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Upper-limb Robots after Stroke: How to Get beyond the Hype?

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Abstract

Introduction: Upper limb (UL) rehabilitation is driven by intensive, task-specific training. In this article we further elaborate on the results of a systematic review and meta-analysis on the effectiveness of UL-robots (UL-RTs) to recovery of UL-motor impairment, UL-capacity, and basic-ADLs post-stroke when compared to any non-UL-RT. Our second aim was to identify patient, trial, robot and other intervention variables that are associated with found effect sizes (ESs).

Material and Methods: Relevant randomized controlled trials (RCTs) were identified in electronic searches until August 1, 2022. Meta-analyses were performed for measures of UL muscle synergism, muscle power, muscle tone, UL-capacity, performance, and basic ADLs. Methodological quality was assessed with a risk of bias tool. Sensitivity and meta-regression analyses were applied to identify factors potentially associated with found trial-ESs.

Results: Ninety RCTs (N=4.311) were included. Meta-analyses of 86 trials (N=4.240) showed small, significant improvements in UL-muscle synergism (Fugl-Meyer Assessment of the UL [FM-UL]) (mean difference [MD] 2.23[1.11–3.35]), muscle power (standardized mean difference [SMD] 0.39[0.16–0.61]), motor performance (SMD 0.11[0.00–0.21]), and basic ADLs (SMD 0.28[0.10–0.45]). No overall effects were found for muscle tone (SMD −0.10[−0.26 to 0.07]) or UL-capacity (SMD 0.04[−0.10 to 0.18]), except with exoskeletons (SMD 0.27[0.10–0.43]). Meta-regressions showed a significant positive association between baseline mean FM-UL and ESs for UL-capacity (r=0.339; p=0.03). No other significant subgroup differences or associations were found in our sensitivity analyses and meta-regression.

Conclusions: The present research synthesis shows a small (~3%), but significant homogeneous effects in favor of UL-RTs of motor impairment. However, this favorable effect did not generalize to clinically meaningful improvements at level of UL-capacity. The robustness and consistency of our findings suggest that a better mechanistic understanding is required about the assumed interaction effects between motor control and motor learning during recovery of UL-capacity when designing UL-RTs for subjects with a stroke. To achieve this, longitudinal studies are needed that investigate recovery of quality of movement in terms of behavioral restitution and compensation post stroke.

Keywords: Stroke, Robotics, Upper limb, Review, Meta-analysis, Motor recovery, Motor learning, Motor control, Neurorehabilitation

Introduction

Although proper prospective epidemiological studies are lacking, several cohort studies suggest that impairments of motor function and activities of the upper limb (UL) affect up to 80% in acute stroke [1,2]. As a consequence, most patients with stroke experience a reduced upper limb capacity characterized by an inferior quality of movement (QoM) [3,4], independency in their activities of daily living (ADL) [5,6] and health-related quality of life (HrQoL) post stroke [7]. In

a recent longitudinal study combining four different cohort studies (N=412) with weekly or biweekly measurements in time, we showed that the time course of upper limb function measured with Fugl-Meyer Upper Extremity (FM-UE) scores is heterogeneous and follows a proportional amount of spontaneous neurobiological recovery in most subjects with a first ischemic stroke [8,9]. Forty to 50% of all subjects suffering from a minor stroke show good or excellent motor recovery with recovery coefficients beyond 80% that plateaus within the first 2 to 3 weeks post stroke [8]. Another 20 to 30% of stroke survivors show moderate to mild recovery coefficients ranging from 10 to 80% and plateauing mainly within 5 to 8 weeks post stroke [8], whereas 20 to 30% showed poor recovery in which the coefficients remained below the 10% [8]. Longitudinal kinematic analyses showed that the intra-limb coordination in multi-joint movements like reaching or pointing is *always* compromised and characterized by a reduced ability to control simultaneously all degrees of freedom (DoF) when performing a multi-joint movement like reaching or pointing, even in those subjects with a minor stroke [10,11] Interestingly, this recovery in intra-limb coordination occurs within the same time window of 5 to 8 weeks [2,12-14], indicating that behavioral restitution (or recovery) in intralimb coordination parallels recovery of muscle synergies, and metrics that characterizes return of QoM such as precision, speed and smoothness [2,4]. Importantly, the window of behavioral restitution of 5 to 8 weeks defining 'recoverers' and 'non-recoverers', is not unique for the most affected upper limb but also found for recovery of the lower limb [14,15] and other neurological impairments, such as visuospatial neglect [16,17], aphasia [18,19] and somatosensory deficits [20]. These findings suggest that behavioral and cognitive restitution is mainly driven by the same, underlying processes of intrinsic, spontaneous neurobiological recovery [9,21,22]. The next challenge is to investigate the causal factors that drive these intrinsic processes of recovery [8] as well as variables that may interact with these processes [22,23] such as tasks-specific practice [24], neuromodulation therapies [25] and other innovative technologies like upper limb robotics (UL-RT) [26].

