Title: Timing and dose of upper limb motor intervention after stroke: A systematic review.

Cover title: Timing and dose of upper limb intervention.

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Abstract

This systematic review aimed to investigate timing, dose and efficacy of upper limb intervention during the first 6-months post-stroke. Three online databases were searched up to July 2020. Titles/abstracts/full-text were reviewed independently by two authors. Randomized and non-randomized studies that enrolled people within the first 6-months post-stroke, aimed to improve upper limb recovery, and completed pre- and post-intervention assessments were included. Risk of bias was assessed using Cochrane reporting tools. Studies were examined by timing (recovery epoch), dose and intervention type. Two hundred and sixty-one studies were included, representing 228 (n=9,704 participants) unique datasets. The number of studies completed increased from one (n=37 participants) between 1980-1984 to 91 (n=4417 participants) between 2015-2019. Timing of intervention start has not changed (median 38 days, IQR 22-66) and study sample size remains small (median n=30, IQR 20-48). Most studies were rated high risk of bias (62%). Study participants were enrolled at different recovery epochs: 1 hyperacute (<24hr), 13 acute (1-7days), 176 early subacute (8-90days), 34 late subacute (91-180days), and 4 were unable to be classified to an epoch. For both the intervention and control groups, the median dose was 45(IQR 600-1430) minutes/session, 1(IQR 1-1) session/day, 5(IQR5-5) days/week for 4(IQR3-5) weeks. The most common interventions tested were electromechanical (n=55 studies), electrical stimulation (n=38 studies) and constraint induced movement (n=27 studies) therapies. Despite a large and growing body of research, intervention dose and sample size of included studies were too small to detect clinically important effects. Furthermore, interventions remain focussed on subacute stroke recovery with little change in recent decades. A united research agenda that establishes a clear biological understanding of timing, dose and intervention type is needed to progress stroke recovery research. PROSPERO ID: CRD42018019367/CRD42018111629.

Non-standard Abbreviations and Acronyms

Action Research Arm Test (ARAT)

Box and Block Test (BBT)

Cochrane Risk of Bias (ROB-2)

Fugl Meyer Upper Limb assessment (FMUL)

International Committee of Medical Journal Editors (ICMJE)

Minimal clinical important difference (MCID)

Prospective Register of Systematic Reviews (PROSPERO)

Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)

Risk Of Bias In Non-Randomized Studies - of Interventions (ROBINS-I)

Template for Intervention Description and Replication (TIDieR)

Wolf Motor Function Test (WMFT)

INTRODUCTION

Up to 80% of stroke survivors have upper limb motor impairment early after stroke[1-3], and few demonstrate complete recovery at 6-months post-stroke[4]. Upper limb motor intervention trials designed to improve recovery within the first 6-months of stroke have yielded mostly neutral findings[5]. As a result, the burden of upper limb impairment after stroke remains high. Understanding how to improve upper limb recovery is a scientific, clinical and patient priority[6-8]. Indeed, a number of fundamental questions exist concerning upper limb intervention after stroke[7]. The Stroke Recovery and Rehabilitation Roundtable taskforce used upper limb recovery as the exemplar for their trial development framework,[7] and demonstrated current uncertainty about: 1) the optimal timing of post-stroke motor intervention, 2) the optimal intervention dose, and 3) what intervention(s) might offer the most benefit. Our aim was to systematically review upper limb intervention studies that commenced within the first 6-months post-stroke to investigate timing, dose and efficacy.

METHODS

This systematic review was prospectively registered on PROSPERO (CRD42018019367/CRD42018111629) and a protocol paper was published[9]. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 statement provided the framework for reporting[10].

Search strategy for identification of relevant studies

Electronic searches were conducted in MEDLINE (via Ovid), EMBASE (via Ovid) and Cochrane Controlled Register of Trials on 17 April 2018, and updated on 16 July 2020. The search strategy included terms related to stroke, upper limb function and movement, and

127 therapy and intervention (see Supplemental A, page 2). The only search strategy limit was
128 'human'.
129
130 **Study eligibility**
131 Inclusion criteria were:
132 • Adults (>17 years) with a diagnosis of stroke (ischemic or hemorrhagic) and average
133 (mean/median) stroke onset ≤6-months (or at least 50% of the sample had a diagnosis
134 of stroke within the time frame) to reflect the window of presumed heightened
135 potential for motor recovery[11-13].
136 • Undergoing hospital-based (in or outpatient) rehabilitation to reflect where most
137 rehabilitation takes place during the first 6-months post-stroke.
138 • Upper limb intervention(s) (experimental or usual care) that aimed to improve upper
139 limb function (see below for intervention type description). No restrictions were made
140 on the comparison or control group, e.g., attention and active control groups were
141 eligible.
142 • At least two waves (excluding mid-intervention) of motor impairment or activity
143 assessment were required i.e., pre- and post-intervention.
144 • Study design of RCT, non-RCT, cohort including observational, and pre-post single
145 group.
146 • Languages: English, Dutch, French, German (SFK/VT/TK fluent).
147
148 Exclusion criteria were:
149 • Interventions that were delivered in the home.
150 • Interventions that were pharmacological e.g., recovery-promoting drugs or
151 complimentary e.g., acupuncture, non-invasive brain stimulation or priming.

- Interventions that were focussed on reducing secondary impairments e.g., pain, contracture, spasticity, subluxation; did not include any upper limb motor practice e.g., mental/motor imagery practice alone; general motor practice e.g., activities of daily living; or non-motor impairment practice e.g., sensory, hemispatial neglect.
- Designs of single case, case series, qualitative, surveys, protocols, cross-sectional and single session intervention.
- Conference proceedings or reviews.

Screening of studies

All studies identified by the search strategy were uploaded to Covidence (https://www.covidence.org/[14]) and duplicates were removed. Two authors (KSH/SFK/EJD/GRH/VR) independently screened studies for eligibility based on title/abstract using the prespecified eligibility criteria. Full-text for all remaining studies were retrieved and reviewed independently (KSH/SFK/EJD/GRH/VR). Reports from the same study population were linked (KSH/EJD /GRH) to ensure that data were only included once. This was achieved by review of study authorship, clinical trial registration details (if available) and study methods for reference to linked studies. Disagreements were resolved by discussion and review of criteria between at least two additional authors (KSH/SFK/EJD/GRH).

Data extraction

Due to the large volume of studies, all authors completed data extraction (n≥10 articles each) using a predetermined custom-built data collection excel spreadsheet. Two virtual training sessions and three check-in sessions were held with authors via Zoom. Emails addressing queries and frequently asked questions during extraction were distributed as required. All

demographics, time post-stroke, intervention type and dose, as well as clinical outcome data were cross-checked by a second reviewer (KSH/EJD/GRH). All discrepancies were discussed with a third reviewer for consensus (KSH/SFK/EJD/GRH). If a resolution could not be achieved, a statistician (LC) reviewed the paper to make the final decision. The data extraction form was detailed in the protocol paper[9] and summarized below.

