thus significantly contribute to the personalization of the rehabilitative interventions, optimizing therapeutic outcomes.

From a clinical perspective, robot-assisted therapy using a bilateral exoskeleton significantly improved the UL motor performance and strength, with no significant difference between the two investigated groups (UG vs. BG). This result suggests that the robotic treatment with the investigated exoskeleton, regardless of unilateral or bilateral modalities, can promote significant functional recovery of the upper extremity in patients with stroke outcomes. These findings are in agreement with recent literature showing that robot-assisted training improves UL motor function and performance in activities of daily living in patients with stroke undergoing UL robotic rehabilitation [48].

A relevant clinical aspect of our results is the lack of increase in spasticity. This evidence contrasts with possible concerns regarding the use of robotic systems in post-stroke rehabilitation, suggesting instead that the use of an exoskeleton does not result in increased spasticity, as already supported in previous research [49], thus underlining the safety and efficacy of this treatment modality.

Regarding the evaluation session on the usability of the device and enjoyment of the treatment, patients expressed good levels of satisfaction and positively assessed the robot's usability, with no differences being seen between the unilateral and bilateral groups.

The two interventions used in our study involved, by study design, different challenges in both motor and cognitive terms. The complexity of some tasks (mainly exergames of archery and cooking) and the associated different levels of cognitive demand posed by the bilateral protocol could have contributed to the observed differences. Importantly, the intentional design differences between the bilateral and unilateral training were intrinsic to our research question, with the aim of evaluating the effects, in terms of interhemispheric rebalancing, of incorporating complex, real-life activities into bilateral rehabilitation protocols. Moreover, it is possible that some of the observed changes in the pdBSI could represent typical neurophysiological changes occurring during subacute post-stroke phase. The absence of a control group not receiving robotic therapy limits our ability to distinguish the specific effects of the intervention from natural recovery processes. However, the return to high pdBSI values observed at the follow-up, one week after rehabilitation (T2), suggests that the improvement seen at T1 can indeed be attributed to the intervention.

Overall, our results suggest that the proposed robotic treatment through the bilateral exoskeleton effectively reduces interhemispheric power asymmetry, enhancing neuroplasticity and functional recovery. This study also promotes the use of the pdBSI as a means of investigating the mechanisms of neuronal plasticity involved in robotic rehabilitation, and thus serving as a valuable marker for monitoring recovery in patients with stroke. Incorporating pdBSI into clinical settings would provide a quantitative and objective measure of interhemispheric balance, offering clinicians a tool to assess the efficacy of rehabilitation interventions and to tailor rehabilitation strategies to the patient's characteristics. This aligns with the broader trend in neurology literature to employ qEEG indices as neural markers for various pathological conditions, as both diagnostic and prognostic tools, or as measures of disease severity and progression [50], [51], [52].

Further research in different populations of subjects with stroke, i.e., including a variety of demographic and clinical variables, will be instrumental in enhancing the generalizability of our findings and in solidifying the efficacy and reliability of pdBSI as an informative clinical factor. In this direction, the experience gained from our pilot study was instrumental in defining the neurophysiological assessment of a multicentre study protocol using HD-EEG, with the aim of evaluating the interhemispheric symmetry as a prognostic factor for recovery in a large cohort of patients with stroke (trial registered at ClinicalTrials.gov with identifier NCT06547827).

A. Limitations

Our sample size was relatively small and further studies on a larger population should be conducted to understand the sensitivity and specificity of pdBSI in stroke. We used only one qEEG index to evaluate the interhemispheric balance in our cohort. Further complementary EEG measures, such as those derived from resting-state connectivity analysis should provide a more comprehensive overview of brain status, and additional prospective studies shall evaluate its usefulness to predict the success of rehabilitation in patients with stroke.

In addition to the mentioned limitations, the relatively short duration of the follow-up period may constrain the interpretation of our results at T2. Future studies with extended monitoring periods are necessary to fully understand the long-term effects of the interventions.