Currently, there are more than 38 different types of UL-RTs that have flooded the market in recent 2 decades, allowing that more subjects are able to increase the number of repetitions and thus intensity of practice [26,27]. Importantly, UL-RTs do not get tired, are more precise in their guidance during movement and able to make exercises more attractive by offering simultaneously features such as serious gaming, in contrast to physical (PT) and occupational therapists (OT). Our main question we addressed in our recently published comprehensive systematic review and meta-analysis (i.e., research synthesis) [26] was: *What is the current evidence that these expensive devices work?* [26] Subsequently, we did investigate how patient, trial, robot and other intervention variables are associated with found effect sizes (ESs). On request of the editorial board of Journal of Experimental Neurology, in this article we will briefly present the main findings of our research synthesis and elaborate on more fundamental questions that need to be addressed for designing the next generation of commercial UL-RTs as well as futures trials after stroke.

Materials and Methods

Search strategy

Randomized controlled trials (RCTs) comparing UL-RTs with any other intervention on patients with UL limitations post-stroke were identified in electronic searches from PubMed, Wiley/Cochrane Libraries, Embase, Cumulative Index of Nursing and Allied Health Literature (CINAHL), Web of Science, SportDISCUS, Physiotherapy Evidence Database (PEDro), and Google Scholar from inception until August 1st, 2022. The full search strategy and further details about data selection and extraction are available in the published report of our research synthesis [26]. The cited report follows the PRISMA guidelines [28].

Methodological quality

We assessed the methodological quality of included trials using the PEDro scale [29]. The analysis was performed using published data only.

Quantitative analysis

The extracted data were pooled in a meta-analysis using Review Manager (RevMan) Version 5.4 (Copenhagen: The Nordic Cochrane Centre, Cochrane Collaboration, 2014). RevMan, version 5.4, using Hedges' g model for continuous outcomes, is a widely used tool for data management, analysis and reporting [30,31] provided by The Cochrane Collaboration, a renowned institution in high quality research syntheses. We applied sensitivity analyses to identify interference variables that may be significantly associated with the individual ESs found, in terms of UL-muscle synergies, muscle strength and/or capacity. We investigated the relationship of each candidate modifier with the individual ESs using meta-regression analyses. The significance of associations between continuous outcomes and individual ESs was investigated by calculating Pearson or Spearman rank correlation coefficients, depending on the distribution of the data. Associations with binary outcomes were investigated using Mann-Whitney U-tests for independent samples. Meta-regression analyses were performed using SPSS (IBM Corp. Released 2021. IBM SPSS Statistics for Windows, Version 28.0. Armonk, NY: IBM Corp). SPSS is a valuable and widely used tool in statistical analysis in various research fields [32]. A two-tailed p-value <0.05 was considered statistically significant.