Demographics: Mean/median study sample age, proportion of male and female participants, mean/median days post-stroke to trial enrolment or treatment commencement, and proportion of ischemic and hemorrhagic participants, as well as country where the study was conducted were extracted.

Study design: Study design (RCT, non-RCT, cohort, pre-post), clinical trial registration (yes/no), trial phase (phase I/II/III/IV[15]), safety (i.e., planned safety protocol in method and actual report of adverse events in the results, yes/no), assessment time-points (i.e., pre, post, follow-up), and stratification (performed yes/no) were extracted. Report of eligibility criterion (yes/no) related to upper limb function (impairment or activity), stroke severity, first stroke, cognition, language, sensation, perception and time post-stroke were also extracted.

Time post-stroke: Mean/median group values from stroke onset to study enrolment or intervention start as reported by each study, and reported study eligibility criterion related to timing were extracted. All time post-stroke data were transformed into days (i.e., for multiplication of month data, 1-month = 30-days). Each study was allocated to a post-stroke recovery epoch based on mean/median group values. If these data were not available, we classified studies based on their eligibility criterion. The Stroke Rehabilitation and Recovery Roundtable taskforce defined recovery epochs were used to standardize allocation[16]:

hyperacute, ≤24-hours post-stroke; acute, >24-hours but ≤7-days post-stroke; early subacute, >7-days but ≤3-months post-stroke, and late subacute, >3-months (>90-days) but ≤ 6-months (≤180-days) post-stroke. If required (e.g., number of studies per epoch ≥50), early subacute and late subacute were further subcategorized into 1-month epochs (e.g., early subacute epoch 1: 8- to 30-days; early subacute epoch 2: 31- to 60-days etc.).

Dose: To gather the most consistent data across studies[17], dose dimensions[18] pertaining to interventions provided to the hemiplegic upper limb for duration (weeks of intervention), days (days/week intervention provided), sessions (number/day) and session length (minutes/session) and were extracted from the methods (planned dose). Dose dimensions related to an episode within a single session were not examined i.e., intensity or difficulty[18]. Using these data, total intervention dose (minutes) was calculated if not reported by study authors. If only some dose dimensions were provided (e.g., total intervention dose and number of sessions), this information was used to define missing dose dimension(s) (e.g., session length). In line with capturing hemiplegic limb intervention dose only, non-hemiplegic intervention dose was not extracted (e.g., sling use within constraint protocols). The proportion of studies that delivered a potentially important threshold dose (≥2-hours/day) for motor recovery was noted[19]. We extracted (yes/no) if any dimensions of actual dose completed within the intervention were reported in the study results. Where able, the same dose dimensions were extracted for the control intervention and usual (or standard/conventional) therapy.

Upper limb intervention type: Categorized based on the intervention description of the comparison of interest in the aim, description in the methods, or pictures included. Intervention type categories were consistent with a previously published Cochrane review of

upper limb intervention[20]: bilateral arm training, biofeedback, bobath approach, constraint-induced movement therapy, electrical stimulation, hands-on therapy (manual therapy techniques), repetitive task training, electromechanical devices (including robotics), strength training, task-specific training, virtual reality, standard therapy, mirror therapy, video game-based intervention, music therapy or other.

Outcome measures: To document upper limb recovery, change (impairment or activity) across two assessment waves (e.g., pre- to post-intervention) was examined. The clinical outcome considered to best reflect recovery of upper limb impairment, and recommended by the international Stroke Rehabilitation and Recovery Roundtable taskfroce,[21] was the Fugl Meyer Upper Limb (FMUL) assessment[9]. The order for upper limb activity measures was Box and Block Test (BBT), Wolf Motor Function Test (WMFT) rate, Action Research Arm Test (ARAT), and WMFT scale, which reflects prioritisation of timed measures (e.g., BBT) over observational measures (e.g., ARAT)[9]. Data were extracted (mean(SD) or median(IQR)) for each assessment wave by study group, as well as within group change scores (post-intervention minus pre-intervention). PlotDigitizer V2.6.9 interpretive software was used to extract missing data from figures. Using pre- to post-intervention mean/median change scores, two authors (KSH/EJD) determined if a minimal clinical important difference (MCID) was achieved for the intervention group (or largest dose contrast to the control or intervention of contrast per the study aim if multiple intervention groups) and the control group. If there was uncertainty in data reporting, a third reviewer reviewed the data (NAL). Accepted MCID scores were applied to inform efficacy: FMUL ≥5.25 points[22], BBT ≥5.5 points[23], WMFT-rate ≥2 seconds and WMFT-scale ≥0.4 points[24], and ARAT ≥5.7 points[25]. Data were considered missing if there were no outcome data for a particular measure or data

were not extractable (e.g., data had been log transformed so could not be used to determine MCID, FMUL was not reported out of 66 points as reflex items were not performed).

Risk of bias and intervention reporting

Cochrane Risk of Bias (ROB-2) tool was used to rate bias across five domains for RCTs[26]. All other designs were rated using the Risk Of Bias In Non-Randomized Studies - of Interventions (ROBINS-I) tool[27]. These tools were completed during data extraction. Intervention reporting was rated using the TIDieR checklist[28]. At least 30% of each author's ROB/TIDieR ratings were crosschecked by another author (EJD/GRH). If consistent errors were identified within a rater, all ROB/TIDieR ratings for a rater were cross-checked. All inconsistencies were discussed between two authors (KSH/SFK/EJD).

Data synthesis

Demographics and study design variables were tallied, and reported as median (IQR), minimum to maximum range, or number of studies (percentage) as appropriate. Due to the heterogeneity of data across recovery epochs, dose and efficacy outcomes, as well as the high proportion of study with bias concerns, no pooled analyses were performed. Descriptive data for each recovery epoch, as well as dose and intervention type by recovery epoch were tallied, and reported as median (IQR), minimum to maximum range, or number of studies (percentage) as appropriate.

RESULTS

Summary of included studies

Database searching yielded 16,399 results, with 261 included studies that represented 228 unique study datasets (n=9,704 participants). The PRISMA flow chart is provided in Figure

1. The primary reason for exclusion at full-text was recruitment of participants more than 6-months post-stroke (43%). The demographics of participants across studies are reported in Table 1. A summary of each included study is provided in Supplemental B (see page 3) and C (see page 8) and references for included studies are in Supplemental D (see page 56). Most studies had an eligibility criterion related to upper limb impairment or activity (n=201, 88.2%; e.g., available range of movement or outcome on a particular measure such as Fugl Meyer Upper Limb), cognition (n=184, 80.7%; e.g., general statements such as capacity to follow instructions or give informed consent, as well as outcome on a particular measure such as Mini-Mental State Examination), first stroke only (n=133, 58.3%), and language (n=118, 51.8%; e.g., primary language spoken, aphasia status). Few studies had an eligibility criterion related to sensation or perception (n=85, 37.3%; e.g., neglect or sensory loss) or stroke severity (n=16, 7.0%; e.g., using NIHSS, Scandinavian Stroke Scale or modified Rankin Scale).

