Journal of
Clinical Medicine

Review

A Scoping Review of Technology-Based Approaches for Upper Limb Motor Rehabilitation after Stroke: Are We Really Targeting Severe Impairment?

Emma Colamarino [1,2], Giovanni Morone [3,*], Jlenia Toppi [1,2], Angela Riccio [2], Febo Cincotti [1,2], Donatella Mattia [2] and Floriana Pichiorri [2]

[1] Department of Computer, Control, and Management Engineering "Antonio Ruberti", Sapienza University of Rome, 00185 Rome, Italy; emma.colamarino@uniroma1.it (E.C.); jlenia.toppi@uniroma1.it (J.T.); cincotti@diag.uniroma1.it (F.C.)
[2] IRCCS Fondazione Santa Lucia, 00179 Rome, Italy; a.riccio@hsantalucia.it (A.R.); d.mattia@hsantalucia.it (D.M.); f.pichiorri@hsantalucia.it (F.P.)
[3] Department of Life, Health and Environmental Sciences, University of L'Aquila, 67100 L'Aquila, Italy
* Correspondence: giovanni.morone@univaq.it

Abstract: Technology-based approaches for upper limb (UL) motor rehabilitation after stroke are mostly designed for severely affected patients to increase their recovery chances. However, the available randomized controlled trials (RCTs) focused on the efficacy of technology-based interventions often include patients with a wide range of motor impairment. This scoping review aims at overviewing the actual severity of stroke patients enrolled in RCTs that claim to specifically address UL severe motor impairment. The literature search was conducted on the Scopus and PubMed databases and included articles from 2008 to May 2024, specifically RCTs investigating the impact of technology-based interventions on UL motor functional recovery after stroke. Forty-eight studies were selected. They showed that, upon patients' enrollment, the values of the UL Fugl-Meyer Assessment and Action Research Arm Test covered the whole range of both scales, thus revealing the non-selective inclusion of severely impaired patients. Heterogeneity in terms of numerosity, characteristics of enrolled patients, trial design, implementation, and reporting was present across the studies. No clear difference in the severity of the included patients according to the intervention type was found. Patient stratification upon enrollment is crucial to best direct resources to those patients who will benefit the most from a given technology-assisted approach (personalized rehabilitation).

Keywords: technological interventions; motor rehabilitation; upper limb; stroke; severe impairment

check for updates

Citation: Colamarino, E.; Morone, G.; Toppi, J.; Riccio, A.; Cincotti, F.; Mattia, D.; Pichiorri, F. A Scoping Review of Technology-Based Approaches for Upper Limb Motor Rehabilitation after Stroke: Are We Really Targeting Severe Impairment? *J. Clin. Med.* **2024**, *13*, 5414. https://doi.org/10.3390/jcm13185414

Academic Editor: Deed E. Harrison

Received: 12 August 2024
Revised: 5 September 2024
Accepted: 8 September 2024
Published: 12 September 2024

1. Introduction

Most technology-based approaches for motor rehabilitation after stroke have been originally designed and developed with severely affected patients in mind [1,2]. In post-stroke rehabilitation, traditional approaches targeting upper limb function often rely on the presence of residual motor capabilities and are, therefore, precluded to very severe (i.e., plegic) patients. Furthermore, technology can provide treatment with increased intensity, which is established as a crucial determinant of rehabilitation outcome [3]. In this regard, Constraint-Induced Movement Therapy (CIMT), which is still one of the most effective approaches for the upper limbs [4], represents a clear example of how technology can impact motor recovery only in those patients with residual motor function of the affected limb. The lack or scarceness of such residual motor function can be, at least partially, overcome with technology, such as neuromuscular stimulation combined with CIMT [5]. Thus, technology can not only enhance the intensity of the treatment but also increase the number of patients that can have access to a given therapy, increasing the chances for all patients (including those more severely affected) to regain independence.

However, randomized controlled trials (RCT) testing these technology-based rehabilitation approaches often include patients with a wide range of motor impairment and, sometimes, only a small proportion of patients actually fall in the severe range as defined by clinical scales. Indeed, patients' recruitment in rehabilitation is influenced by numerous factors and is still one of the most challenging steps for researchers aiming to bring technology into clinical practice [6]. The severity of motor deficit often comes with concomitant conditions, such as bed-confinement status (especially in the acute and subacute phases), cognitive impairment, pain, and depression, that altogether limit the ability of patients to participate in such trials. As the motor status at baseline is probably the most consistent prognostic factor of rehabilitation outcome [7], we believe that this factor accounts for the hesitating translational success of many of these technological approaches for several reasons. On one hand, the success of clinical trials may be facilitated by the participation of less severe patients who increase trial feasibility, especially in the subacute phase, and are naturally destined to a more favorable outcome. Consequently, the actual application of a given technology in severe patients may turn out disappointing in terms of outcome, regardless of the successful trial. On the other hand, some of these technological aids may provide little added benefit for less severe patients who can take advantage of other more traditional and less expensive rehabilitative exercises [4]. Furthermore, several aspects related to patients' recruitment add complexity to the ambitious task of proving the efficacy of novel rehabilitation strategies, such as post-stroke stage and the related adaptive and maladaptive changes that occur both at the central nervous system level and in peripheral tissues (e.g., spasticity).

In this scoping review, we provide an overview on the actual severity of patients recruited in RCTs carried out to analyze the efficacy of technology-based rehabilitation approaches targeting severe upper limb impairment (explicitly mentioning patients' severity in the title and/or abstract). According to our question, our research returned clinical studies investigating robotics, electrical or magnetic stimulation of the central nervous system (non-invasive brain stimulation, NIBS) or of peripheral structures (peripheral stimulation, PS), brain–computer interfaces (BCIs), virtual reality (VR), and, in general, advanced technological devices purposely developed for post-stroke motor rehabilitation. While the identification of the most effective approaches is out of the scope of this review [8], here we intend to verify the following:

(i) The actual severity of patients included in trials that explicitly declare to enroll severe subjects to confirm or refute the anecdotal notion of extreme variability in baseline motor impairment, which might be responsible for the hesitating translational success of such interventions [9];

(ii) Whether some of these technological approaches have been more consistently tested on severe patients than others and eventually speculate on why they have.

Furthermore, we check whether the severity of patients was considered as an inclusion criterion and/or employed for stratification for primary or secondary analyses. We take into account whether each considered study was or was not successful in confirming the efficacy of a given intervention, that is, the superiority/not superiority of the target intervention vs. the control condition (positive/negative results), also highlighting possible secondary analyses carried out by the authors to support their hypotheses.

The ultimate goal of this scoping review is to provide useful hints to improve patients' inclusion in RCTs evaluating novel technologies for motor rehabilitation in order to favor the optimization of resources and efforts towards tailored, highly technological rehabilitation interventions, which is instrumental to foster technology transfer into clinical practice.

2. Methods

2.1. Protocol and Eligibility Criteria

This scoping review was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) standards. Our protocol was drafted using the PRISMA extension for Scoping Reviews (PRISMA—ScR, [10]) and revised by the research team. To be included in the review, papers needed to describe technology-based rehabilitative interventions targeting the recovery of motor function of the upper limb in a stroke population.

Peer-reviewed journal papers were included as follows:

- Published between the period of 2008 and 2024;
- Written in English;
- Involved human participants in the framework of a randomized controlled trial.

Papers were excluded as follows:

- If they did not fit into the conceptual framework of the study (not a technology-based rehabilitative approach, wrong outcome);
- If they were reviews, study protocols, and meta-analyses.

2.2. Information Sources and Search Strategy

Studies eligible for review were identified through electronic databases, such as Scopus and PubMed, from 2008 to 23 May 2024. Grey literature was excluded from the search process. The search strategies consisted of free text terms in the topic “stroke” AND “severe” AND “rehabilitation” AND “Action Research Arm Test” OR “Fugl-Meyer Assessment” AND “randomised controlled trial” AND “upper limb” OR “hand”. The complete search terms and strategy are provided in the Supplementary Materials (Table S1). The search strategies were developed and executed by a biomedical engineer (EC) and further refined through team discussion. The search was peer-reviewed by other expert researchers, i.e., a neurologist (FP) and a physiatrist (GM), using the Peer Review of Electronic Search Strategies checklist and modified as required [11]. The final search results were imported into the online systematic review software Rayyan [12]. Duplicates were identified by means of the Rayyan duplicates search algorithm and removed by a researcher.

2.3. Selection of Sources of Evidence

Two reviewers (EC, FP) independently screened titles and abstracts for inclusion. For full-text screening, two reviewers (EC, FP) subsequently screened the full text of potentially relevant articles to determine inclusion using similar inclusion and exclusion criteria. We resolved disagreements on study selection by consensus and discussion with other reviewers if needed or by a single arbitrator (GM). To ensure reliability between reviewers, a series of training exercises were conducted prior to commencing screening. Inter-rater agreement for study inclusion was calculated using percent agreement; when it reached >80% across the team, we proceeded to the next stage. If lower agreement was observed, the inclusion and exclusion criteria were clarified, and another pilot test occurred.

2.4. Data Charting Process and Data Items

A data charting form was jointly developed by three reviewers to determine which variables to extract. Three reviewers (EC, FP, GM) independently charted the data, discussed the results, and continuously updated the data charting form in an iterative process.

For each article, data on the following characteristics were extracted:

- First Author Name;
- Year of publication;
- Source;
- Population sample size (participants per group);
- Severity of the upper limb impairment, i.e., Upper Extremity Fugl-Meyer Assessment score, FMA [13], and/or Action Research Arm Test, ARAT [14], expressed as the mean ± standard deviation (SD) or median and first and third quartile (Q1–Q3), per group, whenever available;
- Inclusion criteria in the RCT related to the upper limb impairment;
- Availability of the dataset used (Yes/No);
- Time since injury (TSI), i.e., stroke event, classified, according to [15,16], as

  - ≤1 month (acute)
  - ≤3 months (early subacute)
  - ≤6 months (subacute)
  - >6 months (chronic)
- Intervention type, classified as
  - Brain–Computer Interface (BCI)
  - Non-Invasive Brain Stimulation (NIBS)
  - Peripheral Stimulation (PS)
  - Robotic
  - Virtual Reality (VR) and Visual
- Comparator, i.e., control interventions and/or comparison conditions;
- Active motor action required (Yes/Yes whenever possible/No):
  - *Yes*, if the intervention type requires the participant's residual motor ability (active motor exercise from the participant)
  - *Yes whenever possible* refers to conditions foreseeing active motor exercise when feasible, with the technology providing assistance as needed (e.g., robotics)
  - *No* otherwise
- Combination of technological interventions (Yes/No);
- Dose, expressed as minutes x number of sessions;
- Primary and secondary outcomes;
- Key Findings, classified as Positive, Positive on secondary analyses, and Negative. We define Key Findings as the following:
  - *Positive* if between-group statistical analyses evaluated for the primary outcomes statistically confirm the hypothesis investigated in the study.
  - *Positive on secondary analyses* if between-group statistical analyses evaluated for sub-items of the primary/secondary outcomes or considering sub-groups of the population under investigation confirm the hypothesis investigated in the study or if within-group statistical analyses evaluated for the primary/secondary outcomes reveal a statistical improvement only for the experimental group.
  - *Negative* if between- and within-group analyses do not reveal statistically significant differences among groups.

  The threshold for statistical significance was set to 0.05.
- Stratification for secondary analyses according to an upper limb impairment criterion;
- Follow-up (Yes/No), i.e., if *Yes*, we reported the number of months after the end of the intervention;
- Setting: Inpatient/Outpatient.

The extracted data were collected in a table in which the rows represent the included articles and the columns represent variables (data items). The spreadsheet software Microsoft Excel (Version 2408) was used to create our custom extraction form. The choice was based on its ease of use, high customizability, and worldwide diffusion. Before extracting the data from all papers included in the scoping review, the extraction form was tested for further refinements and underwent a calibration phase. This entailed three reviewers independently extracting data from 5 papers each and meeting afterward to discuss any discrepancies, with further refinement of the form if a high level of agreement between reviewers was not obtained.

2.5. Synthesis of Results

To analyze the database, the following explanatory approaches are used: descriptive and frequency analysis and association analysis.

2.5.1. Descriptive and Frequency Analysis

Descriptive statistics are relative to the overall population of participants that was included in the selected studies in terms of the number of participants, sample size of intervention and control groups, dose of intervention, and severity of upper limb motor impairment upon enrollment as described by FMA and/or ARAT. The data have been summarized according to their distribution (modality and dispersion) by means of the mean and standard deviation (SD) or median and interquartile range (IQR), presented as the difference between the first quartile (Q1) and the third quartile (Q3), i.e., Q1–Q3.

Frequency analyses are relative to the following variables: time since injury (at least 4 classes, i.e., acute, early subacute, subacute, chronic participants), setting (at least 3 classes, i.e., inpatient/outpatient, inpatient, and outpatient), availability of the dataset used (2 classes, i.e., Yes or No), technological rehabilitative intervention type (at least 5 classes, i.e., BCI, NIBS, PS, Robotic, VR and Visual) and whether it did or did not require an active motor exercise from the participants (3 classes, i.e., Yes/Yes whenever possible/No), comparison conditions, primary and secondary outcome measures, presence/absence of follow-up evaluations (2 classes, i.e., Yes or No), key findings (3 classes, i.e., positive, negative, and positive on secondary analyses), and severity of upper limb deficit employed as an inclusion criterion for participant enrollment and/or stratification for secondary statistical analyses. In frequency analysis, the counts and percentages of articles in each cluster are calculated. Studies that share a similar approach towards a specific variable are clustered together, and those following different approaches are assigned to different groups. Clustering can be carried out based on the values of a single variable on the entire dataset or on a subset of articles that already belong to a cluster on a higher level.

