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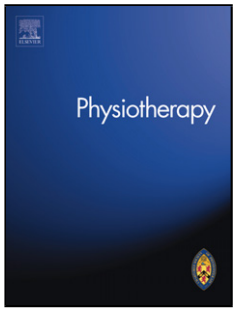

Neurophysiological changes accompanying reduction in upper limb motor impairments in response to exercise-based virtual rehabilitation after stroke: systematic review

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Neurophysiological changes accompanying reduction in upper limb motor impairments in response to exercise-based virtual rehabilitation after stroke: systematic review.

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Abstract

Background

Virtual reality-augmented therapist-delivered exercise-based training has promise for enhancing upper limb motor recovery after stroke. However, the neurophysiological mechanisms are unclear.

Objective

To find if neurophysiological changes are correlated with or accompany a reduction in motor impairment in response to virtual reality-aided exercise-based training

Data sources

Databases searched from inception to August 2020: MEDLINE, AMED, EMBASE, PUBMED, COCHRANE, CINHAL, PROQUEST and OPEN GREY.

Eligibility criteria

Studies that investigated virtual reality-augmented exercise-based training for the upper limb in adults with stroke, and, measured motor impairment and neurophysiological outcomes. Studies that combined VR with another technology were excluded.

Data extraction and synthesis

Using pre-prepared proformas, three reviewers independently: identified eligible studies, assessed potential risk-of-bias, and extracted data. A critical narrative synthesis was conducted. A meta-analysis was not possible because of heterogeneity in participants, interventions and outcome measures.

Results

Of 1,387 records identified, four studies were eligible and included in the review. Overall, included studies were assessed as having high potential risk-of-bias. The VR equipment, and control interventions varied between studies. Two studies measured motor impairment with the Fugl-Meyer Assessment but there was no commonality in the use of neurophysiological measures. One study found improvement in neurophysiological measures only. The other three studies found a reduction in motor impairment and changes in neurophysiological outcomes, but did not calculate correlation coefficients.

Conclusion

There is insufficient evidence to identify the neurophysiological changes that are correlated with, or accompany, reduction in upper limb motor impairment in response to virtual reality-augmented exercise-based training after stroke.

Contribution of paper statement

- Virtual reality-aided exercise-based training is a promising intervention for upper limb motor recovery after stroke but the neural mechanisms are unclear
- This systematic review of studies, not just controlled designs, found evidence for a reduction in motor impairment and changes in neurophysiology but the relationship could not be determined
- More research is needed to understand the neural mechanisms associated with a reduction in upper limb motor impairment in response to virtual reality-aided exercise-based training

Prospero Database Registration number: 2017 CRD42017071312

Keywords: Stroke; Rehabilitation; Virtual Reality; Motor recovery; Upper limb; Neuromuscular.

Introduction

Stroke is a leading cause of disability globally. Notably, as many as 75% of stroke survivors are left with an upper limb impairment that impacts adversely on their quality of life [1,2]. Current evidence-based guidelines for rehabilitation recommend providing high doses of repetitive functional exercises (exercise-based training), to facilitate neural plasticity and promote motor recovery [1,3]. In clinical practice, delivering high-dose exercise-based training is challenging due to resource constraints, time and stroke survivor adherence to therapy prescription [4,5]. The need for solutions to these challenges is accentuated by the increasing incidence and prevalence rates of stroke [6]. Technology is a proposed solution to augment therapist-delivered exercise-based training including Virtual Reality platforms (VR) [7]. Non-immersive VR (e.g. translation of real-time movements onto an onscreen avatar) could be an economical and safe way to augment delivery [8]. However, the evidence-base is limited by small sample sizes and the use of heterogeneous outcome measures and protocols [8–17].

Further improvements in stroke rehabilitation are promised by promoting motor recovery and limiting compensatory behaviour [18,19]. The indications of motor impairment reduction in response to VR are promising, but to understand how it may effect motor recovery, it is important to identify the neurophysiological underpinnings (correlates) [20]. A systematic review was undertaken to address the following research questions: (1) What are the neurophysiological correlates of upper limb motor impairment response to VR augmented

exercise-based training following a stroke, and (2) Is there evidence that an improvement of motor impairment occurs alongside change in neurophysiological measures?