Insert here

Figure 1: *PRISMA study selection flow diagram.*

Insert here:

Table 1: *Study demographics*

Trends across upper limb studies completed during the first 6-months post-stroke

The number of studies per 5-year window increased from one (n=37 participants) between 1980-1984 to 91 (n=4,417 participants) between 2015-2019 (Figure 2 Panel A). The median

days post-stroke (median 37.7 days IQR 22.0-65.9; Figure 2, Panel B) and sample size (median 30.0, IQR 20.0-48.0; Figure 2 Panel C) have remained stable over time.

The majority of studies were rated to have high (ROB-2, n=97 out of 174 RCTs) or serious/critical (ROBINS-I, n=44 out of 54 non-RCTs) risk of bias. Intervention reporting using TIDieR was variable. While overall, most studies reported few TIDieR intervention items (53% scored 6 or less out of 12 on TIDieR), there was demonstration of an improvement in the median TIDieR scores in the last decade. Risk of bias and TIDieR outcomes by calendar year are presented in Figure 2 Panel A (for each study see Supplemental B, page 3).

Insert here:

Figure 2: Number of studies, Risk of Bias, TIDieR, time post-stroke and sample size over time across included upper limb studies.

Panel A: *Stacked bar chart defines the number of studies per year (black) and the number of high/serious/critical risk of bias (red) for n=228 studies. The blue dashed line represents the median TIDieR score for studies reported per calendar year.*

Panel B: *Median time post-stroke in days for studies per calendar year for n=219 with reported data out of 228 studies.*

Panel C: *Median sample size for studies per calendar year for n=228 studies. Note: 2020 was an incomplete year with the search last updated in July 2020.*

Timing of intervention

Out of 228 studies, 188 studies (82%) determined eligibility using time post-stroke. A total of 219 studies (96%) reported the actual mean or median time from stroke onset to study

enrolment or intervention start. Only 47 studies (21%) provided a justification for intervention timing. Across all studies the median days to intervention start was 37.7 (IQR 22.0 to 65.9); consistent with early subacute recovery epoch 2 (30- to 60-days). There was one study (n=128 participants) that started intervention during the hyperacute phase, 13 (n=652) during the acute phase, 176 (n=7,803) during the early subacute phase (88 [n=4,485] epoch 1: 8-30 days, 60 [n=2,470] epoch 2: 31-60 days, and 22 [n=610] epoch 3: 61-90 days; 6 (n=238) unable to be further classified), and 34 (n=1,024) in the late subacute phase. There were 4 (n=97) studies completed within the first 6-months with insufficient information to allocate a recovery epoch.

Dose of intervention

The proportion of studies that reported each dose dimension for intervention, control and usual care, as well as by recovery epoch, are presented in Table 2. The poorest dimension reported was total intervention dose. Reporting of actual dose completed was also poorly reported: 11 studies reported any dimension of actual intervention dose, 8 studies reported any dimension of actual control dose, and 5 studies reported any dimension of actual usual care dose. In the intervention group, 71% (n=163) received usual care on top of the intervention dose, while when the control group was not usual care, but another intervention, 53% (n=100) received usual care on top of the control dose.

The intervention group was dose matched to the control group in the majority of studies (124 out of 188 studies with 2 or more groups; 66%). Therefore, for both the intervention and control groups, the median dose was 45 minutes/session, 1 session/day, 5 days/week for 4 weeks. Few studies (n=28, 12%) provided at least 2 hours/day of intervention. In general, the largest median total dose in minutes tested was during the acute recovery epoch.

Efficacy of upper limb intervention

A summary of MCID outcomes by recovery epoch are presented in Figure 3A for impairment and Figure 3B for activity (for individual studies see Supplemental B, page 3). Irrespective of the recovery epoch, the MCID (dichotomized as achievement or not) for studies with at least two groups was mostly the same i.e., if the intervention achieved a MCID, the control group also achieved a MCID. For impairment, 102 studies contained data to permit interpretation of a MCID. In 69% (n=70) of these studies, impairment outcomes were similar: 62% (n=63) showing MCID in both groups, and 7% (n=7) showing neither group achieved MCID. For the activity outcome, 107 studies contained data to permit interpretation of a MCID. In 67% (n=72) of these studies, activity outcomes at end of intervention were similar: 55% (n=59) showing MCID in both groups, and 12% (n=13) showing neither group achieved MCID. Across all studies with MCID data (and within each recovery epoch), less than one third demonstrated an MCID in the intervention group but not in the control group.

Insert here:

Table 2: *Median, minimum and maximum for common dose dimensions, and proportion of studies that reported each dose dimension.*

Insert here:

Figure 3: A. Impairment and B. Activity outcomes. *Minimal clinical important difference (MCID) for intervention and control groups by recovery epoch post-stroke. There was one study in hyperacute phase of recovery, 13 in the acute phase, 176 in the early subacute phase (88 in epoch 1, 60 in epoch 2, and 22 in epoch 3), 34 in the late subacute phase, and 10 unable to be subcategorised. No control group applies to the single group non-RCT studies.*

Upper limb intervention type

The number of studies per intervention type are reported in Table 1 and distribution by recovery epoch in Figure 4.

Insert here:

Figure 4: *Stacked bar chart demonstrating when each upper limb intervention type has been tested across the first 6-months post-stroke.*

DISCUSSION

This systematic review shows an increase over time in stroke recovery research focused on improving upper limb recovery during the first 6-months post-stroke. However, timing of intervention start post-stroke and sample size have remained relatively stable, and risk of bias remained modest. Intervention reporting has seen an improvement in the last decade (TIDieR[28]). The dose chosen for testing in most studies was less than 1 hour/day, which may be too low to drive best motor recovery[17,19]. Most interventions tested did not result in a MCID in favour of the intervention group. These findings from over 40 years of research, highlight the need to reflect and consider how our research needs to change to create opportunities to identify interventions that deliver the recovery gains that people living with stroke, their carers and clinicians need.

