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A comparison of the rehabilitation effectiveness of neuromuscular electrical stimulation robotic hand training and pure robotic hand training after stroke: A randomized controlled trial

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ABSTRACT

Objective: To compare the rehabilitation effects of the electromyography (EMG)-driven neuromuscular electrical stimulation (NMES) robotic hand and EMG-driven robotic hand for chronic stroke.
Methods: This study was a randomized controlled trial with a 3-month follow-up. Thirty chronic stroke patients were randomly assigned to receive 20-session upper limb training with either EMG-driven NMES robotic hand (NMES group, n = 15) or EMG-driven robotic hand (pure group, n = 15). The training effects were evaluated before and after the training, as well as 3 months later, using the clinical scores of Fugl-Meyer Assessment (FMA), Modified Ashworth Scale (MAS), Action Research Arm Test (ARAT), and Functional Independence Measure (FIM). Session-by-session EMG parameters, including the normalized EMG activation level and co-contraction indexes (CIs) of the target muscles were applied to monitor the recovery progress in muscular coordination patterns.
Results: Both groups achieved significantly increased FMA and ARAT scores ($p < 0.05$), and the NMES group improved more ($p < 0.05$). A significant improvement in MAS was obtained in the NMES group ($p < 0.05$) but absence in the pure group. Meanwhile, better performance could be obtained in the NMES group in releasing the EMG activation levels and CIs than the pure group across the training sessions ($p < 0.05$).
Conclusion: Both training systems were effective in improving the long-term distal motor functions in upper limb, where the NMES robot-assisted training achieved better voluntary motor recovery and muscle coordination and more release in muscle spasticity.
Significance: This study indicated more effective distal rehabilitation using the NMES robot than the pure robot-assisted rehabilitation.
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1. Introduction

Upper limb motor deficits are common after stroke, and observed in over 80% of stroke survivors [1,2]. Various rehabilitation devices have been purposed to assist human physical therapists to provide effective long-term rehabilitation programs [3–5]. Among them, rehabilitation robots and neuromuscular electrical stimulation (NMES) are most widely used in stroke rehabilitation practices. Rehabilitation robots have been recognized as efficient in such cases and could represent a cost-effective addition to conventional rehabilitation services because they provide highly intensive and repetitive training [6–9]. It has been reported that the integration of voluntary effort (e.g. electromyography, EMG) into robotic design could contribute significantly to motor recovery in stroke patients [6,10]. This is because an EMG-driven strategy can maximize the involvement of voluntary effort in the training, and its effectiveness at improving upper limb voluntary motor functions have been proved by many EMG-driven robot-assisted upper-limb training systems [11–13]. However, rehabilitation robots are unable to directly activate the desired muscle groups, which may only assist, or even dominate limb movement such as continuous passive motions (CPM) [14]. In addition, stroke patients usually cooperate with compensatory motions from other muscular activities to activate the target muscles, which

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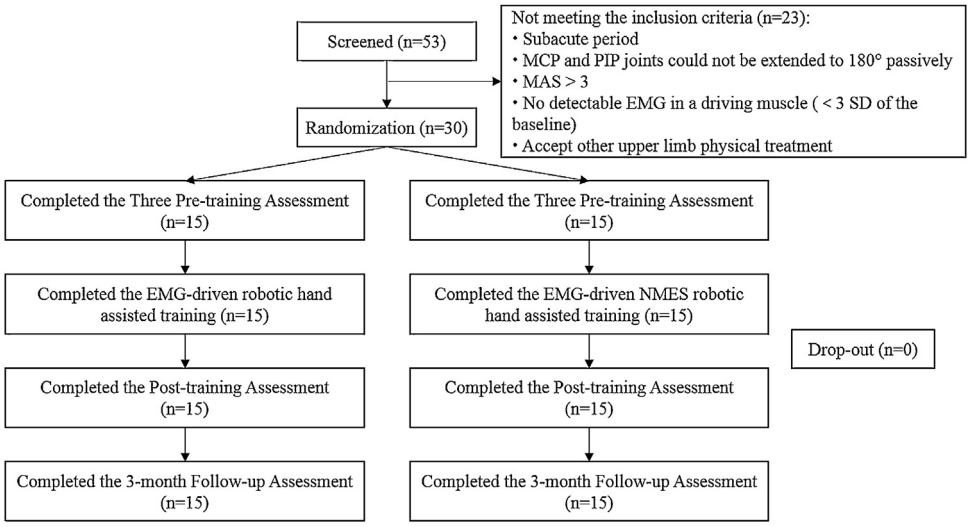

Fig. 1. The consolidated standards of reporting trials flowchart of the experimental design.

may lead to 'learned disuse' [15]. However, NMES can effectively limit compensatory motions by stimulating specific muscles via cyclic electrical currents, which provides repetitive sensorimotor experiences [16]. With the advantage of precisely activating the target muscle, NMES has been reported to be effective in evoking sensory feedback, improving muscle force, and thus promoting motor function in stroke patients [17,18]. Nevertheless, training programs assisted by NMES alone are also suboptimal due to the difficulty of controlling movement trajectories and the early appearance of fatigue [19,20].

Accordingly, various NMES robot-assisted upper-limb training programs which combine these two unique techniques have been proposed to integrate the benefits and minimize the disadvantages [7,12,14,21,22]. The rehabilitation effectiveness of these combined systems has been investigated and reported to be effective in improving motor recovery. Several studies have compared the training outcomes of NMES robot-assisted training and other training programs. For example, Qian et al. [22] reported that NMES-robot-assisted upper-limb training could achieve better motor outcomes when compared with conventional therapies for subacute stroke patients. Meanwhile, another study which compared the training effects between robot-aided training with NMES and robot-aided training solely using the InMotion ARM^{TM} Robot in the subacute period demonstrated that the active ranges of motion of the NMES robot-training group were significantly higher compared with the robot-training group [23]. Coincidentally, investigations into applications in chronic stroke patients have also been carried out. For instance, Hu et al. [14] proposed an EMG-driven NMES robot system for wrist training; this combined device improved muscle activation levels related to the wrist and reduced compensatory muscular activities at the elbow, while these training outcomes were absent for the EMG-driven robot-assisted training alone. Indeed, a similar study by another research group also achieved better rehabilitation outcomes on some clinical assessments using the combined system compared to robot-assisted therapy alone [21].