All results are presented both narratively and by means of plot and pie charts when relevant.

2.5.2. Association Analysis

Association analysis explores the relationships between the variables. Since the number of possible combinations of variables is relatively large, the results are focused on those regarding the research questions. We hypothesize that the characteristics of the technological rehabilitation interventions would determine a difficulty in recruiting severely affected participants. Therefore, we have separately analyzed the severity of upper limb motor impairment at baseline (as assessed via FMA) according to the following:

- Type of intervention (e.g., Robotic, BCI, PS, . . .);
- Required active upper limb motor actions from the participant by the intervention itself.

For each analysis, studies that share a similar approach, i.e., type of intervention or required active motor action, are clustered together. For each level of the analyzed variable, i.e., 5 levels for the variable TYPE OF INTERVENTION and 3 levels for the variable MOTOR ACTION, the FMA data are pooled together. If needed, the mean and SD data are estimated from the data reported in the paper as the median and IQR by means of the formula in [17].

All results are expressed as the mean ± SD and presented both narratively and by means of plot charts.

3. Results

3.1. Selection of Sources of Evidence

The search returned a total of 189 papers. After the duplicate removal (96), 93 articles were screened. After screening of titles and abstracts, 41 papers were excluded due to the following reasons:

- The rehabilitative intervention under investigation does not include a technology-based approach; videos/instruction displayed on screens or other devices of everyday use (personal computers, tablet, smartphones) were not included;
- The design of the study does not follow the randomized controlled trial design (wrong study design);

- The effectiveness of the rehabilitative intervention under investigation was not assessed in terms of motor function improvement (wrong outcome);
- The paper presents a study protocol, a review, or a meta-analysis.

A total of 52 full-text papers were examined. Four studies were excluded during the full-text search and check. Thus, 48 articles were included in the scoping review.

The flowchart in Figure 1 presents the detailed search and selection process.

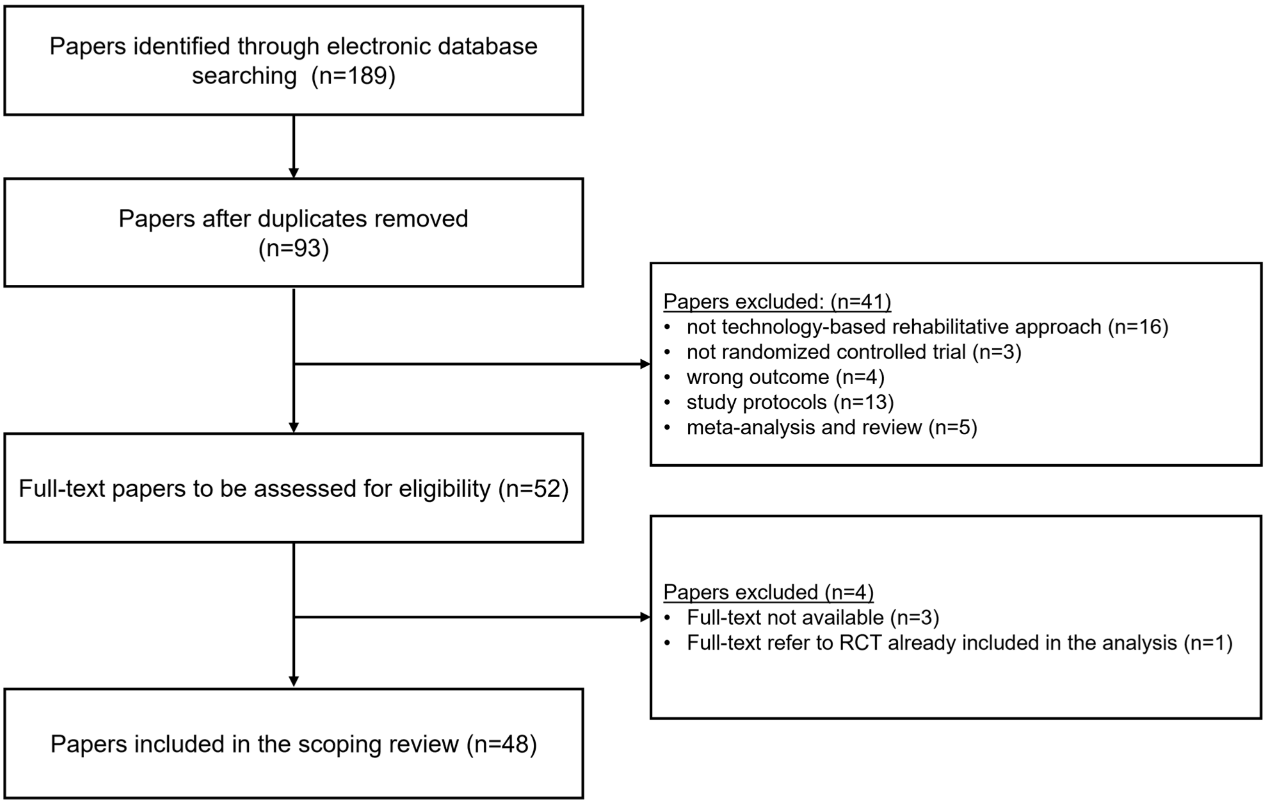

Figure 1. Flowchart of search and selection process.

3.2. Results of Individual Sources of Evidence

The results of individual sources of evidence are shown in Table 1. Table 1 reports a subset of the items described in the section *Data charting process and data items*.

Table 1. Studies included in this review. The following data are reported: name of first author and publication year, population sample size (number of participants per group, whenever available), severity of the impairment assessed via UE-FMA and ARAT (per group, whenever available), if inclusion criteria related to the upper limb impairment for the participant enrolment (IC) were defined, time since injury, intervention type, active motor action required, comparator, primary outcome measures, and key findings. UE-FMA and ARAT values are reported as the mean ± standard deviation or median and interquartile range (Q1–Q3).

First Author Name, Year of Publication	Population Sample Size (Participants per Group)	Severity of the Impairment (UE-FMA and/or ARAT per Group)	IC	Time Since Injury	Intervention Type	Active Motor Action Required	Comparator	Primary Outcome Measures	Key Findings
Hesse, 2008 [18]	EG: 27 CG: 27	UE-FMA EG: 8.8 ± 4.5 CG: 8.6 ± 3.5	Yes	ES	PS, Robotic	Yes, whenever possible	Different Technology	UE- FMA	Neg
Lo, 2010 [19]	EG: 47 CG1: 46 CG2: 27	UE-FMA EG: 19.7 ± 10.7 CG1: 17.3 ± 8.4 CG2: 20.3 ± 9.0	Yes	C	Robotic	Yes	Dose Equivalent UL Training, Usual Care	UE- FMA	Pos On Sec
Weber, 2010 [20]	EG: 10 CG: 13	ARAT EG: 19.5 ± 13.9 CG: 25.8 ± 15.5	Yes	C	PS	Yes	Without Technology	MAL	Neg
Shindo, 2011 [21]	EG: 10 CG: 10	UE-FMA EG: 24.4 ± 10.9 CG: 23.0 ± 13.1 ARAT EG: 9.3 ± 8.4 CG: 15.8 ± 13.7	Yes	ES	PS	Yes	Without technology	UE-FMA	Pos
Rosewilliam, 2012 [22]	EG: 31 CG: 36	ARAT EG: 0.0 ± 0.0 CG: 0.6 ± 3.5	Yes	A/ES	PS	No	Usual Care	ARAT	Neg
Ochi, 2013 [23]	EG: 9 CG: 9	UE-FMA EG: 23.2 ± 16.6 CG: 23.6 ± 16.7	Yes	C	NIBS, Robotic	No	Different Parameters	UE-FMA	Pos On Sec
Cordo, 2013 [24]	EG1: 22 EG2: 21	UE-FMA EG1: 23.1 ± 8.8 EG2: 19.4 ± 6.2	Yes	C	PS, Robotic	Yes	Different Technology	UE-FMA	Pos On Sec
Krewer, 2014 [25]	EG: 31 CG: 32	UE-FMA EG: 5 (4–27) CG: 4 (4–9)	Yes	C	PS	No	Sham Stimulation	MTS UE-FMA	Pos On Sec
Au-Yeung, 2014 [26]	EG: 29 CG1: 21 CG2: 23	ARAT EG: 8.9 ± 17.6 CG1: 3.1 ± 8.2 CG2: 9.2 ± 16.3	Yes	A	PS	No	Sham Stimulation, Usual Care	Force measures	Pos
Ang, 2015 [27]	EG: 11 CG: 14	UE-FMA EG: 26.3 ± 10.3 CG: 26.5 ± 18.2	Yes	C	BCI, Robotic	Yes	Different Combination	UE-FMA	Neg

Table 1. *Cont.*

First Author Name, Year of Publication	Population Sample Size (Participants per Group)	Severity of the Impairment (UE-FMA and/or ARAT per Group)	IC	Time Since Injury	Intervention Type	Active Motor Action Required	Comparator	Primary Outcome Measures	Key Findings
Pichiorri, 2015 [28]	EG: 14 CG: 14	UE-FMA EG: 23.4 ± 17.3 CG: 24.2 ± 18.2	No	ES/S	BCI, VR and Visual	No	Without Technology	UE-FMA	Pos
Pennati, 2015 [29]	EG1: 8 EG2: 7	UE-FMA EG1: 29.25 ± 13.91 EG2: 18.14 ± 5.27	No	C	Robotic	Yes	Different Combination	UE-FMA BBT FIM MAS	Neg
Carrico, 2016 [30]	EG: 18 CG: 18	UE-FMA EG: 25.7 ± 13.3 CG: 22.8 ± 15.0 ARAT EG: 13.9 ± 12.3 CG: 10.4 ± 11.2	Yes	C	PS	Yes	Sham Stimulation	UE-FMA	Pos
Wu, 2016 [31]	EG: 99 CG: 28	UE-FMA EG: 18.5 ± 9.7 CG: 20.3 ± 9.0	Yes	C	Robotic	Yes	Usual Care	UE-FMA	Pos
Frolov, 2017 [32]	EG: 55 CG: 19	UE-FMA EG: 24.0 (12.0–40.0) CG: 12.0 (11.0–49.0) ARAT EG: 4.0 (0.0–31.0) CG: 3.0 (0.0–30.0)	No	S/C	BCI, Robotic	No	Sham Control	UE-FMA ARAT	Pos On Sec
Tomic, 2017 [33]	EG: 13 CG: 13	UE-FMA EG: 26.5 ± 7.7 CG: 26.6 ± 7.5	Yes	ES	Robotic	Yes	Dose Equivalent UL Training	UE-FMA	Pos
Schick, 2017 [34]	EG: 16 CG: 17	UE-FMA EG: 16.67 ± 10.80 CG: 16.29 ± 9.00	Yes	ES	PS	No	Different Combination	UE-FMA	Pos On Sec
Brunner, 2017 [35]	EG: 57 CG: 55	ARAT EG: 25.8 ± 18.3 CG: 24.2 ± 18.6	Yes	ES	VR and Visual	Yes	Dose Equivalent UL Training	ARAT	Neg
Rabadi, 2017 [36]	EG: 8 CG: 8	ARAT EG: 4.0 ± 10.9 CG: 1.9 ± 4.2	Yes	A	NIBS	No	Sham Stimulation	ARAT	Neg
Marquez-Chin, 2017 [37]	EG: 10 CG: 11C	UE-FMA EG: 3.4 ± 4.8 CG: 4.4 ± 4.6	Yes	A/ES	PS	Yes	Usual Care	FIM UE-FMA	Pos
Carrico, 2018 [38]	EG: 33 CG: 22	UE-FMA EG: 18.48 ± 12.75 CG: 18.23 ± 13.34 ARAT EG: 11.58 ± 12.80 CG: 13.36 ± 14.68	Yes	S/C	PS	No	Sham Stimulation	WMFT	Pos