Results

Search strategy

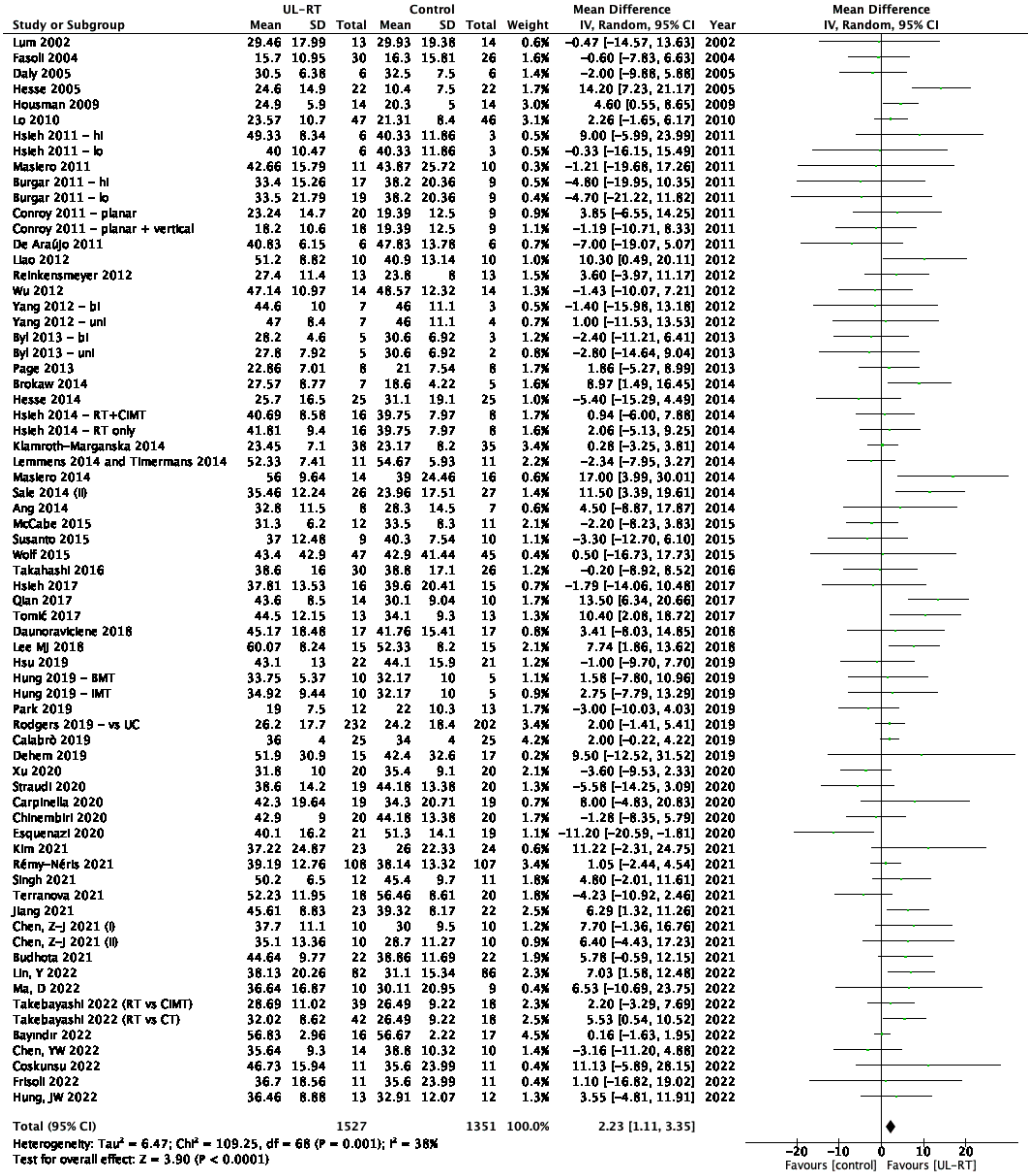
We included 90 RCTs involving 4,311 subjects out of a total of 1625 unique hits in the electronic search. The time gap from

stroke to randomization was less than 3 months in 23 studies, while 43 studies included patients in the late subacute phase post-stroke [33], i.e., after more than 3 months, and in 24 studies the post-stroke phase was not evaluated as a criterion. The duration of the intervention ranged from 2 weeks to 12 weeks (mean 5.81, SD=2.59 weeks), with a mean UL-RT therapy time of 53.55 (SD=33.9) minutes per session and 4.56 (SD 1.73) sessions per week [26]. The number of repetitions performed per session was reported in 23 of the included studies for the intervention groups and in 7 for the control groups. In the intervention groups, the mean number of repetitions per session was 805.89 (SD=656.54), with a range from 50 [34] to 3,600 [35], while in the control groups, the average number of repetitions was 357.84 (SD=385.6), ranging from 50 [34] to 976 [36].

The extracted outcome measures used in these trials were categorized according to the domains described in the ICF [37] to investigate the following constructs: upper limb motor functions, activity, participation and ADLs. Further details are available in the published report [26].