In the literature, most studies on current rehabilitation devices combining the NMES and robotic systems targeted the elbow and wrist joints [7,21–23], while very few focused on the hand and fingers [24]. In addition, a comparison of the training effects for hand rehabilitation between the NMES robot and other hand rehabilitation devices has not yet been adequately conducted. Indeed, the primary upper-limb disability post-stroke is the loss of hand function, and rehabilitation of the distal joints after stroke is much more difficult than the motor recovery of the proximal joints due to the compensatory motions from the proximal joints [25]. Hence, developing effective rehabilitation devices to minimize compensatory movements for hand motor recovery is especially meaningful for stroke rehabilitation. In our previous work, we developed an EMG-driven NMES robotic hand and suggested it for use in hand rehabilitation after stroke [26]. Our device provides fine control of hand movements and activates the target muscles selectively for finger extension/flexion, and its feasibility and effectiveness have been verified by a single group trial [12]. However, whether the long-term rehabilitation effect of this EMG-driven NMES robotic hand is comparable or even better than other hand rehabilitation devices are still unclear and need to be investigated quantitively. Therefore, the objective of this study is to compare the training effects of hand rehabilitation assisted by an NMES robotic hand and by a pure robotic hand though a randomized controlled trial with a 3-month follow-up (3MFU).

2. Methodology

2.1. Participants

This work was approved by the Human Subjects Ethics Sub-Committee of the Hong Kong Polytechnic University. A total of 53 stroke survivors were screened for the training from local districts. 30 participants with chronic stroke satisfied the following inclusion criteria: (1) The participants were at least 6 months after the onset of a singular and unilateral brain lesion due to stroke, (2) both the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints could be extended to 180° passively, (3) muscle spasticity during extension at the finger joints and the wrist joint was below 3 as measured by the Modified Ashworth Scale (MAS) [27], ranged from 0 (no increase in muscle tone) to 4 (affected part rigid), (4) detectable voluntary EMG signals from the driving muscle on the affected side (three times of the standard deviation (SD) above the EMG baseline), and (5) no visual deficit and able to understand and follow simple instructions as assessed by the Mini-Mental State Examination (MMSE > 21) [28].

This work involved a randomized controlled trial with a 3-month follow-up (3MFU). The potential participants were first told that the training program they would receive could be either NMES robotic hand training or pure robotic hand training, and all recruited participants submitted their written consent before randomization. Then, the recruited participants were randomly

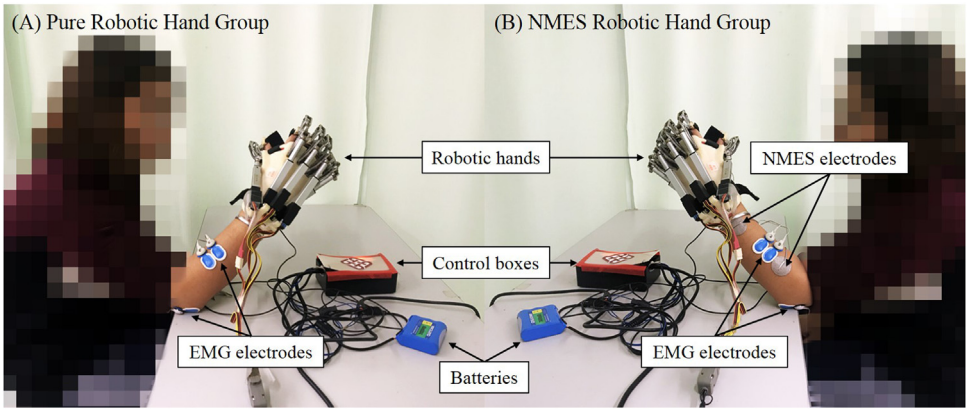

Fig. 2. The experimental setup of the robotic hand training: (A) pure robotic hand group; (B) neuromuscular electrical stimulation (NMES) robotic hand group.

assigned into two groups according to a computer-based random number generator, i.e., the computer program generated either "1" (denoting the NMES robotic hand training group) or "2" (the pure robotic hand group) with an equal probability of 0.5 (Matlab, 2017, Mathworks, Inc.). Fig. 1 shows the Consolidated Standards of Reporting Trials flowchart of the training program.

2.2. Interventions

For both groups, each participant was invited to attend a 20-session robotic hand training with an intensity of 3–5 sessions/week, completed within 7 consecutive weeks. The training setup of both groups is shown in Fig. 2. This robotic hand training system can assist with finger extension and flexion of the paretic limb for patients after stroke. In this work, real-time voluntary EMG detected from the abductor pollicis brevis (APB) and extensor digitorum (ED) muscles were used to control the respective hand closing and opening movements, and the threshold level of each motion phase was set at three times the SD above the EMG baseline at resting state [12]. For example, during the motions of finger flexion, once the EMG activation level of the APB muscle reached a preset threshold, the robotic hand would provide mechanical assistance for hand closing. Similarly, during the motions of finger extension, the robotic hand would assist with hand opening when the EMG activation level of the ED muscle reached a preset threshold. For the NMES robot group, synchronized support from the NMES and the robot were both provided. The NMES electrode pair (30 mm diameter; Axelgaard Corp., Fallbrook, CA, USA) was attached over the ED muscle to provide stimulation during finger extension. The outputs of NMES were square pulses with a constant amplitude of 70 V, a stimulation frequency of 40 Hz, and a manually adjustable pulse width in the range 0–300 μs. Before the training, the pulse width was set at the minimum intensity, which achieved a fully extended position of the fingers in each patient. During the training, NMES would be triggered by the EMG from the ED muscle first and then provided stimulation to the ED muscle to assist hand-opening motions for the entire phase of finger extension, while no assistance from NMES was provided during finger flexion to avoid the possible increase of finger spasticity after stimulation [29]. For the pure robot group, the difference between the two groups was that no NMES was applied in the pure robot group. A detailed account of the working principles of the robotic hand have been described in our previous work [12,30,31].