Table 1. *Cont.*

First Author Name, Year of Publication	Population Sample Size (Participants per Group)	Severity of the Impairment (UE-FMA and/or ARAT per Group)	IC	Time Since Injury	Intervention Type	Active Motor Action Required	Comparator	Primary Outcome Measures	Key Findings
Ding, 2018 [39]	EG: 38 CG: 41	UE-FMA EG: 25.66 ± 17.63 CG: 18.85 ± 16.38	No	S/C	VR and Visual	Yes	Dose Equivalent UL Training	UE-FMA	Pos
Conroy, 2019 [40]	EG: 22 CG: 19	UE-FMA EG: 20.7 ± 8.5 CG: 21.6 ± 8.5	Yes	C	Robotic	Yes	Different Combination	UE-FMA	Pos On Sec
Rodgers, 2019 [41]	EG: 239 CG1: 246 CG2: 223	UE-FMA EG: 18.0 ± 13.1 CG1: 18.2 ± 14.1 CG2: 18.2 ± 13.9 ARAT EG: 8.5 ± 11.9 CG1: 8.7 ± 11.9 CG2: 8.1 ± 11.5	Yes	S/C	Robotic	Yes, whenever possible	Dose Equivalent UL Training, Usual care	ARAT	Neg
Ramos-Murguialday, 2019 [42]	EG: 16 CG: 12	UE-FMA EG: 11.16 ± 1.73 CG: 13.29 ± 2.86	Yes	C	BCI, Robotic	Yes	Sham Control	UE-FMA (54)	Pos On Sec
Takebayashi, 2020 [43]	EG: 30 CG: 26	UE-FMA EG: 47.3 ± 7.4 (mild) CG: 45.1 ± 19.4 (mild) EG: 30.3 ± 12.5 (moderate) CG: 25.8 ± 10.5 (moderate) EG: 16.1 ± 10.5 (severe) CG: 14.8 ± 4.7 (severe)	Yes	ES	Robotic	Yes, whenever possible	Dose Equivalent UL Training	UE-FMA	Pos On Sec
Lee, 2020 [44]	EG1: 19 EG2: 19	UE-FMA EG1: 15.37 ± 5.14 EG2: 15.26 ± 4.37	Yes	S/C	Robotic	Yes, whenever possible	Different Technology	UE-FMA WMFT	(*)
Chew, 2020 [45]	EG: 10 CG: 9	UE-FMA EG: 35.3 ± 7.8 CG: 32.6 ± 8.1	Yes	C	BCI, NIBS	No	Sham Stimulation	UE-FMA	Pos On Sec
Lin, 2021 [46]	EG: 9 CG: 9	UE-FMA EG: 43.4 ± 14.5 CG: 28.3 ± 18.1	Yes	C	VR and Visual	Yes	Without technology	UE-FMA	Pos
Hu, 2021 [47]	EG: 7 CG: 5	UE-FMA EG: 12.70 ± 8.80 CG: 13.80 ± 6.65 ARAT EG: 3.29 ± 5.79 CG: 6.60 ± 12.29	Yes	S/C	BCI, VR and Visual	No	Without technology	UE-FMA	Pos On Sec
Boasquevisque, 2021 [48]	EG: 15 CG: 15	UE-FMA EG: 46 (8–56.8) CG: 22.5 (8.8–43.5)	No	A/ES	NIBS	No	Sham Stimulation	Safety (**)	Neg

Table 1. *Cont.*

First Author Name, Year of Publication	Population Sample Size (Participants per Group)	Severity of the Impairment (UE-FMA and/or ARAT per Group)	IC	Time Since Injury	Intervention Type	Active Motor Action Required	Comparator	Primary Outcome Measures	Key Findings
Dawson, 2021 [49]	EG: 53 CG: 54	UE-FMA EG: 34.4 ± 8.2 CG: 35.7 ± 7.8	Yes	C	PS	Yes	Sham Stimulation	UE-FMA	Pos
Llorens, 2021 [50]	EG: 14 CG: 15	UE-FMA EG: 9.50 ± 5.11 CG: 9.87 ± 4.82	Yes	C	NIBS, VR and Visual	Yes	Usual Care	UE-FMA	Pos
Cantillo-Negrete, 2021 [51]	10 crossover study	UE-FMA 17.5 ± 15.3 ARAT 4.3 ± 6.4	Yes	S/C	BCI, Robotic	No	Usual Care	UE-FMA	Neg
Takebayashi, 2022 [52]	EG1: 17 EG2: 13	UE-FMA EG1: 14.8 ± 7.0 (severe) EG2: 20.0 ± 5.6 (severe) EG1: 44.8 ± 5.2 (moderate) EG2: 46.6 ± 6.8 (moderate)	Yes	ES	Robotic	Yes, whenever possible	Different Parameters	UE-FMA WMFT	Pos On Sec
Jiang, 2022 [53]	EG: 24 CG: 20	UE-FMA EG: 12.38 ± 2.26 CG: 12.30 ± 2.39	Yes	A	PS	No	Usual Care	UE-FMA	Pos
Schrader, 2022 [54]	EG: 14 CG: 10	UE-FMA EG: 4.00 (0.75–8.25) CG: 3.00 (0.00–4.50)	Yes	A/S/C	Robotic	No	Without Technology	UE-FMA (60)	Pos
Ohnishi, 2022 [55]	EG1: 25 EG2: 22 EG3: 26 CG: 26	UE-FMA EG1: 4.0 (4.0–9.0) EG2: 4.0 (4.0–8.8) EG3: 4.0 (3.0–8.8) CG: 4.0 (4.0–5.8)	Yes	ES	PS	Yes	Different Parameters, Usual Care	SIAS UE-FMA MAS FIM	Pos
Huang, 2022 [56]	EG: 13 CG: 11	UE-FMA EG: 39.3 ± 17.9 CG: 34.2 ± 15.9	Yes	C	NIBS	No	Sham Stimulation	UE-FMA	Pos On Sec
Wong, 2022 [57]	EG: 15 CG: 15	UE-FMA EG: 31 ± 11 CG: 35 ± 14 ARAT EG: 19 ± 11 CG: 23 ± 19	Yes	A/ES	PS	Yes	Without Technology	ARAT	Neg
Cordo, 2022 [58]	EG: 44 CG: 39	UE-FMA EG: 20.9 ± 9.9 CG: 23.7 ± 11.2	Yes	ES/S	PS, Robotic	Yes	Different Parameters	UE-FMA	Pos
Takebayashi, 2022 [59]	EG1: 42 EG2: 39 CG: 36	UE-FMA EG1: 25.9 ± 8.6 EG2: 26.5 ± 11.0 CG: 25.0 ± 0.9	Yes	C	Robotic	Yes	Without Technology	UE-FMA	Pos On Sec

Table 1. *Cont.*

First Author Name, Year of Publication	Population Sample Size (Participants per Group)	Severity of the Impairment (UE-FMA and/or ARAT per Group)	IC	Time Since Injury	Intervention Type	Active Motor Action Required	Comparator	Primary Outcome Measures	Key Findings
Williamson, 2023 [60]	8 crossover study	UE-FMA 27.7 ± 16.3	Yes	ES/S/C	NIBS	No	Different Parameters, Sham Stimulation	UE-FMA	Pos
Dawson, 2023 [61]	EG: 53 CG: 55	UE-FMA EG: 34.4 ± 8.2 CG: 35.7 ± 7.8	Yes	C	PS	Yes	Sham Stimulation	UE-FMA	Pos
Wang, 2023 [62]	EG1: 23 EG2: 23 CG: 23	UE-FMA EG1: 9 (IQR: 12) EG2: 11 (IQR: 8) CG: 14 (IQR: 16)	Yes	ES/S	NIBS, Robotic	Yes	Different Technology, Usual care	UE-FMA BI	Pos
Chen, 2023 [63]	EG: 40 CG: 40	UE-FMA EG: 18.5 ± 10.5 CG: 19.4 ± 10.4	Yes	A/ES	Robotic	Yes	Usual Care	UE-FMA	Pos
Feingold-Polak, 2024 [64]	EG1: 10 EG2: 8 CG: 8	UE-FMA (60) EG1: 42 (17–53) EG2: 41 (17–54) CG: 39 (18–58) ARAT EG1: 36 (15–51) EG2: 38 (6–57) CG: 33(17–53)	Yes	S	Robotic	Yes	Different Technology, Usual Care	UE-FMA (60) ARAT MAL SIS	Pos On Sec
Brunner, 2024 [65]	EG: 15 CG: 20	UE-FMA EG: 4 (2–4) CG: 4 (2–4) ARAT EG: 0 (0–0) CG: 0 (0–0)	Yes	A/ES	BCI, PS	No	Usual Care	ARAT	Neg

Legend: A: Acute phase (≤1 month); ARAT: Action Research Arm Test; BCI: Brain–Computer Interface; BBT: Box and Block Test; BI: Barthel Index; CG: Control Group; C: Chronic phase (>6 months); EG: Experimental Group; ES: Early Subacute phase (≤3 months); FIM: Functional Independence Measure; IQR: inter-quartile range; MAL: Motor Activity Log; MAS: Modified Ashworth Scale; MTS: Modified Tardieu Scale; Neg: Negative key findings; NIBS: Non-Invasive Brain Stimulation; Pos: Positive key findings; Pos On Sec: Positive findings on secondary analyses; PS: Peripheral Stimulation; S: Subacute phase (≤6 months); SIAS: Stroke Impairment Assessment Set; SIS: Stroke Impact Scale; UL: upper limb; UE-FMA: Upper extremity Fugl-Meyer Assessment; VR: Virtual Reality; WMFT: Wolf Motor Function Test. (*) Lee et al., 2020 [44]: we did not define key findings because the hypothesis about the effectiveness of the intervention EG1 compared to the EG2 is not clear. (**) Boasquevisque et al., 2021 [48]: safety is defined as primary outcome, but authors stated the primary outcome results were published elsewhere. (60) or (54): the expression (60) and (54) codes for UE-FMA assessed on 60 or 54, respectively.

3.3. Synthesis of Results

3.3.1. Descriptive and Frequency Results

The included articles report data from 3000 adult participants. Three articles [20,25,54] include participants with a diagnosis of stroke and traumatic brain injury (TBI), respectively five and three TBI participants in [20] and [25], for a total of eight participants. No detailed information on stroke/TBI ratio is reported in [54].

The average sample size of the groups (target intervention and control groups) is 29 ± 39 (mean ± SD). The RCT in [41] is the only study in which a very large number of participants, i.e., 770 participants, were enrolled. Conversely, there is more than one study in which a very small number of participants, i.e., less than 10 per group, are analyzed [23,29,36,46,47,51,60]. Therefore, median and quartile values, i.e., 20 (median) and 11–32 (Q1–Q3), provide more accurate estimates on the target intervention and control groups sample size. Among the included studies, only 45.83% [18,19,22,25–27,30,32–35,38,41,45,46,49,50,53,58,59,62,63] performed a sample size calculation, and 81.82% [18,22,25,26,30,32–35,38,41,46,49,50,53,59,62,63] of them actually enrolled the foreseen number of patients.

Enrolled participants include stroke in acute, early subacute, subacute, and chronic phases. Most studies (62.53%) consider a homogeneous group of participants: 6.25% acute stroke participants [26,36,53], 16.70% early subacute stroke participants [18,21,33–35,43,52,55], 2.08% subacute stroke participants [64], and 37.50% chronic stroke participants [19,20,23–25,27,29–31,40,42,45,46,49,50,56,59,61]. The remaining studies (37.47%) include more than one group of stroke participants who differ in terms of time from the cerebral lesion to enrollment, e.g., early subacute and subacute. The distribution of studies across TSI classes is reported in Figure 2.

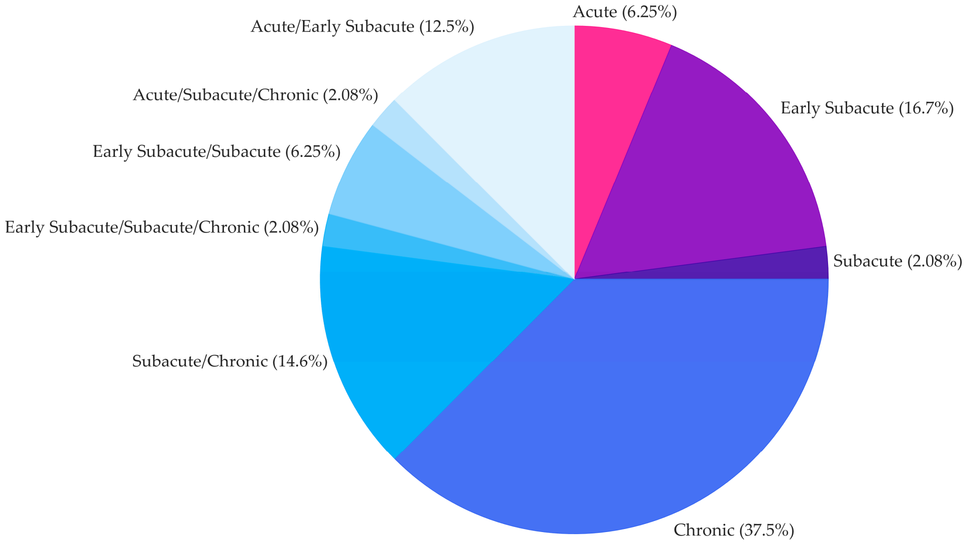

Figure 2. Distribution across studies (n = 48) of the stroke population enrolled and classified in terms of time from the cerebral lesion to enrollment in the study as follows: ≤1 month (acute), ≤3 months (early subacute), ≤6 months (subacute), >6 months (chronic).

Most of the participants enrolled in the studies are inpatient (60.40%, [18,21,22,25,26,28,32–35,37,39,43,44,47–57,61–63,65]). Outpatient studies and those considering both inpatient and outpatient participation are 20.85% [19,20,23,24,27,29,42,58,59,64] and 6.25% [38,40,41], respectively. For the remaining 12.5%, there are no clear indications referring to the setting [30,31,36,45,46,60].