Methods

Design

A systematic review conducted according to the Cochrane Collaboration guidelines [21]. Three reviewers worked independently, using pre-prepared proformas to (a) identify eligible studies, (b) assess the potential risk of bias and (c) extract data. Disagreements were resolved through referral to the full text with a fourth reviewer arbitrating if an agreement could not be achieved.

Searching for studies

The search strategy was developed in collaboration with a research librarian. Eight online databases were searched from their inception to August 2020: MEDLINE, AMED, EMBASE, PUBMED, COCHRANE, CINHAL, PROQUEST and OPEN GREY. The search combined MeSH and non-MeSH terms. An example of the search strategy, that used for MEDLINE, is provided in the online supplement. The search strategy was adapted as appropriate for different databases. The reference lists of eligible articles were hand-searched for potential studies not identified using the databases.

Eligibility Criteria

Types of studies

All experimental study designs were included if they investigated an experimental and a control condition before and after the provision of a VR intervention (defined in subsection – types of intervention).

Types of participants

Participants were at least 18 years old and had an upper limb motor impairment at any time point after stroke. Studies were excluded if they investigated participants who had a diagnosis of a neurological condition in addition to stroke.

Types of intervention

Studies were eligible if they included VR-augmented exercise-based training designed to reduce motor impairment and used an electronic screen. All VR devices were included, ranging from immersive (i.e. using headsets) to non-immersive (i.e. real-time movement replicated via an onscreen avatar). However, studies that investigated VR combined with another rehabilitation technology (e.g. a robotic arm device) were excluded. This was because the focus was understanding how VR might augment the effects of therapist-delivered exercise-based training.

Types of measures

Studies were eligible if they reported measures of motor impairment (i.e. Fugl-Meyer, biomechanical variables) and neural measures (i.e. EMG, TMS, fMRI – derived measures).

Assessment of potential risk of bias

The Cochrane risk of bias tool (CROB) was used [22].

Data extracted

At the baseline point for included studies, the data extracted were the number of participants in experimental and control condition; age; time since stroke; and the values for motor and neurophysiological impairment. For each included study, the intervention characteristics extracted were: number of weeks, number of sessions, duration of each session, device details and training task. At the outcome point for included studies, the data extracted were: the number of participants in each condition; time since baseline; and the values for motor and

neural impairment. If data was not available within the publications, then the authors were contacted for the data required.

Synthesis

A meta-analysis was not possible because of the heterogeneity in participants, interventions and outcome measures. A narrative synthesis was, therefore undertaken to address the research questions.

Results

Identification of studies

The PRISMA flowchart is provided in Figure 1. Initially, 1764 records were identified from the electronic searches. Removal of duplicates left 1387 records, of which 1296 were excluded. Consequently, 91 full-text articles were screened for eligibility. No additional records were identified from searching the reference lists of eligible full-text articles. Four articles met the eligibility criteria [23–26]. The main reasons for records to be excluded were: a lack of neurophysiological outcome measures, using virtual reality combined with another intervention, and no control condition.

[Figure 1]

Characteristics of included studies

Types of studies

The four included studies had different experimental designs:

- parallel-group controlled trial [24];
- randomised cross-over trial [23];

- single-group repeated measures study, with the control phase preceding the intervention phase [26];
- pre/post-test randomised controlled design [25].

Participants

The included studies reported baseline characteristics for a total of 74 participants (table 1). The mean (SD) age of participants was 62.35 (10.5) years with no discernable difference between the VR conditions, 62.67 (9.41) years, and the control conditions 61.39 (10.42) years. The median (IQR Q1 to Q3) time since stroke onset was: 2 (1.2 to 5) years for all participants, 3 (1.5 to 5.9) years for participants in the VR conditions, and 2.2 (1.2 to 5.4) years for participants in the control conditions.

The severity of motor impairment at baseline of participants in included studies ranged from moderate to severe as reported in the studies' inclusion criteria and demonstrated in the various baseline measures reported (i.e. passive paretic hand extension-flexion [23], FMA scores [24,25], paretic finger and elbow AROM [26].

[Table 1]

Virtual Reality intervention equipment and procedures

There was a variety of equipment used for VR conditions (table 2). All included studies used a computer and screen in their set-up [23–26]. Three included studies used types of data collection gloves [23–25]. One study used surface Electromyography (sEMG) to map upper extremity movements [26]. The upper limb tasks were tailored for individuals. Planned amounts (doses) of the intervention varied between studies with only one reporting actual dose completed [26].