Risk of bias

The PEDro score was calculated for each study, and the median PEDro score was 6 [6-7]. The PEDro score was confirmed on the PEDro platform for 52.22% of the included studies (47/90), the other 43 studies were either not present on the platform (K=33) or had a different scoring (K=10). The methodological quality of the included studies based on the PEDro assessment tool ranged from 3 to 9.



Study or Subgroup	UL-RT Mean	UL-RT SD	UL-RT Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI	Year
Lum 2002	29.46	17.99	13	29.93	19.38	14	0.6%	−0.47 [−14.57, 13.63]	2002
Fasoli 2004	15.7	10.95	30	16.3	15.81	26	1.6%	−0.60 [−7.83, 6.63]	2004
Daly 2005	30.5	6.38	6	32.5	7.5	6	1.4%	−2.00 [−9.88, 5.88]	2005
Hesse 2005	24.6	14.9	22	10.4	7.5	22	1.7%	14.20 [7.23, 21.17]	2005
Housman 2009	24.9	5.9	14	20.3	5	14	3.0%	4.60 [0.55, 8.65]	2009
Lo 2010	23.57	10.7	47	21.31	8.4	46	3.1%	2.26 [−1.65, 6.17]	2010
Hsieh 2011 – hi	49.33	8.34	6	40.33	11.86	3	0.5%	9.00 [−5.99, 23.99]	2011
Hsieh 2011 – lo	40	10.47	6	40.33	11.86	3	0.5%	−0.33 [−16.15, 15.49]	2011
Maseiro 2011	42.66	15.79	11	43.87	25.72	10	0.3%	−1.21 [−19.68, 17.26]	2011
Burgar 2011 – hi	33.4	15.26	17	38.2	20.36	9	0.5%	−4.80 [−19.95, 10.35]	2011
Burgar 2011 – lo	33.5	21.79	19	38.2	20.36	9	0.4%	−4.70 [−21.22, 11.82]	2011
Conroy 2011 – planar	23.24	14.7	20	19.39	12.5	9	0.9%	3.85 [−6.55, 14.25]	2011
Conroy 2011 – planar + vertical	18.2	10.6	18	19.39	12.5	9	1.1%	−1.19 [−10.71, 8.33]	2011
De Araújo 2011	40.83	6.15	6	47.83	13.78	6	0.7%	−7.00 [−19.07, 5.07]	2011
Liao 2012	51.2	8.82	10	40.9	13.14	10	1.0%	10.30 [0.49, 20.11]	2012
Reinkensmeyer 2012	27.4	11.4	13	23.8	8	13	1.5%	3.60 [−3.97, 11.17]	2012
Wu 2012	47.14	10.97	14	48.57	12.32	14	1.3%	−1.43 [−10.07, 7.21]	2012
Yang 2012 – bi	44.6	10	7	46	11.1	3	0.5%	−1.40 [−15.98, 13.18]	2012
Yang 2012 – uni	47	8.4	7	46	11.1	4	0.7%	1.00 [−11.53, 13.53]	2012
Byl 2013 – bi	28.2	4.6	5	30.6	6.92	3	1.2%	−2.40 [−11.21, 6.41]	2013
Byl 2013 – uni	27.8	7.92	5	30.6	6.92	2	0.8%	−2.80 [−14.64, 9.04]	2013
Page 2013	22.86	7.01	8	21	7.54	8	1.7%	1.86 [−5.27, 8.99]	2013
Brokaw 2014	27.57	8.77	7	18.6	4.22	5	1.6%	8.97 [1.49, 16.45]	2014
Hesse 2014	25.7	16.5	25	31.1	19.1	25	1.0%	−5.40 [−15.29, 4.49]	2014
Hsieh 2014 – RT+CIMT	40.69	8.58	16	39.75	7.97	8	1.7%	0.94 [−6.00, 7.88]	2014
Hsieh 2014 – RT only	41.81	9.4	16	39.75	7.97	8	1.6%	2.06 [−5.13, 9.25]	2014
Klamroth–Marganska 2014	23.45	7.1	38	23.17	8.2	35	3.4%	0.28 [−3.25, 3.81]	2014
Lemmens 2014 and Timermans 2014	52.33	7.41	11	54.67	5.93	11	2.2%	−2.34 [−7.95, 3.27]	2014
Maseiro 2014	56	9.64	14	39	24.46	16	0.6%	17.00 [3.99, 30.01]	2014
Sale 2014 (II)	35.46	12.24	26	23.96	17.51	27	1.4%	11.50 [3.39, 19.61]	2014
Ang 2014	32.8	11.5	8	28.3	14.5	7	0.6%	4.50 [−8.87, 17.87]	2014