Figure 3 summarizes the results about the severity of upper limb motor impairment upon enrollment based on FMA (panel a) and ARAT (panel b) scores at baseline. Forty-two studies assess baseline motor impairment in stroke participants by means of the FMA score, while in fifteen studies, the baseline assessment was performed by means of the ARAT score. As can be noted in Figure 3, both FMA and ARAT scores at baseline extend across the whole range, i.e., FMA: 21.71 ± 11.41 (mean ± SD across 42 studies) and ARAT: 12.28 ± 10.85 (mean ± SD across 15 studies). Of note, among the seven studies for which the mean or median FMA value falls below 10, three of them included acute patients [37,54,65].

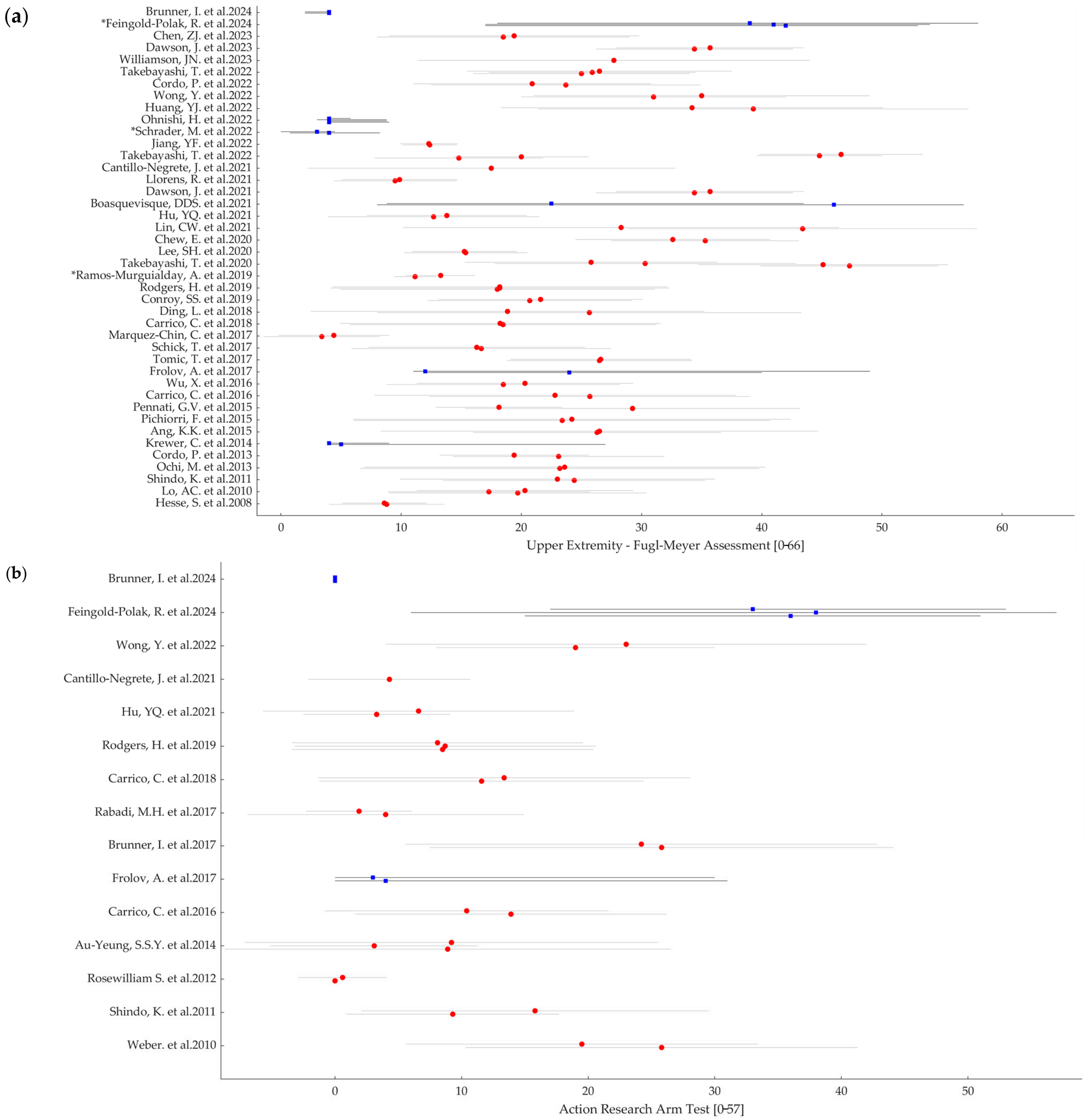

Figure 3. (**a**) Upper Extremity Fugl-Meyer Assessment (FMA) score: minimum score 0, maximum score 66 equal to normal. (**b**) Action Research Arm Test score: minimum score 0, maximum score 57 equal to normal. Red circle and grey line code for studies presenting FMA or ARAT score expressed as the mean (red circle) ± standard deviation (grey line). Blue square marker and black line code for studies presenting FMA or ARAT score expressed as the median (blue square) and first/third quartile (black line running from the first to the third quartile). (*) marker codes for two studies [54,64] that assess FMA out of a maximum of 60 score and codes for one study [42] that assesses FMA out of a maximum of 54 score.

The complete dataset about the characteristics of each participant enrolled in the study (e.g., individual FMA or ARAT scores) is available in 15% of studies.

The pie chart in Figure 4 shows the distributions of studies across technological rehabilitative intervention types. Rehabilitative interventions administered by means of robotic devices and peripheral stimulation and their combination cover more than half of the tested interventions: 27.08% [19,29,31,33,40,41,43,44,52,54,59,63,64], 29.17% [20–22,25,26,30,34,37,38,49,53,55,57,61], and 6.25% [18,24,58], respectively. Fewer studies focus on BCI-based and NIBS interventions, both combined with other intervention types, and Virtual Reality and Visual rehabilitative interventions: 16.66% (eight articles [27,28,32,42,45,47,51,65]), 14.58% (seven articles [23,36,48,50,56,60,62]), and 6.25% (three articles [35,39,46]), respectively.

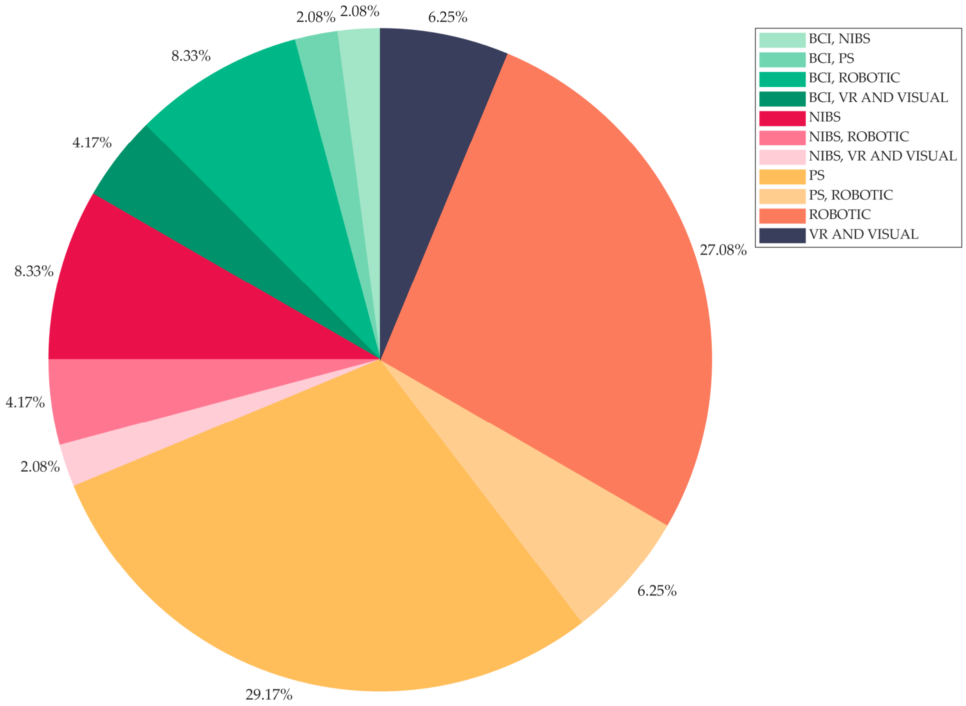

Figure 4. Distribution across studies ($n = 48$) of the technology-based rehabilitative intervention types, grouped as Brain–Computer Interface (BCI), Non-Invasive Brain Stimulation (NIBS), Peripheral Stimulation (PS), Robotic, Virtual Reality (VR) and Visual, and their combination.

The majority (52.10%) of rehabilitative intervention approaches require participant's residual motor ability (active motor exercise by the participants) [19–21,24,27,29–31,33,35,37,39,40,42,46,49,50,55,57–59,61–64]; 10.40% are categorized as "Yes whenever possible", referring to conditions foreseeing active motor exercise when feasible with the technology providing assistance as needed (e.g., robotics) [18,41,43,44,52]; and 37.50% do not require any active motor action from the participants [22,23,25,26,28,32,34,36,38,45,47,48,51,53,54,56,60,65].

Regarding the dose of rehabilitative intervention, the studies differ in terms of both minutes of each training session, 40 min (median) and 30–60 min (Q1–Q3), and number of training sessions (21.78 ± 14.39, mean ± SD), ranging from 12 sessions (Q1) to 28 sessions (Q3). The overall dose of intervention, resulting from the multiplication of minutes per session and number of sessions, is 13h (median) and 8–27 h (Q1–Q3).

Table 2 shows the number of studies in which each surveyed primary and secondary outcome is used either as primary or secondary. As for the primary outcome, the Upper Extremity FMA results are the most frequent scale administered to assess the efficacy of the rehabilitative interventions (38 on 48 studies, 79.17%) [18,19,21,23–25,27–34,37,39,40,42–47,49–56,58–64]. Conversely, several evaluations, such as clinical/functional as well as instrumental, are considered for the secondary outcomes. Among the clinical/functional secondary outcomes, the most frequent are the Stroke Impact Scale [66]

(22.92% of studies, [19,24,31,38,40,41,44,48,49,58,59]), the Barthel Index [67] (22.92% of studies, [22,25,33,34,39,41,47,48,53,57,63]), the Wolf Motor Function Test [68] (20.83% of studies, [19,30,31,33,40,44,49,50,56,61]), and the Action Research Arm Test [14] (16.67% of studies, [20,21,26,30,38,47,51,59]); transcranial magnetic stimulation, electroencephalographic, electromyographic, kinematic, and kinetic parameters are considered as brain and motor outcomes in 27.08% of the studies [22,28,42,45,47,51,53,58–60,62–64].

Table 2. List of the primary and secondary outcomes and number of studies that consider each one as a primary (column on the left side) or secondary (column on the right side) outcome.

Outcome	As Primary Number of Studies	As Secondary Number of Studies
Upper Extremity Fugl-Meyer Assessment	38	5
Action Research Arm Test	8	8
Wolf Motor Function Test	3	10
Functional Independence Measure	3	2
Modified Ashworth Scale	2	9
Motor Activity Log	2	6
Stroke Impact Scale	1	11
Barthel Index	1	11
Box and Block Test	1	4
Stroke Impairment Assessment Set: knee–mouth and finger function test	1	
Modified Tardieu Scale	1	
Goal Attainment Scaling		2
Motricity Index		2
Medical Research Council Scale		2
National Institutes of Health Stroke Scale		2
Finger–Nose Test		1
Jebsen–Taylor Hand Function Test		1
Hamilton Depression Scale		1
Mental Rotation Task		1
Modified Rankin Scale		1
Montreal Cognitive Assessment		1
Nine-hole peg test		1
Nottingham Sensory Assessment		1
Numeric Rating Scale Pain		1
Rancho Los Amigos Scale		1
Rivermead Assessment of Somatosensory Performance		1
Stroke Specific Quality of Life Scale		1
Motor Outcome (kinematic, kinetic, electromyographic parameters)	1	10
Brain Outcome (transcranial magnetic stimulation and electroencephalographic parameters)		5
Safety (adverse events)		1

In 37.50% of the studies, the participants are followed-up from 2 weeks to 9 months after the end of the rehabilitation, i.e., 3 months (median) and 3–5 months (Q1–Q3), [18,19,22,25–27,30,31,35,36,38,41,44,45,48,49,61]. No follow-up evaluations are reported in 62.50% of the studies.

As for the comparison conditions, most studies (81.25%) are two-arm RCTs. The remaining 18.75% of studies [19,26,41,43,52,55,59,62,64] compare more than two groups, up to four groups in [55]. For the two-arm studies, the control conditions that are most commonly observed can be categorized as follows:

- Sham Stimulation/Control (applies in NIBS/PS and BCI studies, referring to conditions where the participants are induced to believe they are receiving stimulation or controlling a BCI system while they are not): 28.20% of studies [25,30,32,36,38,42,45,48,49,56,61];
- Similar intervention "without technology" (e.g., mirror therapy in contrast to VR-based mirror therapy): 17.95% of studies [20,21,28,46,47,54,57];
- Usual care: 17.95% of studies [22,31,37,50,53,63,65];

- Dose equivalent upper limb training (dose equivalent therapy session focused on the upper limb, considered an add-on to usual care): 10.26% of studies [33,35,39,43];
- Different combinations of technology-based approaches: 10.26% of studies [27,29,34,40];
- Different technology: 7.69% of studies [18,24,44];
- Different parameters of the same technology (e.g., different robotic assistance, anodal vs. cathodal transcranial direct-current stimulation): 7.69% of studies [23,52,58].