In each session, the participants in both groups were first required to perform a maximum voluntary contraction (MVC) test for the following five target muscles: APB, ED, flexor digitorum (FD), biceps brachii (BIC), and triceps brachii (TRI) muscles. Each MVC test on each target muscle was maintained for 5 s and repeated twice. Following this, the participants were asked to use their paretic limbs (without assistance from NMES or the robotic hand) to perform bare-hand evaluation tasks, which included lateral and vertical arm reaching-grasping tasks. For the lateral task, participants were asked to hold a sponge (thickness 5 cm, weight 30 g), and move it 50 cm horizontally from one side of a table to the other. Then, to release it, grasp it again, and finally move it back to its original position. For the vertical task, each participant was asked to grasp the sponge from the midline of a lower layer of a shelf, and then raise up it to a vertical distance of 17 cm and position it in the middle of upper layer of the shelf. After this, participants were asked to pick the sponge up and position it back at the starting point. Both lateral and vertical tasks were repeated three times. To avoid muscle fatigue, there was a 2-min break between two consecutive contractions for both the MVC test and the bare-hand evaluation task. The evaluation procedures of the MVC and the bare-hand evaluation task have been described in detail in our previous work [12,30]. After the pre-training evaluation task, participants were instructed to carry out repetitive upper-limb movements as in the lateral and vertical tasks in the evaluation with assistance from either the EMG-driven robotic hand or the EMG-driven NMES robotic hand. In each training session, the participants performed 30-min lateral and vertical tasks respectively, with a 10-min break between the two tasks to avoid muscle fatigue.

2.3. Evaluation of training effects

2.3.1. Clinical assessments

The functional evaluations for each participant were conducted by a blinded assessor, assessed by Fugl-Meyer Assessment [32] (FMA with a full score of 66 for the upper-limb assessment was further divided into shoulder/elbow (FMA-S/E, 42/66) and wrist/hand (FMA-W/H, 24/66)), Modified Ashworth Scale (MAS) [27] on the flexors related to the fingers, wrist, and elbow, Action Research Arm Test (ARAT) [33], and Functional Independence Measure (FIM) [34]. In this work, a multiple baseline design was used. There were a total 5 time points for the clinical assessment, which included three pre-training assessments, a post-training assessment, and a 3MFU. The pre-training assessment was measured three times in two weeks before the training every 2–3 days to ensure the stability of the baseline. The post-training assessment was evaluated immediately after the last training session, and the 3MFU was assessed three months after the last training session.

2.3.2. EMG parameters

In this study, EMG signals from both groups in each session were recorded from the APB, ED, FD, TRI and BIC muscles. In order to quantitatively monitor the variations in muscle activa-

Table 1
Demographic characteristics of the participants.

Characteristics	NMES group (n = 15)	PURE group (n = 15)	P value
Gender[a] (male/female)	12/3	12/3	1
Stroke side[a] (right/left)	7/8	5/10	0.710
Type of stroke[a] (ischemic/hemorrhagic)	8/7	10/5	0.710
Age[b] in years (mean ± SD)	57.33 ± 9.19	60.07 ± 6.88	0.353
Times since stroke[b] in years (mean ± SD)	8.27 ± 4.32	6.20 ± 3.41	0.296

No statistical differences are found between the groups (P > 0.05, independent t-test).
[a] Fisher's exact test.
[b] Independent t-test.

tion and coordination patterns across the training sessions, two EMG parameters were calculated and used: (1) the normalized EMG activation level of each target muscle, and (2) the normalized EMG Co-contraction Index (CI) between a muscle pair [35,36]. The EMG activation level of a muscle was calculated as follows:

$$\overline{\mathrm{EMG}} = \frac{1}{T}\int_0^T EMG_i(t)\,dt \tag{1}$$

where $\overline{\mathrm{EMG}}$ referred to the EMG activation level of a muscle i, $\mathrm{EMG}_i(t)$ was the EMG envelope signal after normalization with respect to the EMG maximum value of the muscle, and T was the length of the signal. In order to minimize the variations in the EMG activation level of each participant, each EMG activation level value in each session for each participant was further normalized with respect to the maximal and minimal EMG activation levels of each participant recorded across the 20 training sessions (Eq. (2)). After this operation, the tendency of the EMG activation level values (varying from 0 to 1) of a single participant across the 20 training sessions was obtained.

$$\mathrm{EMG_N} = \frac{\overline{\mathrm{EMG}} - \overline{\mathrm{EMG}}_{\min}}{\overline{\mathrm{EMG}}_{\max} - \overline{\mathrm{EMG}}_{\min}} \tag{2}$$

where $\mathrm{EMG_N}$ was the normalized EMG activation level of muscle i. $\overline{\mathrm{EMG}}$ referred to the averaged EMG envelope value of muscle i. $\overline{\mathrm{EMG}}_{\min}$ was the minimum value of the averaged EMG envelope across the 20 training sessions, and $\overline{\mathrm{EMG}}_{\max}$ was the maximum value of the averaged EMG envelope across the 20 training sessions.

The CI between a pair of muscles was calculated as follows:

$$\mathrm{CI} = \frac{1}{T}\int_0^T A_{ij}(t)\,dt \tag{3}$$

where $A_{ij}(t)$ was the overlapping activity of EMG linear envelopes for muscles i and j, and T was the length of the signal. CI represents the extent of a co-contraction phase of a pair of muscles. The increase of the CI value indicates a broadened overlapping area of a muscle pair while the decrease of CI value represents a lessened overlapping area of a muscle pair. To obtain the tendency of a muscle coordination, the CI value was also further normalized using a similar operation with the EMG activation level, with respect to the maximal and minimal CI values of each participant recorded across the 20 training sessions. The varying patterns of the two EMG parameters across the training sessions provided a complete picture of the recovery progress of the affected limb. The EMG parameters of the normalized EMG activation level and CI values have been applied in our previous studies [12,14,22].

2.4. Statistical analysis

The variation in demographic characteristics among the participants between the two groups was evaluated using the Fisher exact test or the independent t-test. The normality tests on the clinical scores and EMG data were evaluated using the Lilliefors method with insignificant probabilities (P > 0.05) [37]. Then, the baselines of the clinical scores for the two groups were compared using a two-way analysis of variance (ANOVA) with an insignificant statistical difference (P > 0.05) on the primary clinical assessments (i.e., pre-training assessments on FMA). To further minimize possible baseline differences between the groups, a two-way analysis of covariance (ANCOVA) was used to evaluate the differences with respect to the independent factors of the groups (i.e., the NMES group and the pure group) and the time points on the clinical assessment (i.e., the three pre-training assessments, post-training assessment, and the 3-month follow-up assessment) by taking the mean of the three pre-assessments as a covariate. Following this, a one-way ANOVA was performed to investigate the intragroup differences between the two groups at different time points with Bonferroni post hoc tests. The post hoc between-group comparisons on the clinical scores at the respective post- and 3MFU assessments were evaluated using a one-way ANCOVA with the mean of the three pre-assessments as a covariate. However, the interaction between the mean of the three pre-training assessments and the group factor of the MAS wrist score was significant (P < 0.05), and therefore a one-way ANCOVA could not be used to evaluate the 3MFU assessment of MAS wrist scores between the two groups. Therefore, the intergroup comparison of the MAS wrist scores were further evaluated by the independent t-test. The EMG parameters (i.e., EMG activation levels and CI values) across the 20 sessions were analyzed using a two-way ANOVA to investigate the recovery process across the whole set of training sessions in both groups. Then, the intragroup difference between the two groups across the 20 sessions was evaluated using a one-way ANOVA with Bonferroni post hoc tests, and the intergroup difference at each training session was compared using an independent t-test. The level of statistical significance was set at 0.05 and was further indicated at 0.01 and 0.001 in this study.