We deliberately restricted this review to studies that enrolled participants within 6-months of stroke onset as this is considered to reflect a window of heightened potential for motor recovery[11-13]. Within this period, the recovery epoch with the highest proportion of studies

included was early subacute epoch 1 (8- to 30-days post-stroke), which corresponds with engagement in inpatient rehabilitation services in many countries. Whether the timing of intervention start in these studies was pragmatically driven or specifically selected to take advantage of the hypothesised 'plasticity window' was not clear. Few authors provided a rationale for their timing choice (20.6%). Establishing a strong biological rationale for selection of clinical intervention timing would complement the preclinical evidence that exists[11,29], and strongly guide timing selection in future studies. If the optimal time is within the first few weeks of stroke onset, it must be acknowledged that trials starting this early can be challenging. People can be awaiting tests to confirm a stroke diagnosis, may be medically unstable or experiencing neurological decline, or may be processing the acute event preventing consideration of therapy focused research requests[30]. Furthermore, considerable spontaneous biological recovery occurs during this early epoch[12,16,31]. This means that not all recovery achieved early after stroke can be attributed to the intervention tested. Disentangling spontaneous and intervention related recovery is currently difficult. This is often the rationale for starting upper limb recovery studies beyond 6-months post-stroke (i.e., stable motor status[32]). Moving forward we need to identify efficient and effective ways to recruit and treat stroke patients in earlier epochs if indeed a window exists in which our interventions should be applied at high(er) doses for maximum benefit.

Both the lack of justification for and variability in dose prescribed across included studies suggests dose selection to date has been pragmatic. There was little difference in the median dose for intervention and control groups, nor between the median dose within each recovery epoch. All were broadly consistent with standard care descriptions from recent observational reports i.e., 45 to 60-minutes/day[33]. Yet, such a dose has been acknowledged to be insufficient to optimise upper limb recovery in systematic reviews with meta-analysis[17,19].

The most recent suggestion is that 2 or more hours/day represents a dose threshold that leads to clinically meaningful improvements[19]. We found few studies (<13%) delivered a dose at or beyond this threshold within the first 6-months post-stroke. On top of low dose therapy, most studies were dose-matched (>65%). Dose matched studies are largely comparative effectiveness in design, suggestive of phase IIb or III trials. Only one phase I trial[34] has been completed to date, limiting the articulation of safe and tolerable dose ranges for a given upper limb intervention, and few phase IIa trials to identify the optimal dose(s) to take forward into a comparative effectiveness trial[35]. The lack of early phase trials adds further weight to the likelihood that dose selection within included studies was likely pragmatic. Completion of phase I and IIa trials requires adherence to systematic clinical trial phasing[15,36], which could see trials deliver a dose that is biologically and mechanistically informed.

This review highlights the need to improve the design of recovery studies[7] and the quality of reporting[37]. One in four studies were registered with a clinical trial registry. The International Committee of Medical Journal Editors (ICMJE) encouraged registration of trials from July 2005[38], and some rehabilitation journals mandated registration in the late 2000s (e.g., *Physical Therapy* transparently reported starting January 1, 2008[39]). As of May 2021, 12 of the top 20 ranked journals (2019 'Rehabilitation' Journal Citation Reports, Web of Science) mandated prospective clinical trial registration on their website. This highlights a key gap to close. Surprisingly, very few studies reported (15%) or collected (30%) safety data (i.e., adverse events). Adverse events reporting should be standard in clinical research[40], and assuming that therapy-based interventions are safe is naïve[41,42]. The impact of upper limb intervention on pain, contracture, spasticity, falls or other potentially related adverse events needs to be consistently considered. A large proportion of included studies were rated to have a high risk of bias[26], which remained unchanged with time. Higher risk of bias impacts

confidence in the true effect of an intervention. While many studies had modest intervention reporting (TIDieR), there was an indication of improvement in the last decade, which is in line with the TIDieR publication date[28]. Reporting of dose dimensions[18] examined was variable and was particularly poor concerning usual care, which is consistent with previous reviews in stroke recovery[42,43]. Given usual care varies greatly around the world, and in some countries is influenced by payment systems, better reporting than "plus usual therapy" is necessary. Such statements provide no information to understand the dose of background therapy received, which may contaminate study outcomes. There was also little consideration for how much of the planned dose (described in the methods) was actually delivered to participants[44]. While enhanced research training will improve a number of these elements, the role of ethics committees, journals and journal editors to motivate the field to overcome these limitations cannot be ignored. Ethics committees can enforce adherence to good clinical practice standards that include safety data collection, while journals and editors can enforce adherence with standards established by ICMJE, TIDieR, and other reporting guidelines available on EQUATOR network such as CONSORT for RCTs. This may require the use of supplemental materials to enhance transparent reporting.

Appropriate funding of earlier phase stroke recovery research and establishment of stroke recovery research networks could help overcome many problems highlighted by this review. It is expensive to conduct systematic, phased clinical research that tests high(er) intervention doses, and collects intervention, control, and usual care dose data in sufficient detail. However, appropriately supporting such research will position the field to learn far more than what can be gleaned from many of the small trials included in this review. To develop an economy of scale, conducting investigator-initiated trials within networks can foster collaborations, leverage and maximize expertise, enhance recruitment, ensure equitable

476 distribution of resources, and promote collection of consistent data elements[45]. Some
477 countries have established stroke recovery trial networks: UK Stroke Research Network (now
478 decommissioned), StrokeNet[46] funded by the NIH and CANSTROKE[47] funded by Brain
479 Research Canada. None have yet reported on their impact to improve trial design, quality or
480 outcomes. The recently formed International Stroke Recovery and Rehabilitation Alliance
481 (ISRRA) aims to develop flagship projects that may build critical trial capacity and
482 partnerships globally[48]. These initiatives are key to align research interests to collectively
483 design and deliver scientifically transformative stroke recovery research.
484
485 *Limitations*
486 This review has limitations. Firstly, we did not conduct pooled analyses due to the large
487 volume of outcome data not collected by individual studies (e.g., did not collect FMUL or
488 used a brief version of the FMUL) or insufficiently reported (e.g., log transformed data
489 without raw scores), large proportion with high risk of bias and generally small sample size
490 of included studies. To support pooled interpretation and comparison of findings across
491 recovery epochs, dose and intervention type, we encourage researchers to use supplemental
492 materials to transparently report the intervention (e.g., TIDieR checklist[28]) and detail dose
493 dimensions[18]; adhere to common data elements[21]; and report original scores along with any
494 transformed data. Secondly, we did not search for gray literature, such as conference
495 abstracts or theses, included non-English studies from a small selection of countries, and
496 searched for articles up to until July 2020. Given the large volume of studies that were
497 included, it is unlikely that the inclusion of additional studies would lead to significant
498 changes in our findings. We did not include home-based interventions as this review was
499 targeting hospital-based interventions. Broadening to home-based interventions would have
500 led to a higher yield of included studies.

501

502 **Conclusions**

503 Due to the lack of consistent data elements, there was insufficient evidence to conclude the
504 optimal time to commence upper limb intervention post-stroke, nor the effect of timing and
505 dose on efficacy. As such, there has never been a more important time for stroke recovery to
506 establish a united agenda to collectively address the biggest problems, whilst adopting a
507 systematic approach to stroke recovery research that adheres to international standards.
508 Similar to our acute stroke colleagues[49], we can expect to have more trial failures before we
509 succeed[50,51]. But with appropriate investment in upper limb recovery research, we can build a
510 clear biological rationale for the selection of timing, dose and intervention type post-stroke.