For studies comparing more than two groups, different interventions are mostly compared to the usual care control condition. Further details about the comparator employed in each study can be found in the Supplementary Materials (Table S2).

As shown in Table 1, most studies (89.58%) employ inclusion criteria related to upper limb impairment for participant enrollment [18–27,30,31,33–38,40–47,49–65]. Figure 5 shows the inclusion criteria and their frequency across studies (43 studies include inclusion criteria). More than half of the studies define the inclusion criteria by means of an FMA score (53.50% of studies, [18,19,23,27,31,33,34,37,38,40,44–46,49,50,54,58–64]) or ARAT (9.30% of studies, [22,35,41,65]). Nevertheless, evaluations based on motor outcome, i.e., range of motion or ability/inability to perform a specific task, such as that involved in the study protocol, are taken into account in 16.3% of studies [20,21,24,30,42,47,57] as well as spasticity-related scales, i.e., Brunnstrom stages and Tardieu scale, in 11.63% of studies [25,43,52,53,56]. Specifically, for the FMA inclusion criteria, Figure 6 shows the reduction gained by defining the inclusion criteria for participant enrollment. That reduction, expressed as percentage, is computed as the one's complement of the ratio between the FMA range defined as in the inclusion criteria and the whole FMA range (0–66), according to the following formula:

$$FMA\ range\ reduction = 100 \times (1 - \frac{FMA\ range\ defined\ as\ inclusion\ criteria}{66})$$

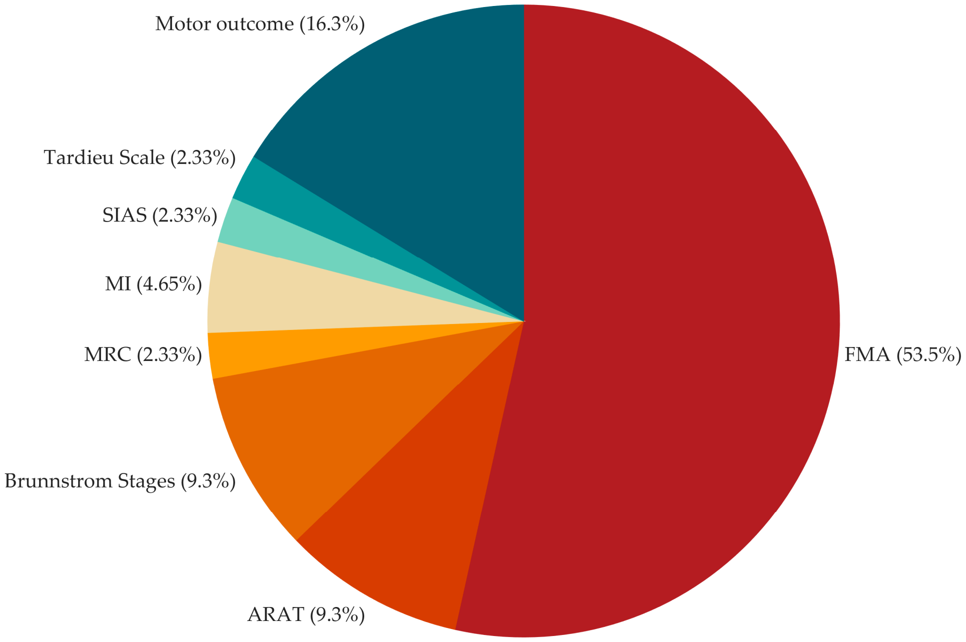

Figure 5. Distribution across studies (n = 43) of the parameters (clinical/functional scale or motor-related evaluation) used for the enrollment inclusion criteria definition and grouped as UE-FMA: Upper Extremity Fugl-Meyer Assessment; ARAT: Action Research Arm Test; MRC: Medical Research Council Scale; MI: Motricity Index; and SIAS: Stroke Impairment Assessment Set; and Motor outcome, which concerns range of motion evaluation and evaluation of ability/inability to perform a specific task.

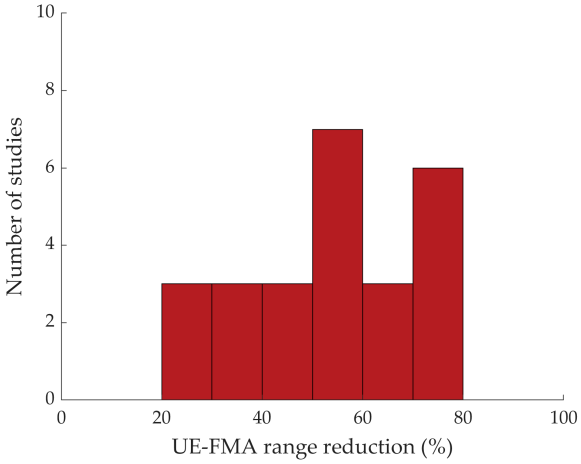

Figure 6. Histogram of number of studies that define inclusion criteria by means of Upper Extremity Fugl-Meyer Assessment (UE-FMA) score, reported as a function of the UE-FMA range reduction achieved by defining inclusion criteria for participant enrollment.

In seven studies, we observed a reduction between 60% and 80% [18,33,34,37,44,50,54]; among them is the study by Schrader et al. [54] in which inclusion criteria have been defined on the basis of the hand section of the FMA scale (maximum value 14). Most of the studies only achieve a 50% reduction [19,31,40,49,60,61,63], thus including in the same analyses participants who differ in FMA score up to 33 points (50% of the whole FMA range [0 66]), for example, in the range [8 38] in the study by Chen and colleagues in [63].

As for the severity of the upper limb impairment at baseline for the stratification of participants in secondary analyses, 25.00% of studies exploit such an evaluation [24,31,34,35,39–41,43,45,52,61,63], defining two or more levels of the variable: FMA (nine studies out of twelve) [24,31,34,39,40,43,52,61,63] and ARAT [41], motor evoked potentials, [45] and range of motion [35] (one per study).

As for the key findings of the trials, (i) 41.67% report positive results, i.e., the studies confirm the hypothesis of efficacy of a given intervention via between-group analysis [21,26,28,30,31,33,37–39,46,49,50,53–55,58,60–63]; and (ii) 31.25% report positive results on secondary analyses, i.e., between-group statistical analyses evaluated for sub-items of the primary/secondary outcomes or considering sub-groups of the population under investigation confirm the original hypothesis or if within-group statistical analyses evaluated for the primary/secondary outcomes reveal a statistical improvement only for the experimental group [19,23–25,32,34,40,42,43,45,47,52,56,59,64]. Negative results are reported by 25.00% of studies, i.e., the target intervention is not superior to the control condition [18,20,22,27,29,35,36,41,48,51,57,65].

3.3.2. Association Results

Figure 7 shows, for each type of intervention (top panel in the figure) and motor action required from the participant by the intervention itself (bottom panel in the figure), the upper limb impairment severity (UE-FMA) of the participants recruited in those studies. Each study has been categorized both according to the intervention type (analysis presented in the top panel) and motor action required (analysis presented in the bottom panel). The data from studies belonging to the same category, e.g., intervention type PS, are pooled together and summarized by means of box charts.

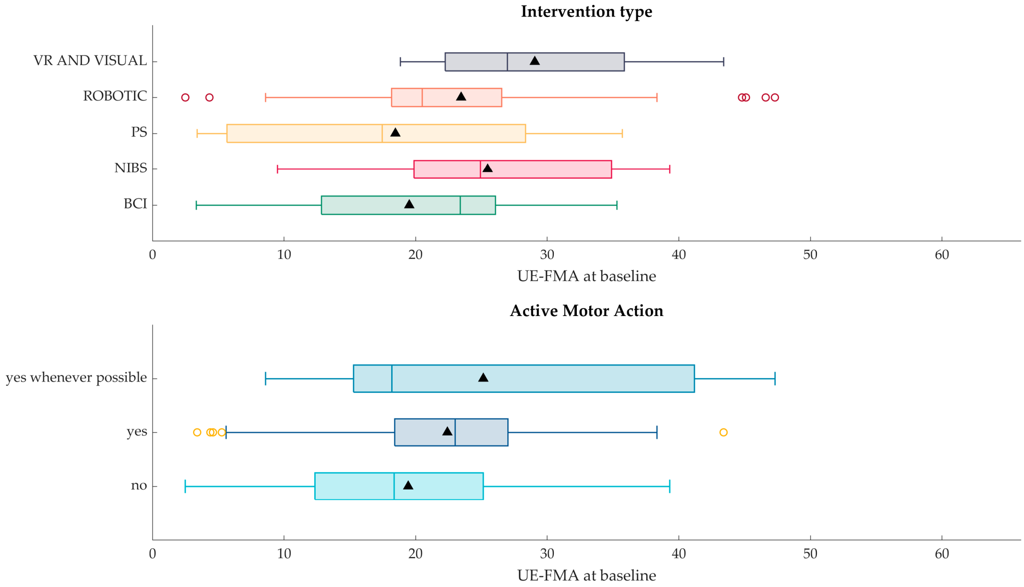

Figure 7. Distribution across studies (n = 42) of UE-FMA at baseline, grouped by intervention type (**top**) and motor action required from the participant (**bottom**). The triangle-up marker codes for the average of each distribution and the circle codes for outliers. Intervention types were categorized as BCI (Brain–Computer Interface), NIBS (Non-Invasive Brain Stimulation), PS (peripheral stimulation), Robotic, and VR (Virtual Reality) and Visual. Each study is assigned to a single category. Studies that investigate combinations of technology-based interventions, e.g., BCI and PS or BCI and Robotic, have been assigned to the most significant intervention type according to the study design, e.g., BCI and PS have been assigned to the BCI category when PS was employed in the control condition as well, thus BCI control resulted to be the core of the rehabilitative intervention in the study. Active motor actions are categorized as no/yes/yes whenever possible.

As for the intervention type, most studies seem to cover almost half of the UE-FMA scale scores. On average, PS-based interventions concern participants with a slightly lower UE-FMA value (18.46 ± 11.55) than the other interventions (BCI: 19.52 ± 9.72, NIBS: 25.47 ± 10.67, Robotic: 23.46 ± 10.74, VR and Visual: 29.05 ± 10.36). Robotic interventions, as shown from the distribution outliers, include studies with UE-FMA values both lower than 5 and higher than 40. As for motor action required from the participant, studies in which the experimental protocol does not require action of the participant enroll participants with UE-FMA on average lower (19.44 ± 10.62) than studies either requiring active motor action (22.41 ± 9.94) or whenever possible (25.14 ± 14.09). Of note, studies that require active motor actions enroll participants with reduced motor action ability (FMA < 5) as well as participants with moderate motor impairment (FMA = 43).

4. Discussion

In this scoping review, we provide a portrait of the current evidence derived from RCTs investigating the efficacy of technology-based interventions targeting upper limb motor recovery in patients with severe impairment after stroke. Our main aim is to verify the actual severity of the included patients enrolled in such trials to confirm or refute the anecdotal notion of extreme variability in baseline motor impairment, which might be responsible for the lack of solid evidence supporting the efficacy of such interventions [9].

We included papers reporting FMA or ARAT or both to assess upper limb motor impairment (Table S1, Supplementary Materials) since they are commonly employed to investigate the efficacy of the rehabilitative treatment [69]. Our results (Table 2) show that FMA is by far the most commonly employed as the primary outcome measure, followed by ARAT; other measures that are specific for upper limb function, such as BBT, WMFT, and MAL, are more commonly employed as the secondary outcome.

According to our descriptive analyses on FMA and ARAT values upon enrollment, we verified that the included patients altogether virtually cover the whole range of both scales (Figure 3a,b). That is, these RCTs that were originally implemented to investigate the efficacy of rehabilitative interventions designed for severe patients often include patients with mild to moderate deficits as well. This occurs despite the fact that almost 90% of the studies actually defined the inclusion criteria based on severity. Actually, there is no unique definition of severity, even for the same assessment scale. To reach such a univocal definition of motor severity is beyond the scope of our work; however, our review allows for us at least to provide a picture of the current state of the art in this aspect. Among those studies in which the inclusion criteria were based on severity, approximately 50% employed FMA for such a definition. However, the references for the proposed stratification did not converge on a unique subdivision. For example, several papers refer to Fugl-Meyer et al. [13] or Gladstone et al. [70] to justify the use of cut-off values for their inclusion criteria or stratification analyses, but no subdivision is provided in either of these papers. Woodbury et al. [71] suggest a cut-off below 19 for severe patients and of 47 for moderately impaired patients, which is applied as an inclusion criterion by Carrico et al. [38]. Ding et al. [39] apply the clustering suggested in Woytowicz et al. [72] to define severity in patients with an FMA < 35. Conroy et al. [40] apply a cut-off of 25 as suggested by Luft et al. [73]. As a possible explanation for such a wide range of severity among the enrolled patients, we hypothesized that the technology in the study could play a role. For example, some robotic devices cannot be proposed to patients with severe spasticity, or an electromyographically triggered orthosis cannot be activated if patients have no residual movement in the target muscles. Thus, we categorized the papers according to the proposed technology. Electrical or magnetic stimulation of peripheral structures (PS) is the most represented technology in our review, followed by robotics. These two or their combinations represent approximately 63% of the studies. The BCI and NIBS (often in combination with other devices) are the topics of approximately 31% of the studies, while the less represented technology is VR, with just approximately 6% of the papers. To further characterize the interventions according to the fact that they required (or not) active motor actions from the patients, we found out that more than 50% of the interventions required some residual motor ability from the patients. This could be an explanation for the trend to include "not-so-severe" patients in order to increase trial feasibility. Nevertheless, we did not observe a clear difference in the severity of the included patients when we divided the studies according to the technology or to the presence/absence of an active motor exercise. The distributions of patients' severity (Figure 7) qualitatively show a tendency towards the more severe range for the interventions based on PS and for interventions not requiring active motor tasks. We also highlighted the heterogeneity of included patients in terms of time since injury. While the majority of studies targeted chronic patients exclusively (37.5%), the studies including mixed groups altogether reached a similar percentage (37.47%). It is well known that brain plasticity that underlies motor recovery is time dependent, and the recovery potential is different according to the post-stroke phase [74]. Moreover, changes occurring in peripheral structures along recovery (e.g., spasticity, complications related to reduced mobility) have a direct impact on the motor status (and, thus, potential motor outcome), further increasing the complexity of the overall picture.