3. Results

A total of 53 stroke patients were screened for the robotic hand training, and 30 participants met the inclusion criteria and were recruited in this work. Each patient was randomly assigned to one of two groups, namely the NMES group (n = 15) and the pure group (n = 15). Table 1 shows the demographic details of the participants following this randomization. There were no statistical differences between the two groups as far as age, gender, stroke side and onset time were concerned.

3.1. Clinical scores

Fig. 3 shows the clinical scores (i.e., FMA, ARAT, MAS, and FIM) of participants in the NMES and the pure group at five different times, including three pre-training assessments, the post-training assessment, and the 3MFU assessment. Table 2 presents the mean scores and 95% confidence intervals for each clinical assessment. The two-way ANCOVA probabilities and predicted effect sizes (EFs) at each point in time and for each group were provided, and the one-way ANOVA probabilities are also given with the EFs within the intra-

Table 2
The clinical assessments of each group.

Assessment	Group	PRE1	PRE2	PRE3	POST	3MFU	1-way ANOVA	2-way ANCOVA		
		Mean Value (95% Confidence Interval)					*P (Partial η2)*	*P (Partial η2)*		
								Time point	Group	T*G
FMA $_{\text{Full score}}$	NMES	27.07 (21.22~32.91)	27.73 (21.57~33.89)	27.13 (21.44~32.83)	42.20 (35.67~48.73)	43.73 (37.10~50.37)	0.000*** (0.337)	0.000### (0.640)	0.000### (0.111)	0.000### (0.157)
	PURE	26.93 (21.69~32.18)	26.33 (21.41~31.25)	26.47 (21.51~31.43)	34.27 (28.01~40.52)	34.93 (29.75~40.11)	0.000*** (0.337)			
FMA $_{\text{Shoulder/Elbow}}$	NMES	18.40 (14.70~22.10)	18.93 (15.09~22.77)	18.73 (15.13~22.34)	28.47 (24.18~32.76)	29.67 (25.52~33.81)	0.000*** (0.357)	0.000### (0.552)	0.000### (0.124)	0.000### (0.174)
	PURE	17.13 (14.02~20.25)	17.07 (14.00~20.25)	16.73 (13.61~19.86)	21.60 (16.98~26.22)	21.13 (17.74~24.53)	0.081 (0.110)			
FMA $_{\text{Wrist/Hand}}$	NMES	8.67 (5.80~11.53)	8.80 (6.04~11.56)	8.40 (5.68~11.12)	13.73 (11.13~16.33)	14.07 (11.32~16.82)	0.001*** (0.227)	0.000### (0.493)	0.114 (0.018)	0.239 (0.039)
	PURE	9.80 (6.81~12.79)	9.27 (6.57~11.97)	9.73 (6.88~12.58)	12.67 (9.45~15.88)	13.80 (10.52~17.08)	0.089 (0.107)			
ARAT	NMES	14.53 (7.96~21.11)	15.73 (9.07~22.40)	15.93 (9.21~22.66)	27.40 (20.41~34.39)	27.93 (19.98~35.89)	0.004** (0.196)	0.000### (0.634)	0.001### (0.075)	0.001### (0.126)
	PURE	15.33 (9.92~20.75)	14.33 (9.30~19.37)	14.87 (9.63~20.11)	23.07 (17.69~28.44)	20.93 (16.41~25.46)	0.032* (0.138)			
MAS $_{\text{Finger}}$	NMES	1.53 (0.91~2.16)	1.45 (0.88~2.03)	1.59 (0.97~2.20)	0.45 (0.13~0.78)	0.43 (0.12~0.73)	0.000*** (0.265)	0.000### (0.500)	0.011## (0.046)	0.032# (0.072)
	PURE	1.73 (1.12~2.34)	1.63 (0.98~2.28)	1.53 (0.88~2.19)	0.84 (0.41~1.27)	1.09 (0.60~1.58)	0.099 (0.104)			
MAS $_{\text{Wrist}}$	NMES	1.51 (0.94~2.08)	1.55 (0.97~2.12)	1.57 (1.01~2.14)	0.61 (0.22~1.01)	0.45 (0.13~0.78)	0.000*** (0.247)	0.000### (0.533)	0.002## (0.069)	0.002## (0.112)
	PURE	1.65 (1.12~2.19)	1.72 (1.20~2.24)	1.71 (1.19~2.22)	0.99 (0.49~1.48)	1.27 (0.73~1.80)	0.136 (0.094)			
MAS $_{\text{Elbow}}$	NMES	1.73 (1.27~2.20)	1.71 (1.24~2.18)	1.64 (1.12~2.16)	0.87 (0.43~1.30)	0.73 (0.32~1.14)	0.001*** (0.230)	0.000### (0.283)	0.001### (0.080)	0.000### (0.184)
	PURE	1.28 (0.83~1.73)	1.21 (0.78~1.65)	1.27 (0.83~1.70)	1.03 (0.58~1.47)	1.20 (0.67~1.73)	0.925 (0.013)			
FIM	NMES	64.93 (63.69~66.18)	65.67 (65.13~66.21)	65.40 (64.54~66.26)	66.47 (65.78~67.16)	65.87 (64.80~66.93)	0.145 (0.092)	0.155 (0.046)	0.276 (0.008)	0.871 (0.009)
	PURE	65.00 (63.84~66.16)	65.07 (63.91~66.23)	64.93 (63.77~66.09)	65.64 (64.49~66.80)	65.93 (64.78~67.09)	0.673 (0.032)			

The mean and 95% confidence intervals for each measurement of the clinical assessments, and the probabilities with the estimated effect sizes of the statistical analyses. Differences with statistical significance are marked with superscripts beside the P values ("*" for 1-way-ANOVA intragroup tests, "#" for 2-way ANCOVA tests on the time point and group effects with the mean value of three pre-assessments as the covariate). Significant levels are indicated as, 1 superscript for <0.05, 2 superscripts for ≤0.01, and 3 superscripts for ≤0.001.
Abbreviations: FMA, Fugl-Meyer Assessment; ARAT, Action Research Arm Test; FIM, Functional Independence Measurement; MAS, Modified Ashworth Scale; ANOVA, analysis of variance; ANCOVA, analysis of covariance; T*G, the interaction between the time point and group; 3MFU, 3-month follow-up.