V. CONCLUSION

Our study shows a restoration of the interhemispheric balance, measured with the EEG-derived Brain Symmetry Index, following robotic rehabilitation in patients with stroke, with differences between unilateral and bilateral robotic treatment groups in the delta and theta bands. This balancing of interhemispheric symmetry comes along with a clinical improvement in the upper extremity. Our results suggest the use of the pdBSI, in frequency-specific bands, as a means of investigating the mechanisms of neuronal plasticity involved in robotic rehabilitation after stroke.

ACKNOWLEDGMENT

The authors would like to thank Dr. Alfredo De Liso for collaborating in the acquisition of EEG signals during the project. They would also like to thank the reviewers for their valuable comments. This study was developed as part of a collaboration between Wearable Robotics, a start-up company producing the device, and Fondazione Don Carlo Gnocchi ONLUS in the context of the BILATERAL REHAB project, funded under the Artes 4.0 Call for Proposals No. 1–2019. Wearable Robotics had no role in data collection and data analysis.

DECLARATION OF INTERESTS

The authors declare no conflict of interest.

REFERENCES

[1] M. Katan and A. Luft, "Global burden of stroke," *Seminar Neurol.*, vol. 38, no. 2, pp. 208–211, Apr. 2018.

[2] V. L. Roger et al., "Heart disease and stroke statistics—2011 update: A report from the American heart association," *Circulation*, vol. 123, no. 4, pp. e18–e209, Feb. 2011.

[3] D. T. Wade, R. Langton-Hewer, V. A. Wood, C. E. Skilbeck, and H. M. Ismail, "The hemiplegic arm after stroke: Measurement and recovery," *J. Neurol., Neurosurgery Psychiatry*, vol. 46, no. 6, pp. 521–524, Jun. 1983.

[4] F. Gómez-Pinilla, Z. Ying, R. R. Roy, R. Molteni, and V. R. Edgerton, "Voluntary exercise induces a BDNF-mediated mechanism that promotes neuroplasticity," *J. Neurophysiology*, vol. 88, no. 5, pp. 2187–2195, Nov. 2002, doi: 10.1152/jn.00152.2002.

[5] S. Micera et al., "A simple robotic system for neurorehabilitation," *Auto. Robots*, vol. 19, no. 3, pp. 271–284, Dec. 2005, doi: 10.1007/s10514-005-4749-0.

[6] M. Germanotta et al., "Reliability, validity and discriminant ability of a robotic device for finger training in patients with subacute stroke," *J. NeuroEngineering Rehabil.*, vol. 17, no. 1, p. 1, Jan. 2020, doi: 10.1186/s12984-019-0634-5.

[7] S. Masiero et al., "The value of robotic systems in stroke rehabilitation," *Expert Rev. Med. Devices*, vol. 11, no. 2, pp. 187–198, Mar. 2014.

[8] Q. Tang et al., "Modulation of interhemispheric activation balance in motor-related areas of stroke patients with motor recovery: Systematic review and meta-analysis of fMRI studies," *Neurosci. Biobehavioral Rev.*, vol. 57, pp. 392–400, Oct. 2015, doi: 10.1016/j.neubiorev.2015.09.003.

[9] G. Liuzzi, V. Horniss, M. Zimerman, C. Gerloff, and F. C. Hummel, "Coordination of uncoupled bimanual movements by strictly timed interhemispheric connectivity," *J. Neurosci.*, vol. 31, no. 25, pp. 9111–9117, Jun. 2011, doi: 10.1523/jneurosci.0046-11.2011.

[10] M. J. Mayston, L. M. Harrison, and J. A. Stephens, "A neurophysiological study of mirror movements in adults and children," *Ann. Neurol.*, vol. 45, no. 5, pp. 583–594, 1999.

[11] C. Calautti and J.-C. Baron, "Functional neuroimaging studies of motor recovery after stroke in adults: A review," *Stroke*, vol. 34, no. 6, pp. 1553–1566, Jun. 2003.