Regarding the study design, we also pointed out extreme variability in terms of the dose/intensity of treatment, type of comparator, and sample size. In almost 20% of the two-arm studies, "usual care" is the only control condition, while an active comparator would be most desirable. Different dosages and very different sample sizes (ranging from 10 to almost 800 participants) limit the potential impact of our attempt to interpret the results of this scoping review that takes into account such a wide scenario of clinical studies. An indirect result of our scoping review derives from the papers that we excluded for reporting study protocols (n = 13). These papers were all published between 2017 and 2023 [75–87], with ten of them being subsequent to 2020, testifying to a progressive increase in the efforts dedicated to rigorous clinical trial design in this field of translational research.

The ultimate goal of our reviewing work is to improve the design of RCTs to boost the translation of rehabilitative technologies into clinical practice. Indeed, the majority of the selected studies report positive results, indicating the efficacy of the proposed technology. However, approximately 30% of the studies required secondary analyses to support the benefit derived from the intervention in the study. Some of them report positive results on secondary outcomes, e.g., SIS and WMFT [19,40], and/or outcome sub-items, e.g., ARAT, FMA, and MAS items [23,43]. Some required subgroup analyses, e.g., proving efficacy only in severe patients [34,43,45,52]. The remaining 25% of openly negative studies (showing non-superiority of the proposed intervention) is likely underestimated, as it is known that publishing a negative result is harder and often occurs only in the case of very well designed and well conducted, large clinical trials.

A further observation derived from our work is that, along with the established clinical and functional scales employed as primary or secondary outcomes (Table 2), 16 papers applied objective measurements of brain and motor activity as a means to verify the effects of the intervention on motor system performance. Advanced analyses on electroencephalographic [28,51] and transcranial magnetic stimulation recordings [45,51,60,62], electromyographic, kinematic, and kinetic data [22,26,42,47,51,53,58,59,62–64] were performed in these studies to identify modifications in motor system performance subserving a favorable motor outcome derived from the intervention in the study. This suggests that technology is not only employed for the design of rehabilitative interventions but may play a crucial role in improving the outcome assessment with more objective, measurable, and reproducible parameters that may serve as biomarkers of motor recovery.

This scoping review has several limitations, mostly related to the heterogeneity of the included studies in terms of numerosity, characteristics of the enrolled patients, trial design, implementation, and reporting. We considered papers published between 2008 and 2024, observing a progressive improvement in all of these aspects, which will hopefully be fruitful in the upcoming years to properly address some of the issues that we raised here and that remain yet unanswered. Only seven studies [28–30,45,51,56,60] provide a complete dataset documenting the individual severity of the enrolled patients, which would allow for a statistical analysis on how effective the interventions were according to a homogeneous stratification of patients based on severity. The policies for data availability are also progressively pointing towards safe data sharing according to internationally agreed upon General Data Protection Regulations.

5. Conclusions

We represented the current evidence derived from RCTs investigating the efficacy of technology-based interventions targeting upper limb motor recovery in patients with severe impairment after stroke. Our aim was to shed light on the problems of the current research in rehabilitation technologies to ultimately boost the translational success of such approaches. There is undoubtedly a need for patient stratification upon enrollment to selectively direct resources to the patients who will benefit the most from a given approach. The correct taxonomy of patient severity and the related correct reporting in clinical trials could significantly improve the transnationality and contextualization of the results obtained, avoiding biases that could affect potential effectiveness. Only severe patients should be recruited for the clinical validation of devices that are designed specifically for them, while the design and development of technologies with adequate sensorimotor and cognitive stimulation would probably increase their salience (and effectiveness) for less affected subjects. Upon the improvement in the design, implementation, and reporting of clinical trials, subsequent systematic reviews will probably help in identifying strong evidence and, thus, evidence-based indications for clinicians operating in the field of neurorehabilitation.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm13185414/s1, Table S1: Database Search Strategies. Table S2: Experimental and control intervention details of the studies included in the review.

Author Contributions: Conceptualization, F.P. and G.M.; methodology, E.C. and G.M.; formal analysis, E.C., F.P. and G.M.; data curation, E.C. and F.P.; writing—original draft preparation, E.C., F.P. and G.M.; writing—review and editing, D.M., F.C., J.T. and A.R.; supervision, D.M. and F.C.; funding acquisition, D.M., F.C. and J.T. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analyzed during this study. Data sharing is not applicable to this article.

Acknowledgments: This work was partially funded by the Italian Ministry of Health (Ricerca Corrente 2024) and by Sapienza University of Rome—Progetti di Ateneo 2023.

Conflicts of Interest: The authors declare no conflicts of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

References

1. Iosa, M.; Morone, G.; Fusco, A.; Bragoni, M.; Coiro, P.; Multari, M.; Venturiero, V.; De Angelis, D.; Pratesi, L.; Paolucci, S. Seven Capital Devices for the Future of Stroke Rehabilitation. *Stroke Res. Treat.* **2012**, *2012*, 187965. [CrossRef] [PubMed]
2. Coscia, M.; Wessel, M.J.; Chaudary, U.; Millán, J.D.R.; Micera, S.; Guggisberg, A.; Vuadens, P.; Donoghue, J.; Birbaumer, N.; Hummel, F.C. Neurotechnology-Aided Interventions for Upper Limb Motor Rehabilitation in Severe Chronic Stroke. *Brain* **2019**, *142*, 2182–2197. [CrossRef] [PubMed]
3. Ward, N.S.; Brander, F.; Kelly, K. Intensive Upper Limb Neurorehabilitation in Chronic Stroke: Outcomes from the Queen Square Programme. *J. Neurol. Neurosurg. Psychiatry* **2019**, *90*, 498–506. [CrossRef] [PubMed]
4. Tenberg, S.; Mueller, S.; Vogt, L.; Roth, C.; Happ, K.; Scherer, M.; Behringer, M.; Niederer, D. Comparative Effectiveness of Upper Limb Exercise Interventions in Individuals with Stroke: A Network Meta-Analysis. *Stroke* **2023**, *54*, 1839–1853. [CrossRef] [PubMed]
5. Dboba, M.M.; Mohd Nordin, N.A.; Manaf, H.; Mohd Rasdi, H.F. Effect of Constraint-Induced Movement Therapy Combined with Neuromuscular Electrical Stimulation on Upper Extremity Function in Stroke Survivors: A Protocol for Systematic Review. *Medicine* **2023**, *102*, e34249. [CrossRef]
6. Morone, G.; Paolucci, S.; Mattia, D.; Pichiorri, F.; Tramontano, M.; Iosa, M. The 3Ts of the New Millennium Neurorehabilitation Gym: Therapy, Technology, Translationality. *Expert Rev. Med. Devices* **2016**, *13*, 785–787. [CrossRef]
7. Coupar, F.; Pollock, A.; Rowe, P.; Weir, C.; Langhorne, P. Predictors of Upper Limb Recovery after Stroke: A Systematic Review and Meta-Analysis. *Clin. Rehabil.* **2012**, *26*, 291–313. [CrossRef]
8. Munn, Z.; Peters, M.D.J.; Stern, C.; Tufanaru, C.; McArthur, A.; Aromataris, E. Systematic Review or Scoping Review? Guidance for Authors When Choosing between a Systematic or Scoping Review Approach. *BMC Med. Res. Methodol.* **2018**, *18*, 143. [CrossRef]
9. Morone, G.; Pichiorri, F. Post-Stroke Rehabilitation: Challenges and New Perspectives. *J. Clin. Med.* **2023**, *12*, 550. [CrossRef]
10. Tricco, A.C.; Lillie, E.; Zarin, W.; O'Brien, K.K.; Colquhoun, H.; Levac, D.; Moher, D.; Peters, M.D.J.; Horsley, T.; Weeks, L.; et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. *Ann. Intern. Med.* **2018**, *169*, 467–473. [CrossRef]
11. McGowan, J.; Sampson, M.; Salzwedel, D.M.; Cogo, E.; Foerster, V.; Lefebvre, C. PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. *J. Clin. Epidemiol.* **2016**, *75*, 40–46. [CrossRef] [PubMed]
12. Ouzzani, M.; Hammady, H.; Fedorowicz, Z.; Elmagarmid, A. Rayyan—A Web and Mobile App for Systematic Reviews. *Syst. Rev.* **2016**, *5*, 210. [CrossRef]
13. Fugl-Meyer, A.R.; Jääskö, L.; Leyman, I.; Olsson, S.; Steglind, S. The Post-Stroke Hemiplegic Patient. 1. a Method for Evaluation of Physical Performance. *Scand. J. Rehabil. Med.* **1975**, *7*, 13–31. [CrossRef] [PubMed]
14. Platz, T.; Pinkowski, C.; van Wijck, F.; Kim, I.-H.; di Bella, P.; Johnson, G. Reliability and Validity of Arm Function Assessment with Standardized Guidelines for the Fugl-Meyer Test, Action Research Arm Test and Box and Block Test: A Multicentre Study. *Clin. Rehabil.* **2005**, *19*, 404–411. [CrossRef]
15. Stinear, C.; Ackerley, S.; Byblow, W. Rehabilitation Is Initiated Early after Stroke, but Most Motor Rehabilitation Trials Are Not: A Systematic Review. *Stroke* **2013**, *44*, 2039–2045. [CrossRef]
16. Bernhardt, J.; Hayward, K.S.; Kwakkel, G.; Ward, N.S.; Wolf, S.L.; Borschmann, K.; Krakauer, J.W.; Boyd, L.A.; Carmichael, S.T.; Corbett, D.; et al. Agreed Definitions and a Shared Vision for New Standards in Stroke Recovery Research: The Stroke Recovery and Rehabilitation Roundtable Taskforce. *Int. J. Stroke* **2017**, *12*, 444–450. [CrossRef]