[Table 2]

Control intervention procedures

The control conditions differed across the included studies (table 2). In two studies, the control condition was no therapy [25,26]. In the other two studies, the control condition was a comparator task designed to mimic the movements of the virtual reality intervention tasks but without the replication of the participants' real-time movements [23,24]. Planned doses for control conditions matched those for VR conditions.

Outcome timepoints

All studies collected data before and after the intervention period for both conditions but the outcome timepoints varied (Table 3) [23–26]. In one study, an additional time point was needed for one participant due to their schedule requiring an eight-week intervention period instead of the intended five [26]. One study included a three-month post-intervention follow-up collection point for the VR condition to check for retention of any changes acquired [23].

[Table 3]

Motor impairment outcome measures

The motor impairment outcome measures varied across included studies (table 4 and online supplement table 2). Only two included studies used the same measure, namely the Fugl-Meyer Upper Extremity (FM-UE) scores to determine the severity of motor impairment [24,25].

[Table 4]

Neurophysiology outcome measures

There was no commonality between the neurophysiological outcome measures used in the included studies (Table 4). Two studies used functional Magnetic Resonance Imaging (fMRI), but within differing anatomical regions of interest collecting measures including:

laterality index; number of significantly activated voxels; and relative volume and intensity index [23,25]. One included study used transcranial magnetic stimulation (TMS) to collect measures (e.g. Motor Evoked Potentials (MEPs)) from the Abductor Pollicis Brevis (ABP) and Extensor Carpi Radialis (ECR) muscles [24]. And then, one study used surface electromyography (sEMG) to measure the co-contraction of wrist flexors and extensors [26].

Risk of potential bias

Overall the included studies were assessed as having a high risk of potential bias, especially for blinding and incomplete outcome data (table 5). Three studies had a low risk of potential bias for random sequence generation (27) and selective reporting (28, 29).

[Table 5]

Narrative Synthesis

The published reports of the included studies did not provide data on the correlation between neurophysiological and motor impairment changes in response to VR augmented exercise-based training after stroke (question 1). Authors of the included papers were contacted and of the three who responded appropriate raw data was not available. Therefore correlations could not be calculated.

Three of the four included studies found an improvement in motor impairment and a change in neurophysiological measures (Question 2, Table 4) [23–25]. One study reported improvement in flexion and extension of the more paretic fingers ($p = 0.01$) and an increase in the stimulation efficacy within the ipsilesional primary motor cortex for the APB representation ($p < 0.01$) and the ECR ($p = 0.05$) [24]. There were no other reported improvements post-intervention within the motor impairment measures used. There was also no significant change within the centroid location of the cortical motor areas producing MEPS for the ABP and ECR within the primary motor cortex [24]. The second included

study found a significant change in the active index finger range of motion post-VR intervention ($p = 0.004$). This was accompanied by a significant decrease in the relative volume within the ipsilesional SMA ($p = 0.008$) [23]. No other significant changes occurred within the other fMRI derived measures (i.e. laterality and intensity index). The third included study found a significant increase in the laterality index ($p < 0.05$) and the number of significantly activated voxels ($p = 0.05$) within the ipsilesional hemisphere for SM1 accompanied by a significant improvement in Fugl-Meyer upper limb score, compared to the control group ($p < 0.05$), during reaching, lifting and grasping motor movements [25].

The fourth included study showed a significant change within the neurophysiological measures collected but no improvement in the motor impairment measures [26].

Discussion

This systematic review found no data with which to identify the neurophysiological correlates of change in motor impairment in response to VR augmented exercise-based training for the upper limb after stroke (question 1). Of the four included studies, three found a change in motor impairment and a neurophysiological change (question 2). However, across the four studies, many outcome measures of motor impairment and neurophysiology showed no change between pre-intervention and post-intervention time points (question 2). Consequently, this systematic review found insufficient robust data to provide an understanding of the neurophysiological changes underlying reduction in motor impairment in response to VR exercise-based intervention. Especially considering the potential high risk of bias identified for included studies.

The findings of this review are in broad agreement with other reviews namely an initial change in motor impairment in response to VR augmented exercise-based training [8–17]. Previous findings have been used to steer the development of VR rehabilitation devices

[8,27] and support the theory that the use of VR training facilitates neural plasticity and reduces motor impairment [28,29]. Although there is a promising reduction in motor impairment reported within the included studies of this review it is important to interpret this in light of methodological strengths and weaknesses.