[12] P.-M. Chen, P. W. H. Kwong, C. K. Y. Lai, and S. S. M. Ng, "Comparison of bilateral and unilateral upper limb training in people with stroke: A systematic review and meta-analysis," *PLoS One*, vol. 14, no. 5, May 2019, Art. no. e0216357.

[13] S. McCombe Waller et al., "Sequencing bilateral and unilateral task-oriented training versus task oriented training alone to improve arm function in individuals with chronic stroke," *BMC Neurol.*, vol. 14, no. 1, p. 236, Dec. 2014, doi: 10.1186/s12883-014-0236-6.

[14] J. H. Cauraugh and J. J. Summers, "Neural plasticity and bilateral movements: A rehabilitation approach for chronic stroke," *Prog. Neurobiol.*, vol. 75, no. 5, pp. 309–320, Apr. 2005.

[15] J. H. Cauraugh, S.-B. Kim, and J. J. Summers, "Chronic stroke longitudinal motor improvements: Cumulative learning evidence found in the upper extremity," *Cerebrovascular Diseases*, vol. 25, nos. 1–2, pp. 115–121, 2008, doi: 10.1159/000112321.

[16] C. M. Stinear, P. A. Barber, J. P. Coxon, M. K. Fleming, and W. D. Byblow, "Priming the motor system enhances the effects of upper limb therapy in chronic stroke," *Brain*, vol. 131, no. 5, pp. 1381–1390, May 2008, doi: 10.1093/brain/awn051.

[17] S. Hesse, G. Schulte-Tigges, M. Konrad, A. Bardeleben, and C. Werner, "Robot-assisted arm trainer for the passive and active practice of bilateral forearm and wrist movements in hemiparetic subjects," *Arch. Phys. Med. Rehabil.*, vol. 84, no. 6, pp. 915–920, Jun. 2003.

[18] M. J. Johnson, H. F. M. Van der Loos, C. G. Burgar, P. Shor, and L. J. Leifer, "Experimental results using force-feedback cueing in robot-assisted stroke therapy," *IEEE Trans. Neural Syst. Rehabil. Eng.*, vol. 13, no. 3, pp. 335–348, Sep. 2005, doi: 10.1109/TNSRE.2005.850428.

[19] B. Sheng, Y. Zhang, W. Meng, C. Deng, and S. Xie, "Bilateral robots for upper-limb stroke rehabilitation: State of the art and future prospects," *Med. Eng. Phys.*, vol. 38, no. 7, pp. 587–606, Jul. 2016.

[20] C. Tang et al., "Bilateral upper limb robot-assisted rehabilitation improves upper limb motor function in stroke patients: A study based on quantitative EEG," *Eur. J. Med. Res.*, vol. 28, no. 1, p. 603, Dec. 2023, doi: 10.1186/s40001-023-01565-x.

[21] P. Trujillo et al., "Quantitative EEG for predicting upper limb motor recovery in chronic stroke robot-assisted rehabilitation," *IEEE Trans. Neural Syst. Rehabil. Eng.*, vol. 25, no. 7, pp. 1058–1067, Jul. 2017, doi: 10.1109/TNSRE.2017.2678161.

[22] A. R. Fugl-Meyer, L. Jääskö, I. Leyman, S. Olsson, and S. Steglind, "The post-stroke hemiplegic patient. 1. A method for evaluation of physical performance," *Scand. J. Rehabil. Med.*, vol. 7, no. 1, pp. 13–31, 1975.

[23] A. Delorme and S. Makeig, "EEGLAB: An open source toolbox for analysis of single-trial EEG dynamics including independent component analysis," *J. Neurosci. Methods*, vol. 134, no. 1, pp. 9–21, Mar. 2004.

[24] T.-P. Jung et al., "Removing electroencephalographic artifacts by blind source separation," *Psychophysiology*, vol. 37, no. 2, pp. 163–178, 2000.