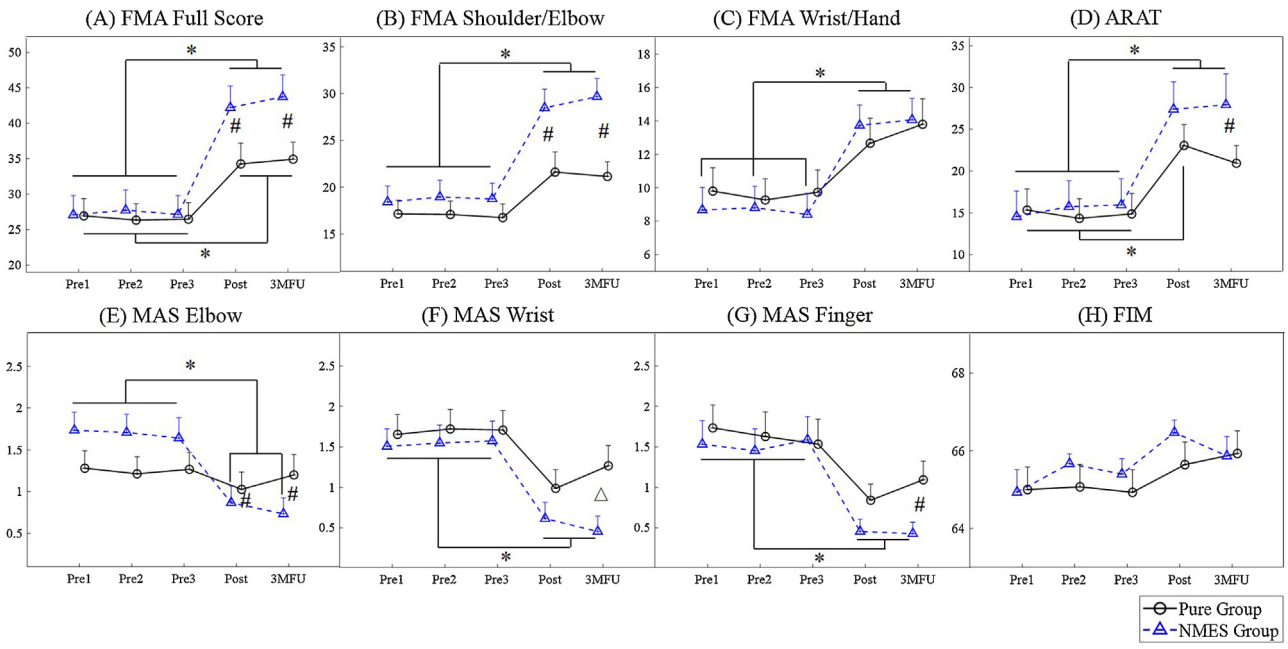

Fig. 3. The clinical scores [evaluated before the first and after the 20th training session, as well as the 3-month follow-up (3MFU)] of the participants in both NMES robotic hand and pure robotic hand groups: (A) Fugl-Meyer Assessment (FMA) full scores, (B) FMA shoulder/elbow scores, (C) FMA wrist/hand scores, (D) Action Research Arm Test (ARAT) scores, (E) Modified Ashworth Scale (MAS) scores at the elbow (F) MAS scores at the wrist, (G) MAS scores at the fingers, and (H) Functional Independence Measure (FIM) scores, presented as mean value with SE (error bar) in each evaluation session. The solid lines are for the pure group, and the dashed lines are for the NMES group. The significant inter-group differences are indicated by "#" ($P < 0.05$, one-way analysis of covariance) and "△" ($P < 0.05$, independent t-test), and "*" is used to indicate the significant intragroup difference ($P < 0.05$, one-way analysis of variance with Bonferroni *post hoc* tests).

Table 3
The statistical probabilities and the estimated effect sizes of the intergroup comparison on the respective post-assessment and 3-month follow-up (3MFU).

Evaluation	Post- and 3MFU assessments between the groups	
	Post (Partial η2/Cohen's d)	3MFU (Partial η2/Cohen's d)
FMA $_{\text{Full score}}$ [a]	0.005$^{\#\#}$ (0.256)	0.005$^{\#\#}$ (0.258)
FMA $_{\text{Shoulder/Elbow}}$ [a]	0.013$^{\#}$ (0.208)	0.001$^{\#\#\#}$ (0.344)
FMA $_{\text{Wrist/Hand}}$ [a]	0.128 (0.084)	0.379 (0.029)
ARAT [a]	0.069 (0.117)	0.007$^{\#\#}$ (0.239)
MAS $_{\text{Finger}}$ [a]	0.114 (0.090)	0.001$^{\#\#\#}$ (0.328)
MAS $_{\text{Wrist}}$ [b]	0.220 (0.459)	0.009$^{\triangle\triangle}$ (1.021)
MAS $_{\text{Elbow}}$ [a]	0.040$^{\#}$ (0.148)	0.005$^{\#\#}$ (0.257)
FIM [a]	0.050 (0.135)	0.536 (0.014)

Differences with statistical significance are marked with superscripts beside the P values ("#" for 1-way ANCOVA intragroup tests, "△" for independent t-test). Significant levels are indicated as, 1 superscript for <0.05, 2 superscripts for ≤0.01, and 3 superscripts for ≤0.001.

[a] 1-way ANCOVA.