Importantly, the potential risk of bias of included studies was high overall. Notably, the attrition rates often were not accounted for, and reasons for withdrawal not reported. It is possible that the VR rehabilitation devices tested did not have the usability and acceptability required for integration into healthcare [30,31]. So, it is necessary to understand if attrition rates could be due to the device features, therapy procedures, and/or dose. Essentially, the lack of reporting within the included studies hindered the author's ability to address the aims of the review (e.g. means, standard deviations, effect sizes and confidence intervals were often missing or incomplete). Although the authors of the included studies were contacted and asked for data for this review this was not forthcoming. All the included studies lacked statistical power due to small sample sizes, including one that only completed neural measures on three control condition participants, as opposed to the fourteen in the VR condition [24].

The previous reviews, and this one, recommend that there is a need for larger well-designed trials [8–17]. This call for robust evidence has not changed in the last decade though the included studies can provide a foundation for further investigative work to be carried out with a rigorous staged approach [18,32]. This is an important future step to evaluate whether motor impairment reduction is based upon neurophysiological [33].

It is important to interpret the findings of this review whilst considering its strengths and limitations. The included studies were heterogeneous which, in part, could be due to the various forms of VR evaluated. An appropriate, concise stratification of devices and

protocols falling under the umbrella 'Virtual Reality' is required. For example, the differing levels of participant engagement particularly with the different levels of immersion [8,34].

It is possible that the eligibility criteria were too restrictive as studies that combined VR with another intervention such as robotic assistive devices were excluded. This decision was made because the clinical focus for the review was using VR to augment therapist-delivered exercise-based intervention.

A strength of this review is that the literature search was not restricted by date, or study design, allowing for a comprehensive overview of potentially relevant studies. Also, a strength is that this was, to our knowledge, the first systematic review that aimed to identify the neurophysiological correlates of changes in upper limb motor impairment in response to VR augmented exercised based interventions.

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Figure 1. Prisma diagram of searches and identification of included studies in this review.