McCabe 2015	31.3	6.2	12	33.5	8.3	11	2.1%	−2.20 [−8.23, 3.83]	2015
Susanto 2015	37	12.48	9	40.3	7.54	10	1.1%	−3.30 [−12.70, 6.10]	2015
Wolf 2015	43.4	42.9	47	42.9	41.44	45	0.4%	0.50 [−16.73, 17.73]	2015
Takahashi 2016	38.6	16	30	38.8	17.1	26	1.2%	−0.20 [−8.92, 8.52]	2016
Hsieh 2017	37.81	13.53	16	39.6	20.41	15	0.7%	−1.79 [−14.06, 10.48]	2017
Qian 2017	43.6	8.5	14	30.1	9.04	10	1.7%	13.50 [6.34, 20.66]	2017
Tomić 2017	44.5	12.15	13	34.1	9.3	13	1.3%	10.40 [2.08, 18.72]	2017
Daunoraviciene 2018	45.17	18.48	17	41.76	15.41	17	0.8%	3.41 [−8.03, 14.85]	2018
Lee MJ 2018	60.07	8.24	15	52.33	8.2	15	2.1%	7.74 [1.86, 13.62]	2018
Hsu 2019	43.1	13	22	44.1	15.9	21	1.2%	−1.00 [−9.70, 7.70]	2019
Hung 2019 – BMT	33.75	5.37	10	32.17	10	5	1.1%	1.58 [−7.80, 10.96]	2019
Hung 2019 – IMT	34.92	9.44	10	32.17	10	5	0.9%	2.75 [−7.79, 13.29]	2019
Park 2019	19	7.5	12	22	10.3	13	1.7%	−3.00 [−10.03, 4.03]	2019
Rodgers 2019 – vs UC	26.2	17.7	232	24.2	18.4	202	3.4%	2.00 [−1.41, 5.41]	2019
Calabrò 2019	36	4	25	34	4	25	4.2%	2.00 [−0.22, 4.22]	2019
Dehem 2019	51.9	30.9	15	42.4	32.6	17	0.2%	9.50 [−12.52, 31.52]	2019
Xu 2020	31.8	10	20	35.4	9.1	20	2.1%	−3.60 [−9.53, 2.33]	2020
Straudi 2020	38.6	14.2	19	44.18	13.38	20	1.3%	−5.58 [−14.25, 3.09]	2020
Carpinella 2020	42.3	19.64	19	34.3	20.71	19	0.7%	8.00 [−4.83, 20.83]	2020
Chinembiri 2020	42.9	9	20	44.18	13.38	20	1.7%	−1.28 [−8.35, 5.79]	2020
Esquenazi 2020	40.1	16.2	21	51.3	14.1	19	1.1%	−11.20 [−20.59, −1.81]	2020
Kim 2021	37.22	24.87	23	26	22.33	24	0.6%	11.22 [−2.31, 24.75]	2021
Rémy–Néris 2021	39.19	12.76	108	38.14	13.32	107	3.4%	1.05 [−2.44, 4.54]	2021
Singh 2021	50.2	6.5	12	45.4	9.7	11	1.8%	4.80 [−2.01, 11.61]	2021
Terranova 2021	52.23	11.95	18	56.46	8.61	20	1.8%	−4.23 [−10.92, 2.46]	2021
Jiang 2021	45.61	8.83	23	39.32	8.17	22	2.5%	6.29 [1.32, 11.26]	2021
Chen, Z–J 2021 (I)	37.7	11.1	10	30	9.5	10	1.2%	7.70 [−1.36, 16.76]	2021
Chen, Z–J 2021 (II)	35.1	13.36	10	28.7	11.27	10	0.9%	6.40 [−4.43, 17.23]	2021
Budhota 2021	44.64	9.77	22	38.86	11.69	22	1.9%	5.78 [−0.59, 12.15]	2021
Lin, Y 2022	38.13	20.26	82	31.1	15.34	86	2.3%	7.03 [1.58, 12.48]	2022
Ma, D 2022	36.64	16.87	10	30.11	20.95	9	0.4%	6.53 [−10.69, 23.75]	2022
Takebayashi 2022 (RT vs CIMT)	28.69	11.02	39	26.49	9.22	18	2.3%	2.20 [−3.29, 7.69]	2022
Takebayashi 2022 (RT vs CT)	32.02	8.62	42	26.49	9.22	18	2.5%	5.53 [0.54, 10.52]	2022
Bayindir 2022	56.83	2.96	16	56.67	2.22	17	4.5%	0.16 [−1.63, 1.95]	2022
Chen, YW 2022	35.64	9.3	14	38.8	10.32	10	1.4%	−3.16 [−11.20, 4.88]	2022
Coskunsu 2022	46.73	15.94	11	35.6	23.99	11	0.4%	11.13 [−5.89, 28.15]	2022
Frisoli 2022	36.7	18.56	11	35.6	23.99	11	0.4%	1.10 [−16.82, 19.02]	2022
Hung, JW 2022	36.46	8.88	13	32.91	12.07	12	1.3%	3.55 [−4.81, 11.91]	2022
Total (95% CI)			1527			1351	100.0%	2.23 [1.11, 3.35]	