[25] R. V. A. Sheorajpanday, G. Nagels, A. J. T. M. Weeren, M. J. A. M. van Putten, and P. P. De Deyn, "Reproducibility and clinical relevance of quantitative EEG parameters in cerebral ischemia: A basic approach," *Clin. Neurophysiol.*, vol. 120, no. 5, pp. 845–855, May 2009, doi: 10.1016/j.clinph.2009.02.171.

[26] M. Sebastián-Romagosa et al., "EEG biomarkers related with the functional state of stroke patients," *Frontiers Neurosci.*, vol. 14, p. 582, Jul. 2020.

[27] R. V. A. Sheorajpanday, G. Nagels, A. J. T. M. Weeren, M. J. A. M. van Putten, and P. P. De Deyn, "Quantitative EEG in ischemic stroke: Correlation with functional status after 6months," *Clin. Neurophysiol.*, vol. 122, no. 5, pp. 874–883, May 2011, doi: 10.1016/j.clinph.2010.07.028.

[28] R. C. Lyle, "A performance test for assessment of upper limb function in physical rehabilitation treatment and research," *Int. J. Rehabil. Res.*, vol. 4, no. 4, pp. 483–492, Dec. 1981.

[29] R. W. Bohannon, "Motricity index scores are valid indicators of paretic upper extremity strength following Stroke," *J. Phys. Therapy Sci.*, vol. 11, no. 2, pp. 59–61, Jan. 1999.

[30] R. W. Bohannon and M. B. Smith, "Interrater reliability of a modified Ashworth scale of muscle spasticity," *Phys. Therapy*, vol. 67, no. 2, pp. 206–207, Feb. 1987.

[31] S. L. Wolf, P. A. Catlin, M. Ellis, A. L. Archer, B. Morgan, and A. Piacentino, "Assessing wolf motor function test as outcome measure for research in patients after stroke," *Stroke*, vol. 32, no. 7, pp. 1635–1639, Jul. 2001.

[32] P. W. Jordan, B. Thomas, I. L. McClelland, and B. Weerdmeester, *SUS: A Usability Scale*. Boca Raton, FL, USA: CRC Press, Jun. 1996, pp. 207–212.

[33] J. Lanzone et al., "Quantitative measures of the resting EEG in stroke: A systematic review on clinical correlation and prognostic value," *Neurological Sci.*, vol. 44, no. 12, pp. 4247–4261, Dec. 2023, doi: 10.1007/s10072-023-06981-9.

[34] J. M. Cassidy et al., "Low-frequency oscillations are a biomarker of injury and recovery after stroke," *Stroke*, vol. 51, no. 5, pp. 1442–1450, May 2020.

[35] B. Foreman and J. Claassen, "Quantitative EEG for the detection of brain ischemia," *Crit. Care*, vol. 16, no. 2, p. 216, Mar. 2012, doi: 10.1186/cc11230.

[36] M. Saes et al., "Is resting-state EEG longitudinally associated with recovery of clinical neurological impairments early post-stroke? A prospective cohort study," *Neurorehabilitation Neural Repair*, vol. 34, no. 5, pp. 389–402, May 2020, doi: 10.1177/1545968320905797.

[37] M. Saes, C. G. M. Meskers, A. Daffertshofer, E. E. H. van Wegen, and G. Kwakkel, "Are early measured resting-state EEG parameters predictive for upper limb motor impairment six months poststroke?" *Clin. Neurophysiol.*, vol. 132, no. 1, pp. 56–62, Jan. 2021, doi: 10.1016/j.clinph.2020.09.031.

[38] K. K. Ang et al., "A randomized controlled trial of EEG-based motor imagery brain–computer interface robotic rehabilitation for stroke," *Clin. EEG Neurosci.*, vol. 46, no. 4, pp. 310–320, Oct. 2015.