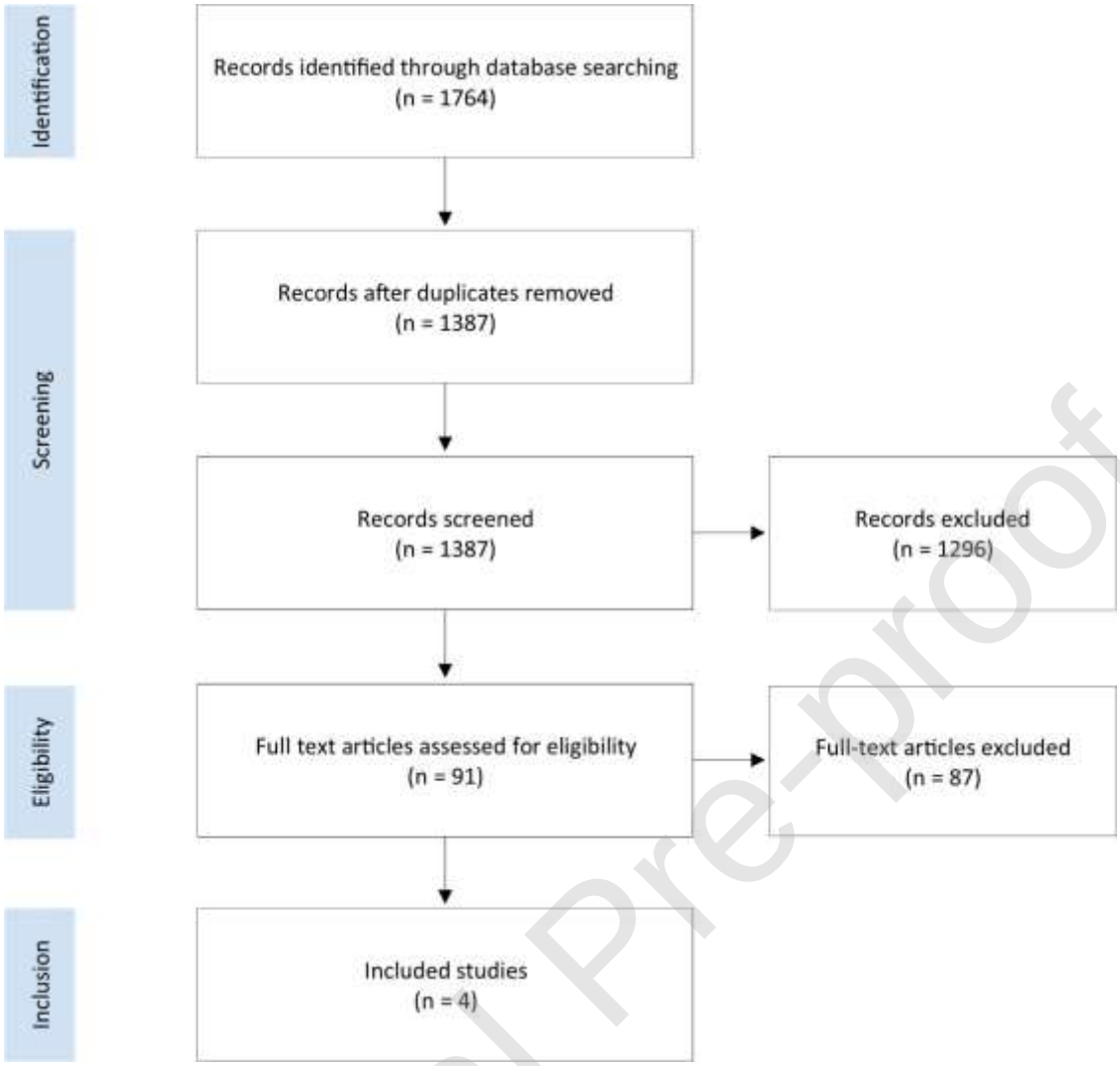

Table 1. Baseline characteristics of participants in included studies

Study reference	**Number of participants**		**Age, years.** mean (standard deviation, unless otherwise stated)		**Gender** (female: male)		**Time since stroke, years.** median (IQR Q1 to Q3)[a]		**More paretic side** (left: right)		**Type** (haemorrhagic: ischemic); **location of stroke lesion**	
	VR	**Ctrl**	**VR**	**Ctrl**	**VR**	**Ctrl**	**VR**	**Ctrl**	**VR**	**Ctrl**	**VR**	**Ctrl**
[24]	17	18	65 (10)	62 (13)	8: 9	11: 6	*Not reported*	*Not reported*	11: 6	9: 9	6: 11; Location not reported.	6: 12; Location not reported.
[23]	10	10	66 (7)	66 (7)	9: 1	6: 4	3 (1.6 to 5.8)	1.9 (1.2 to 4.8)	5: 5	8: 2	Type not reported; cortical (5): subcortical (5)	Type not reported; cortical (3): subcortical (7).
[25]	5	5	55 (SE 5)	55 (SE 5)	3: 2	3: 2	0.8 (0.6 to 1.9)	1 (0.8 to 1.5)	Not reported		2: 3 Thalamic: R =1, L=1; Cortical: R=1, L=0; Corona radiata R=1, L=1	2: 3 Thalamic: R=1, L=1; Corona radiata: R=1, L=2.
[26]	9[a]		60 (9[a])		4:5[a]		5 (2.5 to 9)[b]		6:3[a]		Type not reported[b]; Unknown = 4; Brainstem = 2; Basal Ganglia = 1; Frontal = 1; Parietal/Frontal = 1.	

SE = Standard Error; R = right; L = left; VR = virtual reality condition; Ctrl = control condition; *not reported* = author did not report data for the calculation to be carried out

a, Time since stroke was non-normally distributed

b, repeated measures design, participants took part in both intervention and control conditions.