511

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513

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523

524 **Data availability:** Available upon reasonable request to Dr Kathryn Hayward
525 (kate.hayward@unimelb.edu.au)

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689 **Table 1: Study demographics**

Age, n=210 studies^: from the mean reported in studies	
median (IQR)	61.4 (58.0-65.9)
^n=18 reported median as raw data or did not report age data.	
Sex, n=216 studies*: n participants, proportion	
Male	5429, 58%
Female	3906, 42%
*n=12 studies did not report sex by participant	
Stroke type, n=173 studies*: n participants, proportion	
Ischemic participants	6422, 83%
Hemorrhagic participants	1276, 17%
*n=55 studies did not report stroke type by participant	
Design, n=228: n studies, proportion	
RCT	174, 76%
Non-RCT	54, 24%
Continent, n=228: n studies, proportion	
Europe	97, 43%
Asia	85, 37%
North America	27, 12%
Australia/New Zealand	14, 6%
South America	3, 1%
Africa	2, 1%
Time post-stroke, n=228: n studies, proportion	
Hyperacute, ≤24-h post-stroke	1, <1%
Acute, >24-h but ≤7-days post-stroke	13, 6%

Early subacute, >7-days but ≤3-months post-stroke	176, 77%
Late subacute, >3-months but ≤6-months post-stroke	34, 15%
Not stated	4, 2%
Primary outcome, n=228: n studies, proportion	
Fugl Meyer Upper Limb (FMUL)	31, 14%
Action Research Arm Test (ARAT)	26, 11%
Wolf Motor Function Test-Rate (WMFT-Rate)	5, 2%
Box and Block Test (BBT)	4, 2%
Motor Assessment Scale (MAS)	2, 1%
Wolf Motor Function Test-scale (WMFT-Scale)	3, 1%
Other	26, 11%
Not stated	131, 57%
Intervention type, n=228: n studies, proportion	
Electromechanical and robotic therapy	55, 24%
Electrical stimulation	37, 16%
Constraint-induced movement therapy (CIMT)	28, 12%
Repetitive task training	23, 10%
Virtual reality^	22, 10%
Mirror therapy^	19, 8%
Task-specific training	10, 4%
Video game-based intervention	6, 3%
Strength training	5, 2%
Hands on therapy	5, 2%
Bilateral arm training	4, 2%
Biofeedback	4, 2%

Bobath approach	4, 2%
Music therapy	3, 1%
Mental practice^	2, 1%
Standard therapy	1, <1%
Study design and reporting characteristics, n=228: n studies, proportion	
Trial registration, yes: n studies, proportion	56, 25%
Reported trial phase, yes: n studies, proportion	5, 2.2%
Stratification included in design, yes: n studies, proportion	43, 18%
Included a biomarker assessment, yes: n studies, proportion	23, 10%
Safety described in methods, yes: n studies, proportion	35, 15%
Safety reported in results, yes: n studies, proportion	70, 30%

690 ^All interventions included upper limb motor practice e.g., mental practice was paired with
691 motor intervention.

692 **Table 2:** Median (IQR), minimum to maximum, and reporting by studies for each dose dimension.

Intervention	Total intervention dose, minutes	Session length, minutes	Sessions, per day	Days, per week	Duration, total weeks
All studies, n=229[#] Median(IQR), min-max, n(%)	900(600-1430), 180-7200, 195(85.2)	45(30-60), 10-480, 207(90.4)	1(1-1), 1-4, 214(93.4)	5(5-5), 2-7, 210(91.7)	4(3-5), 1-20, 209(91.3)
Hyperacute, n=1 Median(IQR), min-max, n(%)	1200(NA), NA, 1(100.0)	60(NA), NA, 1(100.0)	2(NA), NA, 1(100.0)	5(NA), NA, 1(100.0)	2(NA), NA, 1(100.0)
Acute, n=13 Median(IQR), min-max, n(%)	1200(1125-1800), 630-3600, 12(92.3)	45(30-98), 20-180, 13(100.0)	1(1-2), 1-3, 13(100.0)	5(5-5), 5-7, 12(92.3)	4(3-5), 2-12, 12(92.3)
Early subacute 1, n=88 Median(IQR), min-max, n(%)	800(600-1350), 180-3600, 78(88.6)	45(30-60), 10-180, 83(94.3)	1(1-1), 1-4, 83(94.3)	5(5-5), 3-6, 79(90.0)	4(2-5), 1-20, 78(90.0)
Early subacute 2, n=60 Median(IQR), min-max, n(%)	900(585-1410), 300-7200, 52(86.7)	45(30-60), 10-480, 54(90.0)	1(1-1), 1-2, 53(88.3)	5(5-5), 3-7, 54(90.0)	4(3-6), 2-12, 54(90.0)
Early subacute 3, n=22 Median(IQR), min-max, n(%)	900(540-1800), 300-3600, 22(100.0)	45(30-60), 10-180, 22(100.0)	1(1-1), 1-2, 21(91.3)	5(5-5), 3-5, 21(91.3)	4(3-4), 2-8, 22(100.0)

Late subacute, n=34 Median(IQR), min-max, n(%)	720(540-1350), 300-4500, 33(97.1)	40(30-60), 20-360, 34(100.0)	1(1-1), 1-2, 33(97.1)	5(5-5), 2-6, 33(97.1)	4(3-4), 2-10, 34(100.0)
Control					
All studies, n=188^ Median(IQR), min*-max, n(%)	900(540-1350), 0-7200, 145(77.1)	45(30-60), 0-480, 153(81.4)	1(1-1), 0-3, 156(83.0)	5(5-5), 0-7, 159(84.6)	4(3-5), 0-20, 160(85.1)
Hyperacute, n=1 Median(IQR), min*-max, n(%)	1200(NA), NA, 1(100.0)	60(NA), NA, 1(100.0)	2(NA), NA, 1(100.0)	5(NA), NA, 1(100.0)	2(NA), NA, 1(100.0)
Acute^, n=12 Median(IQR), min-max, n(%)	300(300-1800), 240-2100, 6(50.0)	60(30-68), 20-180, 7(58.3)	1(1-1), 1-3, 7(58.3)	3.5(2-5), 1-7, 6(50.0)	4(4-5), 2-5, 5(41.7)
Early subacute 1^, n=76 Median(IQR), min*-max, n(%)	900(510-1200), 0-5400, 63(83.0)	45(30-60), 0-360, 66(86.8)	1(1-1), 0-2, 66(86.8)	5(5-5), 0-6, 67(88.2)	4(3-5), 2-20, 66(86.8)
Early subacute 2^, n=49 Median(IQR), min-max, n(%)	960(555-1430), 69-7200, 41(83.7)	30(30-60), 10-480, 41(83.7)	1(1-1), 1-2, 41(83.7)	5(5-5), 3-7, 43(87.8)	4(3-6), 2-12, 44(90.0)
Early subacute 3^, n=17	1080(750-1800), 200-2520, 15(88.2)	60(38-60), 10-90, 15(88.2)	1(1-1), 1-2, 14(82.4)	5(5-5), 3-5, 14(82.4)	4(4-6), 2-8, 16(94.1)