[b] Independent t-test.

group assessments at the five specific points of clinical assessment. The probabilities and EFs of between-group comparison can be seen in Table 3. These are related to the respective post- and 3MFU evaluation scores found by applying a one-way ANCOVA with altered baseline effects and an independent t-test. There were no significant intra- or intergroup differences found for the baseline tests for any of the clinical scores. In the FMA full score, a significant increase could be observed in both groups after the training, and these improvements could be kept for 3 months ($P < 0.05$). It was also observed that the FMA full scores for the NMES group at post-assessment and 3MFU were much higher than the pure group's scores ($P < 0.05$). Significant improvements were found for the FMA S/E and W/H scores in the NMES group post-training ($P < 0.05$), and this enhancement continued after 3 months. Nonetheless, no significant intragroup difference was found for the pure group's FMA S/E and W/H scores. In addition, the NMES group had much greater FMA S/E scores than the pure group after the training, as well as after 3 months ($P < 0.05$). Meanwhile, there were also significant improvements in the ARAT following the training for both groups ($P < 0.05$), although a significant increase was only found after 3 months for the NMES group ($P < 0.05$). It was also observed that the post-assessment of ARAT was comparable between the two groups; however, after 3 months, the ARAT score of the NMES group was significantly higher than the pure group's score ($P < 0.05$). There was a significant decrease in the MAS scores of the elbow, wrist, and finger joints for the NMES group after training, with these lowered scores continuing for 3 months ($P < 0.05$). In the meantime, in the pure group, MAS scores for the elbow, wrist, and finger joints were also reduced, however, there was no statistical significance. Within the MAS scores for wrist, elbow and finger joints, significant intergroup differences ($P < 0.05$) were also revealed respectively. It appeared that there were significantly lower post-assessment and 3MFU scores of the MAS for the elbow joint in the NMES group in comparison to the pure group's scores ($P < 0.05$). In terms of the MAS scores for the wrist and finger joints in the NMES group, significant lower scores were found after 3 months in comparison to those of the pure group ($P < 0.05$). Improvements to FIM scores after training were observed in the two groups, yet there was no statistical significance identified.

3.2. EMG parameters

Fig. 4 shows EMG parameters (namely the normalized EMG activation level and normalized CI), which present differences of statistical significance throughout the assessment and the 20 training sessions. In Table 4, the two-way ANCOVA probabilities, as well as predicted EFs of the EMG parameters for the training sessions and groups are presented. Fig. 4(A) and (B) shows the differences in the normalized EMG activation levels over the 20 training sessions for the two groups, with significantly lowered EMG activation levels being seen in FD and BIC muscles for the NMES group ($P < 0.05$). On the other hand, a significant reduction in the EMG activation level

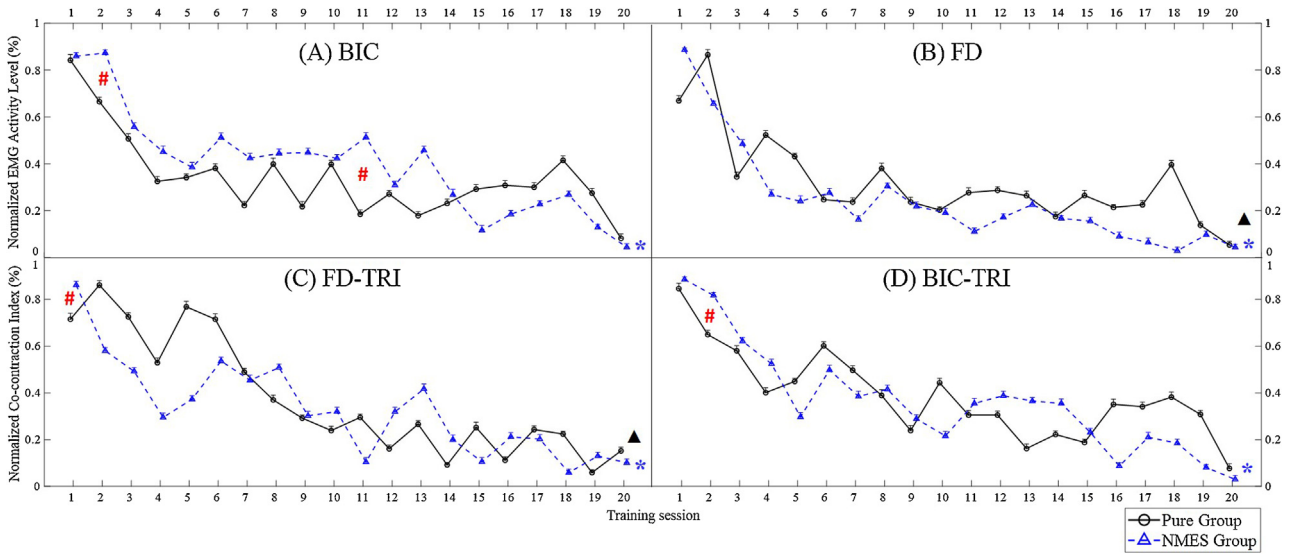

Fig. 4. The variation of electromyography (EMG) parameters recorded across the 20 training sessions in both NMES robotic hand and pure robotic hand groups: (A) The normalized EMG activation levels of the biceps brachii (BIC) muscles during the bare-hand evaluation. (B) The normalized EMG activation levels of the flexor digitorum (FD) muscles during the bare-hand evaluation. (C) The changes of the normalized Co-contraction Indexes (CI) of the FD and triceps brachii (TRI) muscle pairs during the bare-hand evaluation. (D) The changes of the normalized CIs of the BIC and TRI muscle pairs during the bare-hand evaluation. The values are presented as mean values with SE (error bar) in each session. The significant inter-group difference is indicated by "#" ($P < 0.05$, independent t-test), and "*" is used to indicate the significant intragroup difference in NMES group and "▲" is used to indicate the significant intragroup difference in pure group ($P < 0.05$, one-way analysis of variance with Bonferroni *post hoc* tests).

Table 4
The statistical probabilities and the estimated effect sizes of the 2-way ANOVA test on the electromyography (EMG) parameters with respect to the independent factors of the group and session.