Table 2. Characteristics of the virtual reality (VR) and control conditions in included studies

Study reference	VR intervention				Control intervention		
	Equipment	**Task**	**Planned Dose**	**Adherence to planned dose**	**Task**	**Dose**	**Fidelity**
[23]	Computer with customized software. Data gloves containing custom-made electro-goniometers, each with 2 potentiometers capturing (extension/flexion of the index MP joint and wrist). First-person perspective, with real-time hand movements translated on-screen (joint movement, represented through voltage collected at 100hz).	*Target:* Flexion/extension with the index finger and wrist to complete waveforms appearing on the computer. *Game:* The screen showed a target waveform and tracking response from the participants. *Tailored:* Knowledge of results via an accuracy score with text instructions on how to improve.	2 weeks 10 sessions, 120 mins each Paretic side for 90% of the training.	*Not reported*	*Target:* flexion/extension with the index finger and wrist. *Game:* screen displaying a sweeping cursor, but no target shown, no feedback provided	2 weeks 10 sessions, 120 mins each.	*Not reported*
[24]	Computer with customized software. Camera to capture UE movement (trunk movements were filtered out). Data gloves equipped with bend sensors capturing finger	*Target:* bilateral reaching movements with wrist and fingers flexion/extension. *Game:* Interception and grasping of virtual spheres. *Tailored:* performance ratio (successful	3 weeks 15 sessions, 30 mins each Equally split between each hand	*Not reported*	*Target:* Mimic the VR-intervention movements. *Game:* stacking/un-stacking of plastic cups with right and left hand consecutively.	3 weeks 15 sessions, 30 mins each	*Not reported*

Study reference	VR intervention				Control intervention		
	Equipment	**Task**	**Planned Dose**	**Adherence to planned dose**	**Task**	**Dose**	**Fidelity**
	flexion and extension. First-person perspective, with real-time movement translated on-screen	trials over total trials) was kept above 0.6 and below 0.8. *Customized:* trajectories (differing hand and grasp motions); velocity.					
[25]	Computer with customized software. Camera to capture UE movement Data gloves for movement capture. First-person perspective, with real-time movement translated on-screen.	*Target:* reaching, lifting and grasping motor skills (i.e. hand soccer). *Game:* Combination of custom games, such as bide-ball; soccer. *Tailored:* created and overseen by therapists. *Customized:* speed, angles and lifting force for each game. *Feedback:* error rate, speed, direction, joint position and resistive force feedback.	4 weeks 20 sessions, 60 mins each	*Not reported*	No therapy	No therapy	No therapy
[26]	Computer with customized software.	*Target:* Controlled the aim using their affected	4 weeks 5 days per	Sessions: mean16.8 (SD 7.0);	No therapy	No therapy	No therapy

Study reference	VR intervention				Control intervention		
	Equipment	**Task**	**Planned Dose**	**Adherence to planned dose**	**Task**	**Dose**	**Fidelity**
	To detect movements, sEMG used for the wrist flexor carpi radialis and extensor digitorium communis movements. First-person perspective, with real-time movement translated on-screen	upper extremity and launched the ball by clicking a button using the less affected hand *Game:* Peggle - *P*articipants attempt to clear the board of orange pegs by identifying the correct angle to launch a ball to eliminate pegs. *Tailored:* software converted muscle activity into movements used to control the game. Sensitivity can be adjusted to detect very low levels of activations *Customized:* Conversion was adjusted as needed to facilitate challenging but successful game play.	week; up to 45 (mins, per day) or a total of 45 hours a week. .	Hours: mean 11.9 (SD 5.8) Only recorded sessions that lasted more than 5 minutes One participant carried out the intervention at the research lab instead of their home.			

Table 3. Neurophysiological (NP) and motor impairment (MI) data measurement points in included studies.

Study timepoint	Included study reference							
	[24]		[23]		[26] [c]		[25]	
	NP	MI	NP	MI	NP	MI	NP	MI
Day 1					✓	✓	✓	✓
Day 10	✓	✓	✓[a]	✓[a]				
Day 15			✓[b]	✓[b]				
Day 28		✓						
Day 56					✓	✓	✓	✓
Day 84					✓[d]	✓[d]		
Day 91	✓	✓						

[a]: Only the control group received a crossover test after 10 days

[b.] Only the virtual reality group received a follow-up test 3 months post-test

[c.] Day 1 measures were beginning of control phase and day 28 measures were end of the control phase

[d]: One participant undertook outcome measures at day 112

Table 4. Motor impairment and neurophysiological measures before and after the intervention phase