Median(IQR), min-max, n(%)					
Late subacute[^], n=23 Median(IQR), min*-max, n(%)	625(600-1200), 0-4500, 21(91.3)	30(30-60), 0-300, 21(91.3)	1(1-1), 0-2, 21(91.3)	5(5-5), 0-6, 21(91.3)	4(3-4), 0-6, 22(95.7)
Usual care					
All studies, n=229[#] Median(IQR), min-max, n(%)	1200(698-1800), 240-5400, 67(29.3)	60(30-60), 15-360, 77(33.6)	1(1-2), 1-4, 87(38.0)	5(5-5), 1-7, 95(41.5)	4(3-4), 2-20, 4(41.0)
Hyperacute, n=1 Median(IQR), min-max, n(%)	1200(NA), NA, 1(100.0)	60(NA), NA, 1(100.0)	2(NA), NA, 1(100.0)	5(NA), NA, 1(100.0)	2(NA), NA, 1(100.0)
Acute, n=13 Median(IQR), min-max, n(%)	300(300-300), NA, 1(7.7)	20(20-20), NA, 1(7.7)	1(1-1), NA, 1(7.7)	5(5-5), NA, 1(7.7)	3(3-3), NA, 1(7.7)
Early subacute 1, n=88 Median(IQR), min-max, n(%)	1300(765-3450), 300-5400, 32(36.4)	60(47-101), 30-360, 36(40.9)	1(1-1), 1-3, 35(39.8)	5(5-5), 2-6, 39(44.3)	3(3-4), 2-20, 40(45.5)
Early subacute 2, n=60 Median(IQR), min-max, n(%)	1200(900-1800), 450-2700, 24(40.0)	60(30-60), 30-180, 26(43.3)	1(1-2), 1-4, 28(46.7)	5(5-5), 1-7, 30(50.0)	4(3-6), 2-8, 30(50.0)

Early subacute 3, n=22 Median(IQR), min-max, n(%)	720(675-1400), 600-2520, 8(36.4)	45(43-53), 30-60, 8(36.4)	1(1-1), 1-2, 7(31.8)	5(5-5), 2-5, 8(36.4)	4(3-4), 2-8, 9(40.9)
Late subacute, n=34 Median(IQR), min-max, n(%)	600(495-950), 240-1500, 14(41.2)	30(30-45), 15-60, 14(41.2)	1(1-1), 1-2, 13(38.2)	5(5-5), 2-6, 13(38.2)	4(3-4), 2-8, 14(41.2)

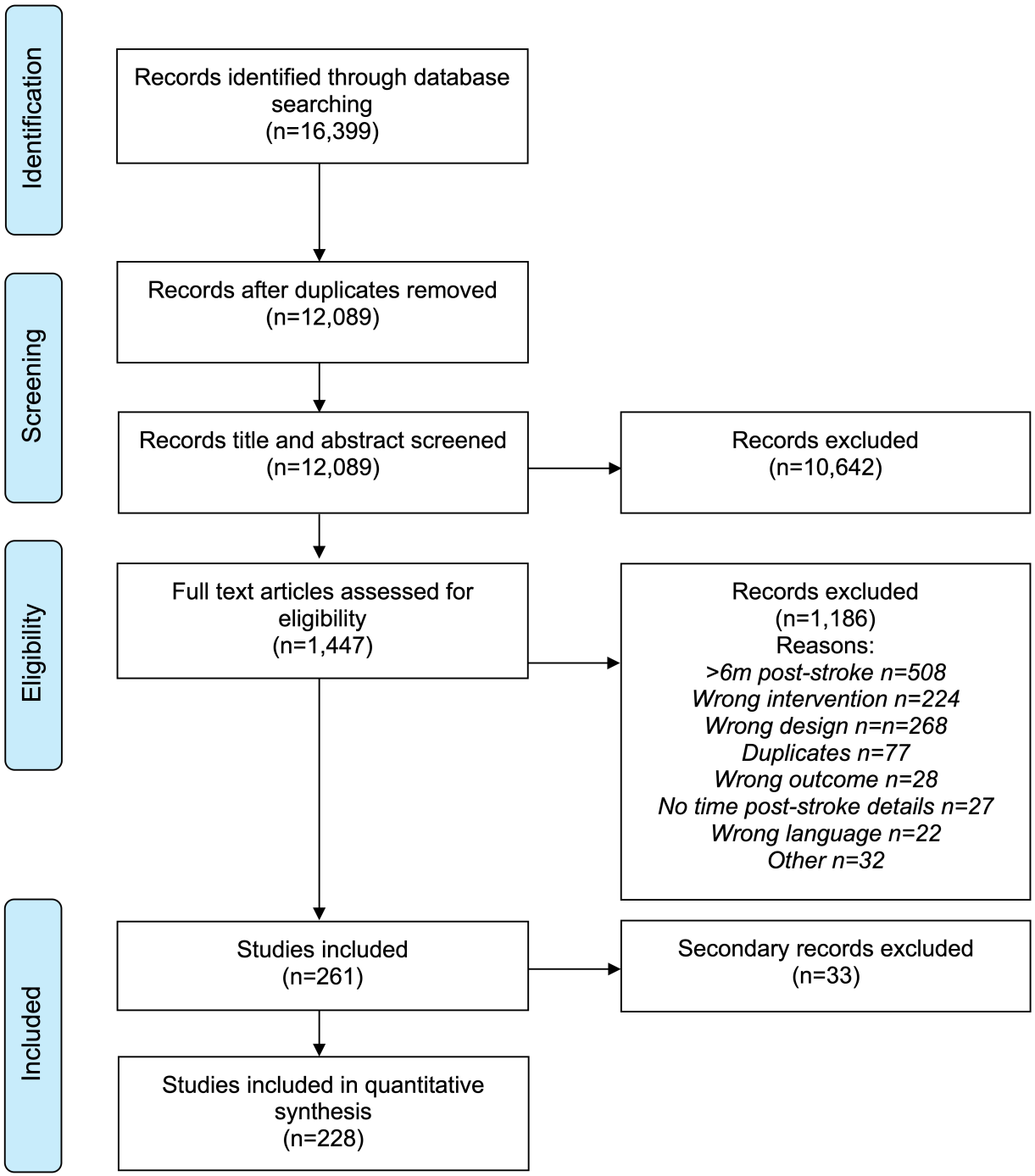
693

694 **Notes:** NA not applicable as only one study had data available. Not all studies could be classified to a recovery epoch (n=10).