Heterogeneity: Tau² = 6.47; Chi² = 109.25, df = 68 (P = 0.001); I² = 38%
Test for overall effect: Z = 3.90 (P < 0.0001)

Figure 1a. Overall effects on outcome of UL-RT on FM-UE scores.

Study or Subgroup	RT-UL Mean	RT-UL SD	RT-UL Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Daly 2005	−1,648	314.4	6	−1,593	496.7	6	1.1%	−0.12 [−1.26, 1.01]	2005
Rabadi 2008	62.21	4.9	10	65.44	5.41	10	1.6%	−0.60 [−1.50, 0.30]	2008
Volpe 2008	65	6.63	11	62.9	5.08	10	1.7%	0.34 [−0.52, 1.20]	2008
Lo 2010	−62.44	37.7	47	−69.21	30.04	46	3.3%	0.20 [−0.21, 0.60]	2010
Conroy 2011 – planar + vertical	−84.25	35.7	18	−81.09	33.3	10	1.9%	−0.09 [−0.86, 0.69]	2011
Masiero 2011	24.83	10.38	11	17.8	11.49	10	1.6%	0.62 [−0.26, 1.50]	2011
Burgar 2011 – hi	1.9	1.74	17	2.3	2.12	9	1.8%	−0.21 [−1.02, 0.60]	2011
Burgar 2011 – lo	2.3	1.94	19	2.3	2.12	9	1.9%	0.00 [−0.79, 0.79]	2011
Conroy 2011 – planar	−67.12	40.2	20	−81.09	33.3	9	1.9%	0.35 [−0.44, 1.15]	2011
Hwang 2012	−76	87	9	−98.5	159.6	6	1.3%	0.18 [−0.86, 1.21]	2012
Reinkensmeyer 2012	2	4.1	13	0.6	1.1	13	1.9%	0.45 [−0.33, 1.23]	2012
Wu 2013 – uni	3.3	0.82	18	3.51	0.79	9	1.8%	−0.25 [−1.05, 0.55]	2013
Yoo 2013	−43.4	15.9	11	−33.3	6.3	11	1.6%	−0.80 [−1.68, 0.07]	2013
Wu 2013 – bi	3.06	0.63	18	3.51	0.79	8	1.7%	−0.64 [−1.49, 0.21]	2013
Hsieh 2014 – RT+CIMT	2.58	0.49	16	2.93	0.76	8	1.7%	−0.57 [−1.44, 0.29]	2014
Hsieh 2014 – RT only	2.98	0.76	16	2.93	0.76	8	1.7%	0.06 [−0.79, 0.91]	2014
Masiero 2014	24.3	6.67	14	15.3	11.85	16	2.0%	0.89 [0.14, 1.65]	2014
Sale 2014 (I)	9.09	13.5	9	9.11	12.02	11	1.6%	−0.00 [−0.88, 0.88]	2014
Brokaw 2014	26.71	12.6	7	19	3.32	5	1.1%	0.71 [−0.49, 1.91]	2014
Hesse 2014	14.1	15.5	24	20.3	15.4	25	2.6%	−0.39 [−0.96, 0.17]	2014
Klamroth-Marganska 2014	−60.5	23	38	−59.44	29	35	3.1%	−0.04 [−0.50, 0.42]	2014
Lemmens 2014 and Timermans 2014	34	11.86	11	43	14.08	11	1.7%	−0.67 [−1.53, 0.20]	2014