Study reference	**Motor impairment changes reported**				**Neurophysiological changes reported**				
	measure	**Before**	**After**	**Significant change**	**measure**	**Before**	**After**	**Significant change**	
[24]	1. Ashworth proximal	m = 1.24 sd = 1.25	m = 1.18 sd = 1.25	x	1. Stimulation efficacy[1] comparison across hemispheres, APB for the M1	*Not reported*	*Not reported*	↑ Ipsilesional	m = 4.17 sd = 9.86 p < .01
	2. Ashworth distal	m = 1.47 sd = 1.51	m = 1.35 sd = 1.19	x	2. Stimulation efficacy[1] comparison across hemispheres, ECR for the M1	*Not reported*	*Not reported*	↑ Ipsilesional	m = 5.21 sd = 10.98 p = 0.05
	3. More paretic fingers flexion/extension	*Not reported*	*Not reported*	↑ week 2/3 p = 0.01	3. Centroid location of the cortical motor areas, producing MEPs APB in M1	med = 0.1	med = 0.55	x	
	4. Grip force (kg)	m = 6.15 sd = 5.04	m = 6.36 sd = 5.82	x	4. Centroid location of the cortical motor areas, producing MEPs ECR in M1	med = 0.72	med = 1.41	x	

Study reference	Motor impairment changes reported					Neurophysiological changes reported				
	measure	**Before**	**After**	**Significant change**		**measure**	**Before**	**After**	**Significant change**	
	5. MRC proximal	m = 3.47 sd = 0.51	m = 3.35 sd = 86.18	x						
	6. MRC distal	m = 2.82 sd = 1.19	m = 3.12 sd = 1.05	x						
	7. Fugl – Meyer upper limb	m = 42.94 sd = 14.37	m = 42.77 sd = 15.02	x						
[26]	1. Active range of motion wrist extension (deg)	m = 31.6 sd = 17.7	m = 25.4 sd = 17.7	x		1. Maximum Voluntary Contractions (MVCs)	m = 3.47 sd = 5.85	m = 5.84 sd = 9.78	↑ selection activation of the wrist extensor	z = -1.992 p = 0.046
	2. Elbow extension (deg)	m = 96.8, sd = 24.7	m = 95.5, sd = 22.1	x						
	3. Reach time (s)	m = 2.52, sd = 1	m = 95.5, sd = 22.1	x						
	4. Maximum trunk displacement (mm)	m = 123.22 sd = 65.1	m = 131.7 sd = 49.6	x						
[23]	1. Finger active range of motion (deg)	m = 64.5, sd = 10.8	m = 86.5 sd = 8.4	↑ more paretic index finger	p = 0.004	1. Relative volume (fMRI)	*Not reported*	*Not reported*	↓ Ipsilesional in the SMA anatomical region	p = 0.008
						2. Laterality index (fMRI)	*Not reported*	*Not reported*	x	

Study reference	Motor impairment changes reported					Neurophysiological changes reported				
	measure	**Before**	**After**	**Significant change**		**measure**	**Before**	**After**	**Significant change**	
						3. Intensity index (fMRI)	*Not reported*	*Not reported*	x	
[25]	1. Fugl-Meyer upper extremity	m = 51 sd = 7.12	m = 58 sd = 6.25	x		1. Laterality index (fMRI)	m = 0.1 sd = 0.2	m = 0.9 se = 0.1	↑ ipsilesional in the SM1 anatomical region	p < 0.05
						2, Number of significantly activated voxels	m = 57.8 se = 27.2	m = 4.4 sd = 4.4	↑ Ipsilesional in the SM1 anatomical region	p = 0.05

NB. 1. The stimulation efficacy was determined as the greatest value in the 80th percentile of Motor Evoked Potentials (MEPs); divided by the maximum stimulation intensity
m = mean; **sd** = standard deviation; **med** = median; **se** = standard error.
ABP = abductor pollicis longus muscle; **ECR** = Extensor Carpi Radialis; **M1** = primary motor cortex; **SM1** = Sensorimotor cortex
MEPs = Motor Evoked Potentials; **fMRI** = functional magnetic resonance imaging

Table 5. Potential risk of bias assessed with the Cochrane tool.

Study reference	Random sequence generation (selection bias)	Allocation concealment	Selective reporting (reporting bias)	Blinding or participants and personnel (performance bias)	Blinding of outcome assessment (Detection bias)	Incomplete outcome data (attrition bias)

[24]	+	?	-	-	-	-
[23]	?	-	-	-	-	-
[26]	-	-	+	-	-	-
[25]	?	-	+	-	?	-

Key.

+ Low risk of bias

? Unclear risk of bias

- High risk of bias