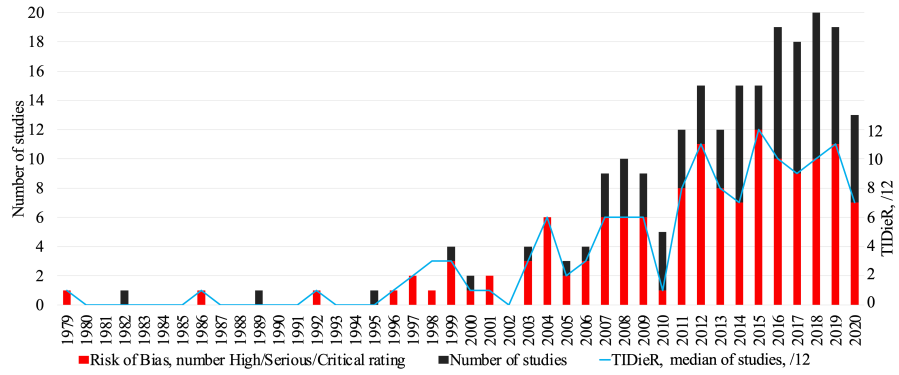
695 [#] One study contained two individual trials which were treated separately.

696 [^] Represents the number of studies after single group studies were removed, ie they did not have a control group.

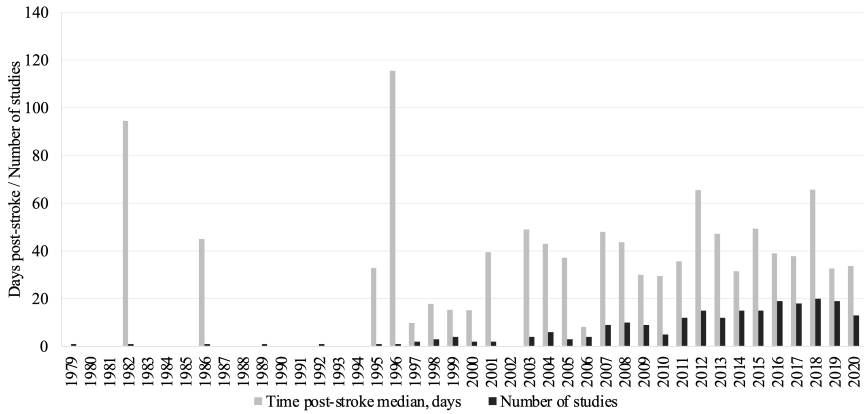
697 [*] There were three studies with a control group that received no intervention. Removing these three studies *across all studies*, the minimum total
698 dose, minute=69; session length, minutes=10; sessions/day=1; days/week=1; and total weeks=2. Removing two relevant studies within the *early*
699 *subacute 1 epoch*, the minimum total dose, minutes=240; session length, minutes=10; sessions/day=1; days/week=1; and total weeks=2.
700 Removing one relevant study within the *late subacute epoch*, the minimum total dose, minutes=400; session length, minutes=20;
701 sessions/day=1; days/week=3; and total weeks=2.


Identification
Screening
Eligibility
Included
Records identified through database searching (n=16,399)
Records after duplicates removed (n=12,089)
Records title and abstract screened (n=12,089)
Records excluded (n=10,642)
Full text articles assessed for eligibility (n=1,447)
Records excluded (n=1,186)
Reasons:
>6m post-stroke n=508
Wrong intervention n=224
Wrong design n=n=268
Duplicates n=77
Wrong outcome n=28
No time post-stroke details n=27
Wrong language n=22
Other n=32
Studies included (n=261)
Secondary records excluded (n=33)
Studies included in quantitative synthesis (n=228)

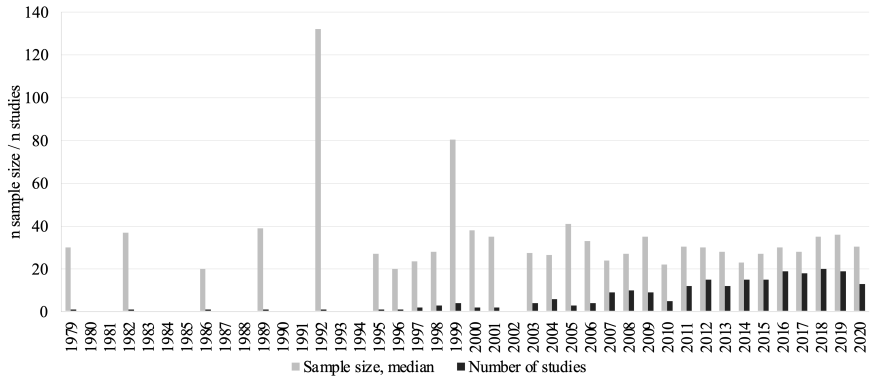
Panel A:



Panel B:



Panel C:



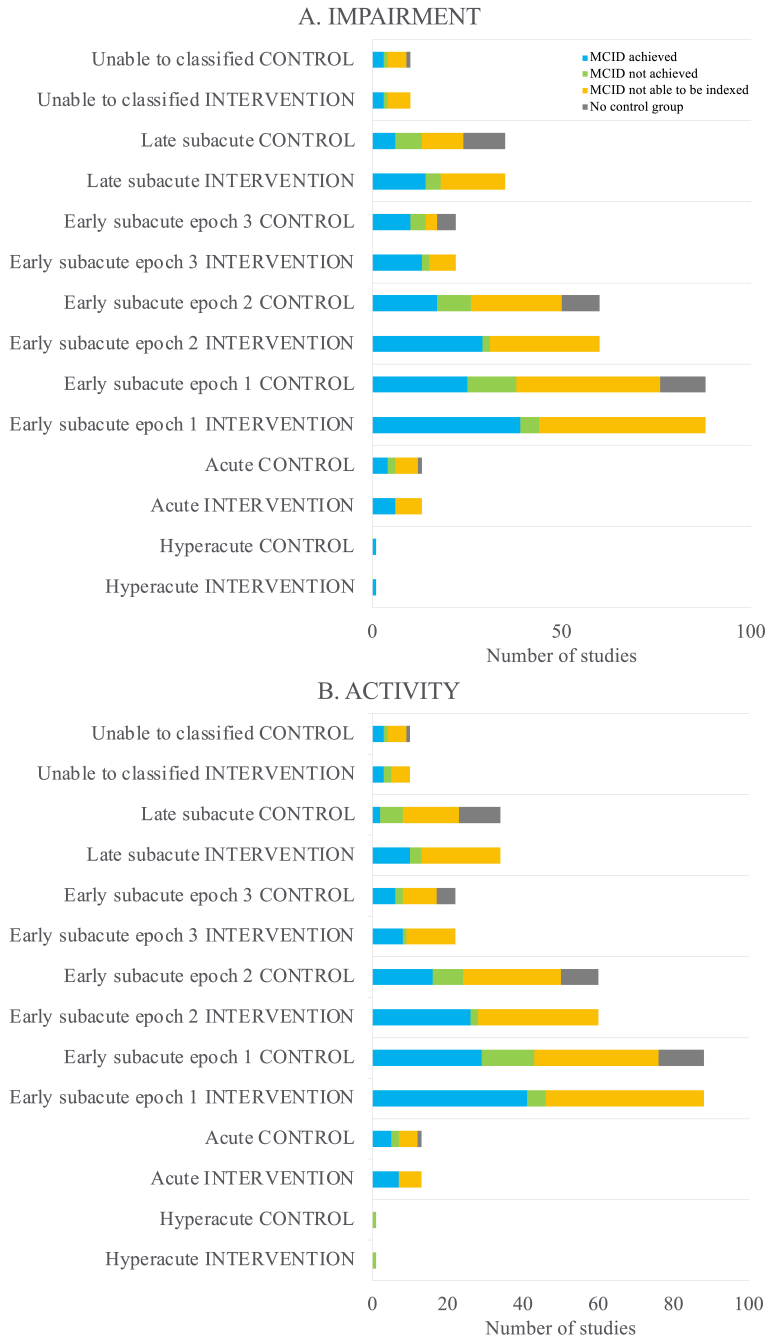

A. IMPAIRMENT
Unable to classified CONTROL
Unable to classified INTERVENTION
Late subacute CONTROL
Late subacute INTERVENTION
Early subacute epoch 3 CONTROL
Early subacute epoch 3 INTERVENTION
Early subacute epoch 2 CONTROL
Early subacute epoch 2 INTERVENTION
Early subacute epoch 1 CONTROL
Early subacute epoch 1 INTERVENTION
Acute CONTROL
Acute INTERVENTION
Hyperacute CONTROL
Hyperacute INTERVENTION
MCID achieved
MCID not achieved
MCID not able to be indexed
No control group
0
50
100
Number of studies
B. ACTIVITY
Unable to classified CONTROL
Unable to classified INTERVENTION
Late subacute CONTROL
Late subacute INTERVENTION
Early subacute epoch 3 CONTROL
Early subacute epoch 3 INTERVENTION
Early subacute epoch 2 CONTROL
Early subacute epoch 2 INTERVENTION
Early subacute epoch 1 CONTROL
Early subacute epoch 1 INTERVENTION
Acute CONTROL
Acute INTERVENTION
Hyperacute CONTROL
Hyperacute INTERVENTION
0
20
40
60
80
100
Number of studies

Figure 3

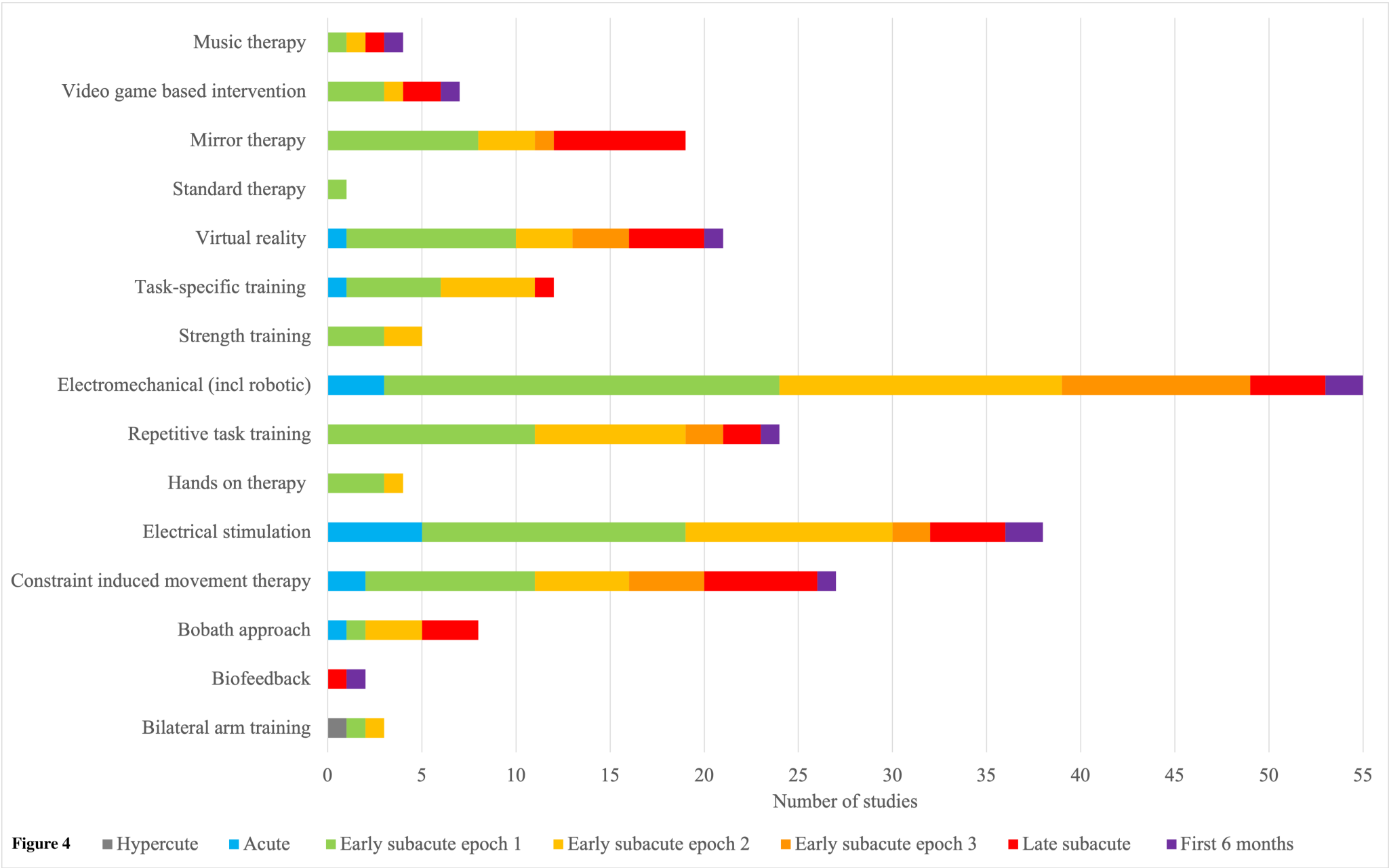

Music therapy
Video game based intervention
Mirror therapy
Standard therapy
Virtual reality
Task-specific training
Strength training
Electromechanical (incl robotic)
Repetitive task training
Hands on therapy
Electrical stimulation
Constraint induced movement therapy
Bobath approach
Biofeedback
Bilateral arm training
0
5
10
15
20
25
30
35
40
45
50
55
Number of studies
Hypercute
Acute
Early subacute epoch 1
Early subacute epoch 2
Early subacute epoch 3
Late subacute
First 6 months

Figure 4