17. Wan, X.; Wang, W.; Liu, J.; Tong, T. Estimating the Sample Mean and Standard Deviation from the Sample Size, Median, Range and/or Interquartile Range. *BMC Med. Res. Methodol.* **2014**, *14*, 135. [CrossRef]
18. Hesse, S.; Werner, C.; Pohl, M.; Mehrholz, J.; Puzich, U.; Krebs, H.I. Mechanical Arm Trainer for the Treatment of the Severely Affected Arm after a Stroke: A Single-Blinded Randomized Trial in Two Centers. *Am. J. Phys. Med. Rehabil.* **2008**, *87*, 779–788. [CrossRef]
19. Lo, A.C.; Guarino, P.D.; Richards, L.G.; Haselkorn, J.K.; Wittenberg, G.F.; Federman, D.G.; Ringer, R.J.; Wagner, T.H.; Krebs, H.I.; Volpe, B.T.; et al. Robot-Assisted Therapy for Long-Term Upper-Limb Impairment after Stroke. *N. Engl. J. Med.* **2010**, *362*, 1772–1783. [CrossRef]
20. Weber, D.J.; Skidmore, E.R.; Niyonkuru, C.; Chang, C.-L.; Huber, L.M.; Munin, M.C. Cyclic Functional Electrical Stimulation Does Not Enhance Gains in Hand Grasp Function When Used as an Adjunct to onabotulinumtoxinA and Task Practice Therapy: A Single-Blind, Randomized Controlled Pilot Study. *Arch. Phys. Med. Rehabil.* **2010**, *91*, 679–686. [CrossRef]
21. Shindo, K.; Fujiwara, T.; Hara, J.; Oba, H.; Hotta, F.; Tsuji, T.; Hase, K.; Liu, M. Effectiveness of Hybrid Assistive Neuromuscular Dynamic Stimulation Therapy in Patients with Subacute Stroke: A Randomized Controlled Pilot Trial. *Neurorehabilit. Neural Repair* **2011**, *25*, 830–837. [CrossRef] [PubMed]
22. Rosewilliam, S.; Malhotra, S.; Roffe, C.; Jones, P.; Pandyan, A.D. Can Surface Neuromuscular Electrical Stimulation of the Wrist and Hand Combined with Routine Therapy Facilitate Recovery of Arm Function in Patients with Stroke? *Arch. Phys. Med. Rehabil.* **2012**, *93*, 1715–1721.e1. [CrossRef] [PubMed]
23. Ochi, M.; Saeki, S.; Oda, T.; Matsushima, Y.; Hachisuka, K. Effects of Anodal and Cathodal Transcranial Direct Current Stimulation Combined with Robotic Therapy on Severely Affected Arms in Chronic Stroke Patients. *J. Rehabil. Med.* **2013**, *45*, 137–140. [CrossRef]
24. Cordo, P.; Wolf, S.; Lou, J.-S.; Bogey, R.; Stevenson, M.; Hayes, J.; Roth, E. Treatment of Severe Hand Impairment Following Stroke by Combining Assisted Movement, Muscle Vibration, and Biofeedback. *J. Neurol. Phys. Ther.* **2013**, *37*, 194–203. [CrossRef]
25. Krewer, C.; Hartl, S.; Müller, F.; Koenig, E. Effects of Repetitive Peripheral Magnetic Stimulation on Upper-Limb Spasticity and Impairment in Patients with Spastic Hemiparesis: A Randomized, Double-Blind, Sham-Controlled Study. *Arch. Phys. Med. Rehabil.* **2014**, *95*, 1039–1047. [CrossRef]
26. Au-Yeung, S.S.Y.; Hui-Chan, C.W.Y. Electrical Acupoint Stimulation of the Affected Arm in Acute Stroke: A Placebo-Controlled Randomized Clinical Trial. *Clin. Rehabil.* **2014**, *28*, 149–158. [CrossRef] [PubMed]
27. Ang, K.K.; Chua, K.S.G.; Phua, K.S.; Wang, C.; Chin, Z.Y.; Kuah, C.W.K.; Low, W.; Guan, C. A Randomized Controlled Trial of EEG-Based Motor Imagery Brain-Computer Interface Robotic Rehabilitation for Stroke. *Clin. EEG Neurosci.* **2015**, *46*, 310–320. [CrossRef]
28. Pichiorri, F.; Morone, G.; Petti, M.; Toppi, J.; Pisotta, I.; Molinari, M.; Paolucci, S.; Inghilleri, M.; Astolfi, L.; Cincotti, F.; et al. Brain-Computer Interface Boosts Motor Imagery Practice during Stroke Recovery. *Ann. Neurol.* **2015**, *77*, 851–865. [CrossRef]
29. Pennati, G.V.; Da Re, C.; Messineo, I.; Bonzaiuti, D. How Could Robotic Training and Botolinum Toxin Be Combined in Chronic Post Stroke Upper Limb Spasticity? A Pilot Study. *Eur. J. Phys. Rehabil. Med.* **2015**, *51*, 381–387.
30. Carrico, C.; Chelette, K.C.; Westgate, P.M.; Powell, E.; Nichols, L.; Fleischer, A.; Sawaki, L. Nerve Stimulation Enhances Task-Oriented Training in Chronic, Severe Motor Deficit after Stroke: A Randomized Trial. *Stroke* **2016**, *47*, 1879–1884. [CrossRef]
31. Wu, X.; Guarino, P.; Lo, A.C.; Peduzzi, P.; Wininger, M. Long-Term Effectiveness of Intensive Therapy in Chronic Stroke. *Neurorehabilit. Neural Repair* **2016**, *30*, 583–590. [CrossRef]
32. Frolov, A.A.; Mokienko, O.; Lyukmanov, R.; Biryukova, E.; Kotov, S.; Turbina, L.; Nadareyshvily, G.; Bushkova, Y. Post-Stroke Rehabilitation Training with a Motor-Imagery-Based Brain-Computer Interface (BCI)-Controlled Hand Exoskeleton: A Randomized Controlled Multicenter Trial. *Front. Neurosci.* **2017**, *11*, 400. [CrossRef] [PubMed]
33. Tomić, T.J.D.; Savić, A.M.; Vidaković, A.S.; Rodić, S.Z.; Isaković, M.S.; Rodríguez-De-Pablo, C.; Keller, T.; Konstantinović, L.M. Arm Assist Robotic System versus Matched Conventional Therapy for Poststroke Upper Limb Rehabilitation: A Randomized Clinical Trial. *BioMed Res. Int.* **2017**, *2017*, 7659893. [CrossRef] [PubMed]
34. Schick, T.; Schlake, H.-P.; Kallusky, J.; Hohlfeld, G.; Steinmetz, M.; Tripp, F.; Krakow, K.; Pinter, M.; Dohle, C. Synergy Effects of Combined Multichannel EMG-Triggered Electrical Stimulation and Mirror Therapy in Subacute Stroke Patients with Severe or Very Severe Arm/Hand Paresis. *Restor. Neurol. Neurosci.* **2017**, *35*, 319–332. [CrossRef]
35. Brunner, I.; Skouen, J.S.; Hofstad, H.; Aßmus, J.; Becker, F.; Sanders, A.-M.; Pallesen, H.; Kristensen, L.Q.; Michielsen, M.; Thijs, L.; et al. Virtual Reality Training for Upper Extremity in Subacute Stroke (VIRTUES): A Multicenter RCT. *Neurology* **2017**, *89*, 2413–2421. [CrossRef]
36. Rabadi, M.H.; Aston, C.E. Effect of Transcranial Direct Current Stimulation on Severely Affected Arm-Hand Motor Function in Patients after an Acute Ischemic Stroke: A Pilot Randomized Control Trial. *Am. J. Phys. Med. Rehabil.* **2017**, *96*, S178–S184. [CrossRef]
37. Marquez-Chin, C.; Bagher, S.; Zivanovic, V.; Popovic, M.R. Functional Electrical Stimulation Therapy for Severe Hemiplegia: Randomized Control Trial Revisited. *Can. J. Occup. Ther.* **2017**, *84*, 87–97. [CrossRef] [PubMed]
38. Carrico, C.; Westgate, P.M.; Salmon Powell, E.; Chelette, K.C.; Nichols, L.; Pettigrew, L.C.; Sawaki, L. Nerve Stimulation Enhances Task-Oriented Training for Moderate-to-Severe Hemiparesis 3-12 Months after Stroke: A Randomized Trial. *Am. J. Phys. Med. Rehabil.* **2018**, *97*, 808–815. [CrossRef]

39. Ding, L.; Wang, X.; Guo, X.; Chen, S.; Wang, H.; Jiang, N.; Jia, J. Camera-Based Mirror Visual Feedback: Potential to Improve Motor Preparation in Stroke Patients. *IEEE Trans. Neural Syst. Rehabil. Eng.* **2018**, *26*, 1897–1905. [CrossRef]
40. Conroy, S.S.; Wittenberg, G.F.; Krebs, H.I.; Zhan, M.; Bever, C.T.; Whitall, J. Robot-Assisted Arm Training in Chronic Stroke: Addition of Transition-to-Task Practice. *Neurorehabilit. Neural Repair* **2019**, *33*, 751–761. [CrossRef]
41. Rodgers, H.; Bosomworth, H.; Krebs, H.I.; van Wijck, F.; Howel, D.; Wilson, N.; Aird, L.; Alvarado, N.; Andole, S.; Cohen, D.L.; et al. Robot Assisted Training for the Upper Limb after Stroke (RATULS): A Multicentre Randomised Controlled Trial. *Lancet* **2019**, *394*, 51–62. [CrossRef] [PubMed]
42. Ramos-Murguialday, A.; Curado, M.R.; Broetz, D.; Yilmaz, Ö.; Brasil, F.L.; Liberati, G.; Garcia-Cossio, E.; Cho, W.; Caria, A.; Cohen, L.G.; et al. Brain-Machine Interface in Chronic Stroke: Randomized Trial Long-Term Follow-Up. *Neurorehabil. Neural Repair* **2019**, *33*, 188–198. [CrossRef] [PubMed]
43. Takebayashi, T.; Takahashi, K.; Domen, K.; Hachisuka, K. Impact of Initial Flexor Synergy Pattern Scores on Improving Upper Extremity Function in Stroke Patients Treated with Adjunct Robotic Rehabilitation: A Randomized Clinical Trial. *Top. Stroke Rehabil.* **2020**, *27*, 516–524. [CrossRef] [PubMed]
44. Lee, S.H.; Park, G.; Cho, D.Y.; Kim, H.Y.; Lee, J.-Y.; Kim, S.; Park, S.-B.; Shin, J.-H. Comparisons between End-Effector and Exoskeleton Rehabilitation Robots Regarding Upper Extremity Function among Chronic Stroke Patients with Moderate-to-Severe Upper Limb Impairment. *Sci. Rep.* **2020**, *10*, 1806. [CrossRef] [PubMed]
45. Chew, E.; Teo, W.-P.; Tang, N.; Ang, K.K.; Ng, Y.S.; Zhou, J.H.; Teh, I.; Phua, K.S.; Zhao, L.; Guan, C. Using Transcranial Direct Current Stimulation to Augment the Effect of Motor Imagery-Assisted Brain-Computer Interface Training in Chronic Stroke Patients—Cortical Reorganization Considerations. *Front. Neurol.* **2020**, *11*, 948. [CrossRef]
46. Lin, C.-W.; Kuo, L.-C.; Lin, Y.-C.; Su, F.-C.; Lin, Y.-A.; Hsu, H.-Y. Development and Testing of a Virtual Reality Mirror Therapy System for the Sensorimotor Performance of Upper Extremity: A Pilot Randomized Controlled Trial. *IEEE Access* **2021**, *9*, 14725–14734. [CrossRef]
47. Hu, Y.-Q.; Gao, T.-H.; Li, J.; Tao, J.-C.; Bai, Y.-L.; Lu, R.-R. Motor Imagery-Based Brain-Computer Interface Combined with Multimodal Feedback to Promote Upper Limb Motor Function after Stroke: A Preliminary Study. *Evid.-Based Complement. Altern. Med.* **2021**, *2021*, 1116126. [CrossRef]
48. Boasquevisque, D.D.S.; Servinsckins, L.; De Paiva, J.P.Q.; Dos Santos, D.G.; Soares, P.; Pires, D.S.; Meltzer, J.A.; Plow, E.B.; De Freitas, P.F.; Speciali, D.S.; et al. Contralesional Cathodal Transcranial Direct Current Stimulation Does Not Enhance Upper Limb Function in Subacute Stroke: A Pilot Randomized Clinical Trial. *Neural Plast.* **2021**, *2021*, 8858394. [CrossRef]
49. Dawson, J.; Liu, C.Y.; Francisco, G.E.; Cramer, S.C.; Wolf, S.L.; Dixit, A.; Alexander, J.; Ali, R.; Brown, B.L.; Feng, W.; et al. Vagus Nerve Stimulation Paired with Rehabilitation for Upper Limb Motor Function after Ischaemic Stroke (VNS-REHAB): A Randomised, Blinded, Pivotal, Device Trial. *Lancet* **2021**, *397*, 1545–1553. [CrossRef]
50. Llorens, R.; Fuentes, M.A.; Borrego, A.; Latorre, J.; Alcañiz, M.; Colomer, C.; Noé, E. Effectiveness of a Combined Transcranial Direct Current Stimulation and Virtual Reality-Based Intervention on Upper Limb Function in Chronic Individuals Post-Stroke with Persistent Severe Hemiparesis: A Randomized Controlled Trial. *J. NeuroEngineering Rehabil.* **2021**, *18*, 108. [CrossRef]
51. Cantillo-Negrete, J.; Carino-Escobar, R.I.; Carrillo-Mora, P.; Rodriguez-Barragan, M.A.; Hernandez-Arenas, C.; Quinzaños-Fresnedo, J.; Hernandez-Sanchez, I.R.; Galicia-Alvarado, M.A.; Miguel-Puga, A.; Arias-Carrion, O. Brain-Computer Interface Coupled to a Robotic Hand Orthosis for Stroke Patients' Neurorehabilitation: A Crossover Feasibility Study. *Front. Hum. Neurosci.* **2021**, *15*, 656975. [CrossRef] [PubMed]
52. Takebayashi, T.; Takahashi, K.; Okita, Y.; Kubo, H.; Hachisuka, K.; Domen, K. Impact of the Robotic-Assistance Level on Upper Extremity Function in Stroke Patients Receiving Adjunct Robotic Rehabilitation: Sub-Analysis of a Randomized Clinical Trial. *J. NeuroEngineering Rehabil.* **2022**, *19*, 25. [CrossRef] [PubMed]
53. Jiang, Y.-F.; Zhang, D.; Zhang, J.; Hai, H.; Zhao, Y.-Y.; Ma, Y.-W. A Randomized Controlled Trial of Repetitive Peripheral Magnetic Stimulation Applied in Early Subacute Stroke: Effects on Severe Upper-Limb Impairment. *Clin. Rehabil.* **2022**, *36*, 693–702. [CrossRef] [PubMed]
54. Schrader, M.; Sterr, A.; Kettlitz, R.; Wohlmeiner, A.; Buschfort, R.; Dohle, C.; Bamborschke, S. The Effect of Mirror Therapy Can Be Improved by Simultaneous Robotic Assistance. *Restor. Neurol. Neurosci.* **2022**, *40*, 185–194. [CrossRef] [PubMed]
55. Ohnishi, H.; Miyasaka, H.; Shindo, N.; Ito, K.; Tsuji, S.; Sonoda, S. Effectiveness of Repetitive Facilitative Exercise Combined with Electrical Stimulation Therapy to Improve Very Severe Paretic Upper Limbs in with Stroke Patients: A Randomized Controlled Trial. *Occup. Ther. Int.* **2022**, *2022*, 4847363. [CrossRef]
56. Huang, Y.-J.; Wang, S.-M.; Chen, C.; Chen, C.-A.; Wu, C.-W.; Chen, J.-J.; Peng, C.-W.; Lin, C.-W.; Huang, S.-W.; Chen, S.-C. High-Definition Transcranial Direct Current with Electrical Theta Burst on Post-Stroke Motor Rehabilitation: A Pilot Randomized Controlled Trial. *Neurorehabilit. Neural Repair* **2022**, *36*, 645–654. [CrossRef] [PubMed]
57. Wong, Y.; Li, C.-J.-Z.; Ada, L.; Zhang, T.; Månum, G.; Langhammer, B. Upper limb training a with hand orthosis in early subacute stroke: A pilot randomized trial. *J. Rehabil. Med.* **2022**, *54*, jrm00279. [CrossRef]
58. Cordo, P.; Wolf, S.; Rymer, W.Z.; Byl, N.; Stanek, K.; Hayes, J.R. Assisted Movement with Proprioceptive Stimulation Augments Recovery from Moderate-To-Severe Upper Limb Impairment during Subacute Stroke Period: A Randomized Clinical Trial. *Neurorehabilit. Neural Repair* **2022**, *36*, 239–250. [CrossRef] [PubMed]