EMG parameters		2-way ANOVA		
		P (Partial η2)		
		Session	Group	S*G
EMG Activity Level	FD	$0.000^{\#\#\#}$ (0.211)	0.876 (0.000)	0.644 (0.028)
	BIC	$0.000^{\#\#\#}$ (0.118)	$0.004^{\#\#}$ (0.015)	0.469 (0.033)
Co-contraction Index	FD-TRI	$0.000^{\#\#\#}$ (0.130)	$0.005^{\#\#}$ (0.014)	0.867 (0.022)
	BIC-TRI	$0.000^{\#\#\#}$ (0.137)	$0.031^{\#}$ (0.008)	0.067 (0.050)

Differences with statistical significance are marked with '#' beside the P values. Significant levels are indicated as, # for <0.05, ## for ≤0.01, ### for ≤0.001.
Abbreviations: FD, flexor digitorum muscle; BIC, biceps brachii muscle; TRI, triceps brachii muscle; S*G, the interaction between the session and group.

was identified in the pure group only for the FD muscle ($P < 0.05$). There was a slow decline in the EMG activation level, with no equilibrium being met throughout the 20 training sessions. Significant group variations were found in the EMG activation levels of BIC muscle when a 2-way ANOVAs ($P < 0.05$) was carried out. To start with, there was a much higher activation level of the EMG for the NMES group than pure group. However, following the 14th session, the EMG activation level appeared to be lower in the NMES group than in the pure robot group. As Fig. 4(C) and (D) demonstrated, there were significant differences in CI values for the FD&TRI and BIC&TRI muscle pairs which were identified in the assessment throughout the 20 training sessions for the two groups. In the NMES group, significantly lower CI values were seen in the FD&TRI and BIC&TRI muscle pairs throughout the training process ($P < 0.05$). In the pure group, there was only a significant reduction for the CI values of the FD&TRI muscle pairs ($P < 0.05$). No descending plateau was met in terms of the CI values of the FD&TRI and BIC&TRI muscle pairs over the training sessions. It was also found that there were significant intergroup variations between the CI values of the FD&TRI and BIC&TRI muscle pairs when a 2-way ANOVAs ($P < 0.05$) was conducted. In terms of the CI value of the FD&TRI muscle pair, the CI value in the first session appeared to be much higher than that of the pure group ($P < 0.05$). Throughout the next five sessions, there was a rapid decline in the CI values of the NMES group, which became lower than the pure group. Then, the CI values of the two groups were gradually decreased to a comparable stage in later sessions (i.e., after 10 sessions). In terms of the CI values for BIC-TRI muscle pair, the NMES group had higher scores than the pure group for the first sessions, however, in later sessions (i.e., after 16 sessions), the NMES group showed lower CI values compared with the pure group. There were no significant increases or decreases found in the EMG parameters of other target muscles or muscle pairs.

4. Discussion

The results of the clinical assessments indicated the motor functions were significantly improved in both groups after training either assisted by the EMG-driven NMES robotic hand or the EMG-driven robotic hand, where the NMES group achieved more improvement in voluntary motor function and muscle coordination. As indicated by the FMA full score and FMA subscores, participants in the NMES group achieved significant improvements to their entire paretic upper limb after the EMG-driven NMES robotic hand training, and these improvements could be maintained for 3 months. For the pure group, a significant improvement to voluntary motor function could only be obtained in the FMA full score post training and at 3MFU, while no significant motor improvement could be found in the FMA subscores (FMA-S/E and FMA-W/H scores). It was also noticed that the NMES group obtained significantly better functional recovery than the pure group in

both the FMA full score and FMA-S/E score at both time points of post-assessment and 3MFU assessment. However, the motor improvement of the two groups indicated by the FMA-W/H score was comparable after the training and at 3MFU. This implied both robotic devices were effective in improving the motor function of the entire upper limb, whereas the proximal joints (e.g., shoulder and elbow) achieved more improvement compared with the distal joints (e.g., wrist and fingers). Similar findings have been widely observed not only in traditional rehabilitation, but also in the robot assisted training detailed in our previous studies [10,12,31] and others [38–40]. The possible reasons for the difficulty in improving functional recovery for the distal parts could be: (1) chronic stroke patients usually use muscles from the proximal to perform distal limb tasks, and this would lead to compensatory muscular activation patterns which differ from the unimpaired [16,38]; and (2) competition for motor recovery between the proximal parts and distal parts would occur when both related muscles are involved in the training program [41]. Additionally, when the compensatory motions from proximal muscles dominated the distal movements, the distal muscles would not be well practiced and remained impaired. On the contrary, the more the proximal muscles were trained, the better outcomes they could achieve. Interestingly, in this study, we found that the NMES group that provided NMES to the distal muscles could obtain significant motor improvement in the distal joints across the barrier of proximal compensation, with motor improvement also achieved in the proximal joints. This result is also in line with other studies on rehabilitation robots with NMES applied on the distal muscle [14,21,22]. Therefore, it is further suggested that the integration of NMES into the robotic system is capable of facilitating better motor recovery for chronic stroke patients. Meanwhile, NMES applied on distal muscle could benefit the recovery in the entire upper limb, particularly in the distal part, during the rehabilitation.

The ARAT score is mainly used to evaluate finger movements such as grasping, gripping, and pinching movements. The significant improvement in the ARAT scores after the training for both groups indicated that joint stability and fine precision in grasping of the fingers was improved. However, after 3 months, only the NMES group maintained a significant improvement in hand function. Conversely, a decrease of 2.14 points in the ARAT at 3MFU was observed in the pure group when compared with the post-assessment score. The better long-term recovery in hand function with the EMG-driven NMES robotic hand could be related to the reduced compensatory motions in the NMES group, who were more willing to practice with the paretic limb in their daily activities, i.e., the main reason leading to the improvements in 3MFU.

The MAS scores in Fig. 3 indicated that both EMG-driven robot and EMG-driven NMES robot assisted training could release muscle spasticity at the elbow, wrist, and finger joints, where only the NMES group achieved statistically significant reductions in MAS scores after the training and at 3MFU. Meanwhile, significantly lower MAS scores at the elbow joint for the NMES group were found after training when compared with the pure group, and this implied that the NMES group could achieve more released muscle spasticity at the elbow joint after the training. When comparing the MAS scores at 3MFU, significantly higher MAS scores of each joint were observed for the pure group in comparison with the NMES group. Furthermore, the recovery trends of muscle spasticity between the two groups after the training differed. For the NMES group, muscle spasticity remained slightly reduced at each joint, while a tendency for stiffness in the upper limb appeared in the pure group with increased MAS scores at each joint. A higher MAS score usually reflects an enhanced muscle tone as well as poorer control of synergic muscle activity [17]. Therefore, the results suggested that the robotic training with NMES was more effective in releasing muscle spasticity than the robotic training alone.