[39] C. Grefkes and G. R. Fink, "Recovery from stroke: Current concepts and future perspectives," *Neurological Res. Pract.*, vol. 2, no. 1, p. 17, Dec. 2020, doi: 10.1186/s42466-020-00060-6.

[40] F. Su and W. Xu, "Enhancing brain plasticity to promote stroke recovery," *Frontiers Neurol.*, vol. 11, Oct. 2020, Art. no. 554089, doi: 10.3389/fneur.2020.554089.

[41] C. Alia et al., "Neuroplastic changes following brain ischemia and their contribution to stroke recovery: Novel approaches in neurorehabilitation," *Frontiers Cellular Neurosci.*, vol. 11, p. 76, Mar. 2017, doi: 10.3389/fncel.2017.00076.

[42] L. Otero-Ortega, M. Gutiérrez-Fernández, and E. Díez-Tejedor, "Recovery after stroke: New insight to promote brain plasticity," *Frontiers Neurol.*, vol. 12, Nov. 2021, Art. no. 768958, doi: 10.3389/fneur.2021.768958.

[43] G. B. Bonifacio, N. S. Ward, H. C. A. Emsley, J. Cooper, and J. Bernhardt, "Optimising rehabilitation and recovery after a stroke," *Practical Neurol.*, vol. 22, no. 6, pp. 478–485, Dec. 2022, doi: 10.1136/practneurol-2021-003004.

[44] P. Praamstra, L. Boutsen, and G. W. Humphreys, "Frontoparietal control of spatial attention and motor intention in human EEG," *J. Neurophysiology*, vol. 94, no. 1, pp. 764–774, Jul. 2005, doi: 10.1152/jn.01052.2004.

[45] M. M. Swerdloff and L. J. Hargrove, "Quantifying cognitive load using EEG during ambulation and postural tasks," in *Proc. Annu. Int. Conf. IEEE Eng. Med. Biol. Soc.*, Jul. 2020, pp. 2849–2852.

[46] F. Klotzsche, M. Gaebler, A. Villringer, W. Sommer, V. Nikulin, and S. Ohl, "Visual short-term memory-related EEG components in a virtual reality setup," *Psychophysiology*, vol. 60, no. 11, Nov. 2023, Art. no. e14378.

[47] R. H. C. E. Souza and E. L. M. Naves, "Attention detection in virtual environments using EEG signals: A scoping review," *Frontiers Physiol.*, vol. 12, Nov. 2021, Art. no. 727840, doi: 10.3389/fphys.2021.727840.

[48] X. Yang, X. Shi, X. Xue, and Z. Deng, "Efficacy of robot-assisted training on rehabilitation of upper limb function in patients with stroke: A systematic review and meta-analysis," *Arch. Phys. Med. Rehabil.*, vol. 104, no. 9, pp. 1498–1513, Sep. 2023, doi: 10.1016/j.apmr.2023.02.004.

[49] I. Aprile et al., "Upper limb robotic rehabilitation after stroke: A multicenter, randomized clinical trial," *J. Neurologic Phys. Therapy*, vol. 44, no. 1, pp. 3–14, 2020.

[50] M. Ahmadlou, H. Adeli, and A. Adeli, "New diagnostic EEG markers of the Alzheimer's disease using visibility graph," *J. Neural Transmiss.*, vol. 117, no. 9, pp. 1099–1109, Sep. 2010, doi: 10.1007/s00702-010-0450-3.

[51] V. J. Geraedts et al., "Clinical correlates of quantitative EEG in Parkinson disease: A systematic review," *Neurology*, vol. 91, no. 19, pp. 871–883, Nov. 2018.

[52] A. Fasano et al., "Maximum downward slope of sleep slow waves as a potential marker of attention-deficit/hyperactivity disorder clinical phenotypes," *J. Psychiatric Res.*, vol. 156, pp. 679–689, Dec. 2022, doi: 10.1016/j.jpsychires.2022.10.057.