59. Takebayashi, T.; Takahashi, K.; Amano, S.; Gosho, M.; Sakai, M.; Hashimoto, K.; Hachisuka, K.; Uchiyama, Y.; Domen, K. Robot-Assisted Training as Self-Training for Upper-Limb Hemiplegia in Chronic Stroke: A Randomized Controlled Trial. *Stroke* **2022**, *53*, 2182–2191. [CrossRef]
60. Williamson, J.N.; James, S.A.; He, D.; Li, S.; Sidorov, E.V.; Yang, Y. High-Definition Transcranial Direct Current Stimulation for Upper Extremity Rehabilitation in Moderate-to-Severe Ischemic Stroke: A Pilot Study. *Front. Hum. Neurosci.* **2023**, *17*, 1286238. [CrossRef]
61. Dawson, J.; Engineer, N.D.; Cramer, S.C.; Wolf, S.L.; Ali, R.; O'Dell, M.W.; Pierce, D.; Prudente, C.N.; Redgrave, J.; Feng, W.; et al. Vagus Nerve Stimulation Paired with Rehabilitation for Upper Limb Motor Impairment and Function after Chronic Ischemic Stroke: Subgroup Analysis of the Randomized, Blinded, Pivotal, VNS-REHAB Device Trial. *Neurorehabilit. Neural Repair* **2023**, *37*, 367–373. [CrossRef] [PubMed]
62. Wang, T.; Liu, Z.; Gu, J.; Tan, J.; Hu, T. Effectiveness of Soft Robotic Glove versus Repetitive Transcranial Magnetic Stimulation in Post-Stroke Patients with Severe Upper Limb Dysfunction: A Randomised Controlled Trial. *Front. Neurol.* **2023**, *13*, 887205. [CrossRef] [PubMed]
63. Chen, Z.-J.; He, C.; Xu, J.; Zheng, C.-J.; Wu, J.; Xia, N.; Hua, Q.; Xia, W.-G.; Xiong, C.-H.; Huang, X.-L. Exoskeleton-Assisted Anthropomorphic Movement Training for the Upper Limb after Stroke: The EAMT Randomized Trial. *Stroke* **2023**, *54*, 1464–1473. [CrossRef] [PubMed]
64. Feingold-Polak, R.; Barzel, O.; Levy-Tzedek, S. Socially Assistive Robot for Stroke Rehabilitation: A Long-Term in-the-Wild Pilot Randomized Controlled Trial. *IEEE Trans. Neural Syst. Rehabil. Eng.* **2024**, *32*, 1616–1626. [CrossRef]
65. Brunner, I.; Lundquist, C.B.; Pedersen, A.R.; Spaich, E.G.; Dosen, S.; Savic, A. Brain Computer Interface Training with Motor Imagery and Functional Electrical Stimulation for Patients with Severe Upper Limb Paresis after Stroke: A Randomized Controlled Pilot Trial. *J. NeuroEngineering Rehabil.* **2024**, *21*, 10. [CrossRef]
66. Duncan, P.W.; Wallace, D.; Lai, S.M.; Johnson, D.; Embretson, S.; Laster, L.J. The Stroke Impact Scale Version 2.0. Evaluation of Reliability, Validity, and Sensitivity to Change. *Stroke* **1999**, *30*, 2131–2140. [CrossRef]
67. Sulter, G.; Steen, C.; De Keyser, J. Use of the Barthel Index and Modified Rankin Scale in Acute Stroke Trials. *Stroke* **1999**, *30*, 1538–1541. [CrossRef]
68. Morris, D.M.; Uswatte, G.; Crago, J.E.; Cook III, E.W.; Taub, E. The Reliability of the Wolf Motor Function Test for Assessing Upper Extremity Function after Stroke. *Arch. Phys. Med. Rehabil.* **2001**, *82*, 750–755. [CrossRef]
69. Sivan, M.; O'Connor, R.J.; Makower, S.; Levesley, M.; Bhakta, B. Systematic Review of Outcome Measures Used in the Evaluation of Robot-Assisted Upper Limb Exercise in Stroke. *J. Rehabil. Med.* **2011**, *43*, 181–189. [CrossRef]
70. Gladstone, D.J.; Danells, C.J.; Black, S.E. The Fugl-Meyer Assessment of Motor Recovery after Stroke: A Critical Review of Its Measurement Properties. *Neurorehabil. Neural Repair* **2002**, *16*, 232–240. [CrossRef]
71. Woodbury, M.L.; Velozo, C.A.; Richards, L.G.; Duncan, P.W. Rasch Analysis Staging Methodology to Classify Upper Extremity Movement Impairment after Stroke. *Arch. Phys. Med. Rehabil.* **2013**, *94*, 1527–1533. [CrossRef] [PubMed]
72. Woytowicz, E.J.; Rietschel, J.C.; Goodman, R.N.; Conroy, S.S.; Sorkin, J.D.; Whitall, J.; McCombe Waller, S. Determining Levels of Upper Extremity Movement Impairment by Applying a Cluster Analysis to the Fugl-Meyer Assessment of the Upper Extremity in Chronic Stroke. *Arch. Phys. Med. Rehabil.* **2017**, *98*, 456–462. [CrossRef] [PubMed]
73. Luft, A.R.; McCombe-Waller, S.; Whitall, J.; Forrester, L.W.; Macko, R.; Sorkin, J.D.; Schulz, J.B.; Goldberg, A.P.; Hanley, D.F. Repetitive Bilateral Arm Training and Motor Cortex Activation in Chronic Stroke: A Randomized Controlled Trial. *JAMA* **2004**, *292*, 1853–1861. [CrossRef]
74. Zeiler, S.R.; Krakauer, J.W. The Interaction between Training and Plasticity in the Poststroke Brain. *Curr. Opin. Neurol.* **2013**, *26*, 609–616. [CrossRef]
75. Alexander, J.; Langhorne, P.; Kidd, L.; Wu, O.; McConnachie, A.; van Wijck, F.; Dawson, J. SaeboGlove Therapy for Upper Limb Disability and Severe Hand Impairment after Stroke (SUSHI): Study Protocol for a Randomised Controlled Trial. *Eur. Stroke J.* **2021**, *6*, 302–310. [CrossRef] [PubMed]
76. Dai, W.; Yang, X.; Liu, C.; Ding, H.; Guo, C.; Zhu, Y.; Dong, M.; Qian, Y.; Fang, L.; Wang, T.; et al. Effects of Repetitive Transcranial Magnetic Stimulation over the Contralesional Dorsal Premotor Cortex on Upper Limb Function in Severe Ischaemic Stroke: Study Protocol for a Randomised Controlled Trial. *BMJ Open* **2023**, *13*, e074037. [CrossRef]
77. Gonzalez-Santos, J.; Soto-Camara, R.; Rodriguez-Fernández, P.; Jimenez-Barrios, M.; Gonzalez-Bernal, J.; Collazo-Riobo, C.; Jahouh, M.; Bravo-Anguiano, Y.; Trejo-Gabriel-Galan, J.M. Effects of Home-Based Mirror Therapy and Cognitive Therapeutic Exercise on the Improvement of the Upper Extremity Functions in Patients with Severe Hemiparesis after a Stroke: A Protocol for a Pilot Randomised Clinical Trial. *BMJ Open* **2020**, *10*, e035768. [CrossRef]
78. Kinoshita, S.; Ikeda, K.; Yasuno, S.; Takahashi, S.; Yamada, N.; Okuyama, Y.; Sasaki, N.; Hada, T.; Kuriyama, C.; Suzuki, S.; et al. Dose-Response of rPMS for Upper Limb Hemiparesis after Stroke. *Medicine* **2020**, *99*, e20752. [CrossRef]
79. Lee, S.H.; Kim, W.-S.; Park, J.; Kim, J.; Paik, N.-J. Effects of Anodal Transcranial Direct Current Stimulation over the Contralesional Hemisphere on Motor Recovery in Subacute Stroke Patients with Severe Upper Extremity Hemiparesis: Study Protocol for a Randomized Controlled Trial. *Medicine* **2020**, *99*, e19495. [CrossRef]
80. Liu, Y.; Zhang, L.; Wang, S.; Long, L.; Zang, Q.; Jia, G. Efficacy and Safety of Electroacupuncture at Auricular Concha Region in Promoting of Rehabilitation of Ischemic Stroke Patients with Upper Limb Motor Dysfunction: A Study Protocol for a Randomized Pilot Trial. *Medicine* **2022**, *101*, e28047. [CrossRef]

81. Mizuno, K.; Abe, T.; Ushiba, J.; Kawakami, M.; Ohwa, T.; Hagimura, K.; Ogura, M.; Okuyama, K.; Fujiwara, T.; Liu, M. Evaluating the Effectiveness and Safety of the Electroencephalogram-Based Brain-Machine Interface Rehabilitation System for Patients with Severe Hemiparetic Stroke: Protocol for a Randomized Controlled Trial (BEST-BRAIN Trial). *JMIR Res. Protoc.* **2018**, *7*, e12339. [CrossRef] [PubMed]
82. Mohan, A.; Knutson, J.S.; Cunningham, D.A.; Widina, M.; O'Laughlin, K.; Arora, T.; Li, X.; Sakaie, K.; Wang, X.; Uchino, K.; et al. Contralaterally Controlled Functional Electrical Stimulation Combined with Brain Stimulation for Severe Upper Limb Hemiplegia-Study Protocol for a Randomized Controlled Trial. *Front. Neurol.* **2022**, *13*, 869733. [CrossRef]
83. Rodgers, H.; Shaw, L.; Bosomworth, H.; Aird, L.; Alvarado, N.; Andole, S.; Cohen, D.L.; Dawson, J.; Eyre, J.; Finch, T.; et al. Robot Assisted Training for the Upper Limb after Stroke (RATULS): Study Protocol for a Randomised Controlled Trial. *Trials* **2017**, *18*, 340. [CrossRef]
84. Stoykov, M.E.; Biller, O.M.; Wax, A.; King, E.; Schauer, J.M.; Fogg, L.F.; Corcos, D.M. Bilateral Upper Extremity Motor Priming (BUMP) plus Task-Specific Training for Severe, Chronic Upper Limb Hemiparesis: Study Protocol for a Randomized Clinical Trial. *Trials* **2022**, *23*, 523. [CrossRef] [PubMed]
85. van Lieshout, E.C.C.; Visser-Meily, J.M.A.; Neggers, S.F.W.; van der Worp, H.B.; Dijkhuizen, R.M. Brain Stimulation for Arm Recovery after Stroke (B-STARS): Protocol for a Randomised Controlled Trial in Subacute Stroke Patients. *BMJ Open* **2017**, *7*, e016566. [CrossRef] [PubMed]
86. Wei, D.; Hua, X.-Y.; Zheng, M.-X.; Wu, J.-J.; Xu, J.-G. Effectiveness of Robot-Assisted Virtual Reality Mirror Therapy for Upper Limb Motor Dysfunction after Stroke: Study Protocol for a Single-Center Randomized Controlled Clinical Trial. *BMC Neurol.* **2022**, *22*, 307. [CrossRef]
87. Wei, X.; Xia, N.; Li, Y.-A.; Gu, M.; Zhang, T.; Gao, W.; Liu, Y. Immediate and Short-Term Effects of Continuous Theta Burst Transcranial Magnetic Stimulation over Contralesional Premotor Area on Post-Stroke Spasticity in Patients with Severe Hemiplegia: Study Protocol for a Randomized Controlled Trial. *Front. Neurol.* **2022**, *13*, 895580. [CrossRef]