The significant improvement in muscle coordination during the training program could also be reflected by the variations of the EMG parameters (i.e., the normalized EMG activation levels and the normalized CIs) across the sessions. The reduced normalized EMG activation levels usually indicate muscle spasticity is released and the overactivation of muscle is reduced when performing a skill-requiring task [42,43]. The significantly decreased EMG activation level of the FD muscle in both groups indicated the released spasticity of the wrist and finger joints, which was consistent with the decreased MAS scores for the wrist and finger joints as shown in Fig. 3. Meanwhile, this also suggested a reduction in the excessive muscular activities in the FD muscle when performing the bare-hand evaluation task in both groups. Furthermore, the reduced excessive muscular activities implied the improvement in voluntary motor controls and muscle coordination during the hand-grasp movements and arm transportation could be obtained by both types of robotic hand training programs. Noticeably, additional improvement in the elbow joint reflected by the significantly decreased EMG activation level of the BIC muscle was obtained in the NMES group, while this finding was absent in the pure group. This indicated the EMG-driven NMES robotic hand training achieved significant improvement for the elbow joint, and an improvement in the wrist and finger joints, as the significantly increased FMA scores in the NMES group demonstrated. Although no significant intergroup differences were found for the EMG activation level of the BIC and FD muscles at the completion of the training program using an independent t-test, lower normalized EMG activation level of both the BIC and FD muscles could still be observed in the NMES group after 14 training sessions compared with the pure group. This might suggest that the robotic training with NMES had the potential to speed up the recovery progress for stroke patients, a finding which was consistent with Hu et al.'s study [14].

For the EMG parameter measured by CI, the decreased CI value of a muscle pair could reflect the released co-contraction between the muscle pair, and the two muscles could contract more independently during the desired task. It was observed that the CI values of the FD&TRI muscle pair were significantly decreased across the training program in both groups. The results suggested a reduction in the muscle coactivity between the proximal joint (i.e., elbow joint) and the distal joint (i.e., finger joints), and this could further imply a lesser compensation movement from the elbow joint after both kinds of training when performing the hand motions. In addition, a significant decrease in the CI values of the BIC&TRI muscle pair were found in the NMES group; this implied that the NMES group could also achieve improved muscle coordination between the elbow extension and flexion during reaching motions whereas the pure group could not. These improvements in the muscle coordination of the elbow and finger joints might also contribute to the significantly increased FMA-S/E and FMA-W/H scores. Meanwhile, a faster release of muscle co-contraction in the NMES group was observed on the CI values of FD&TRI muscle pair in the first 5 sessions and the CI values of BIC&TRI muscle pair in the last 5 sessions, which might suggest that the NMES robotic training could be more effective in promoting muscle coordination for upper limb. However, all the EMG parameters shown in Fig. 4 did not reach a plateau within the 20 sessions, and further improvement could be obtained by providing additional training sessions according to the theory of motor relearning [44].

In our previous study, a comparison between the effectiveness of the EMG-driven NMES robotic system and EMG-driven pure robotic system was conducted on wrist rehabilitation [14]. Similar results could be obtained to support better training efficacy using a combination of NMES and the pure robotic system, with significantly higher clinical scores and lower EMG parameters of CI. Noticeably, in that study [14], significantly faster progress in reducing

co-contraction in the flexor carpi radialis (FCR) and extensor carpi radialis (ECR) muscle pairs was observed in the NMES robot group, and after session 12, most of the CI values of the ECR and FCR pairs in the NMES robot group were significantly lower than those in the pure robot group. Since the ECR muscle controls the wrist extension phase and the FCR muscle controls the wrist flexion phase, the released co-contraction of the ECR and FCR pairs in the NMES robot group implied that the firing phases of the antagonist muscle pairs for the wrist joint were gradually separated across the training sessions. However, in this study, no significant variation was observed in the EMG activation level and CIs related to the ED muscle across the training sessions. A possible reason might be due to the different NMES stimulation strategies. In the previous wrist training study [14], the NMES was provided to the ECR muscle during the wrist extension phase and FCR muscle during the wrist flexion phase, respectively, while the NMES was only provided to the ED muscle for finger extension motions in this hand training. This might suggest that the training effects of NMES targets antagonist muscle pairs were better than NMES targeted on a single muscle. Therefore, in order to promote optimal training efficacy, further study could be conducted on investigating the training effectiveness of NMES with different stimulation strategies.

In this work, although no specific robotic system was applied to the shoulder and elbow joints, the functional recovery of the proximal joints indicated by FMA scores and released muscle spasticity indicated by the MAS scores was still obtained in both groups, where the NMES group were able to achieve more. Consistent results reflected by the EMG parameters (i.e., EMG activation level and CI) further suggested improved muscle coordination in the elbow joint for both groups. One possible reason might relate to the training protocol of task-oriented training including the vertical and lateral task training. It was reported that when such training tasks involve multiple joints, the rehabilitation outcome could be obtained for the entire upper limb [45]. During the vertical and lateral task training in our study, the participants were asked to perform the arm reaching and transportation movements, and these motions engaged the shoulder and elbow muscles. Another possible reason was that the adjacent proximal joint would be improved at the same time as the muscle surrounding the joint was trained. Similar findings have been observed in previous studies; i.e. that elbow training could achieve improvement in shoulder function and wrist training may result in elbow improvement [14,22]. Therefore, when the proximal-to-distal gradient of motor deficit is not present, task-oriented entire upper limb training is more effective than traditional joint-per-joint rehabilitation [46,47].

In the NMES robots adopted in this study and designed in our previous studies [12,14,22], the positions of the NMES are delivered to the main contracting muscles related to the target joints to be trained, e.g., ED muscle for finger extension for the hand [12], ECR and FCR muscles for the wrist [14], and BIC and TRI muscles for the elbow [2,22], with the purpose of improving the muscle force and proprioception of the target muscles by NMES with minimized learned disuse [15]. Different NMES positions other than the main contracting muscles for the target joint could result in varied rehabilitation effects, which will be explored in our future work.

5. Conclusion

This study is the first head-to-head comparison of the training effectiveness of an NMES robot and a pure robot, which provided directly assistance to the distal fingers, based on a randomized clinical trial for chronic stroke patients. The results (i.e., clinical assessments and EMG parameters) demonstrated that both training systems were effective in improving long-term functional recovery in distal joints of the upper limb, where the robotic system with NMES achieved more released muscle spasticity and more improvement in voluntary motor effort and muscle coordination. Additional motor improvements in the proximal joints were observed after NMES robotic hand training when NMES was applied to the distal muscle. This might imply that NMES could facilitate significant improvement for the entire upper limb even with a limited area of stimulation. This study further supports the feasibility and effectiveness of the NMES combined robotic system in upper limb rehabilitation for chronic stroke, especially in the distal part.

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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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