Wolf 2015	39.5	37.8	47	39.9	36.19	45	3.3%	−0.01 [−0.42, 0.40]	2015
McCabe 2015	−1,463	573	12	−1,417	637	11	1.8%	−0.07 [−0.89, 0.75]	2015
Susanto 2015	31.33	8.01	9	28.5	5.95	10	1.6%	0.39 [−0.52, 1.30]	2015
Takahashi 2016	−52.7	36.9	30	−47.4	38.4	26	2.8%	−0.14 [−0.66, 0.39]	2016
Hsieh 2017	12.69	13.57	16	20.87	21.49	15	2.1%	−0.45 [−1.16, 0.27]	2017
Qian 2017	29.2	11.95	14	24.2	11.18	10	1.8%	0.41 [−0.41, 1.24]	2017
Tomić 2017	−58.3	14.53	13	−49.1	15.42	13	1.9%	−0.59 [−1.38, 0.19]	2017
Vanoglio 2017	0.17	0.16	14	0.04	0.07	13	1.8%	1.01 [0.20, 1.82]	2017
Dehem 2019	−32.6	30.1	15	−24.9	33.1	17	2.1%	−0.24 [−0.93, 0.46]	2019
Park 2019	−19.3	11.1	12	−24.4	12.9	13	1.9%	0.41 [−0.39, 1.20]	2019
Rodgers 2019 – vs UC	15.5	19.1	232	14.2	19.6	203	4.2%	0.07 [−0.12, 0.26]	2019
Calabrò 2019	46	5	25	55	6	25	2.3%	−1.60 [−2.25, −0.96]	2019
Xu 2020	38.4	10	20	42.3	8.4	20	2.4%	−0.41 [−1.04, 0.21]	2020
Straudi 2020	−43.1	21.5	19	−25.3	16.1	20	2.3%	−0.92 [−1.59, −0.26]	2020
Kim 2021	17.17	19.08	23	6.96	10.54	24	2.5%	0.66 [0.07, 1.24]	2021
Rémy-Néris 2021	26.5	19.03	107	23.85	19.1	108	3.9%	0.14 [−0.13, 0.41]	2021
Ambrosini 2021	25.1	20.3	32	19.3	20.3	32	2.9%	0.28 [−0.21, 0.77]	2021
Budhota 2021	31.91	17.73	22	23.77	18.31	22	2.5%	0.44 [−0.16, 1.04]	2021
Chen, Z-J 2021 (II)	26.4	14.66	10	20.6	11.8	10	1.6%	0.42 [−0.47, 1.31]	2021
Terranova 2021	202.78	291.54	18	77.54	155.21	20	2.3%	0.53 [−0.12, 1.18]	2021
Ma, D 2022	33.6	16.4	10	30.22	20.02	9	1.6%	0.18 [−0.73, 1.08]	2022
Taravati 2022	22.44	12.78	17	19.89	13.27	20	2.3%	0.19 [−0.46, 0.84]	2022
Abd El-Kafy 2022	58.06	4.12	18	52.11	3.45	18	2.0%	1.53 [0.78, 2.28]	2022
Bayindir 2022	37.5	19.63	16	35	11.1	17	2.2%	0.15 [−0.53, 0.84]	2022
Chen, YW 2022	12.52	5.92	14	11.05	6.03	10	1.8%	0.24 [−0.58, 1.05]	2022
Coskunsu 2022	36	21	11	32.67	17.99	9	1.6%	0.16 [−0.72, 1.04]	2022
Total (95% CI)			1139			1025	100.0%	0.04 [−0.10, 0.18]	

Heterogeneity: Tau² = 0.11; Chi² = 100.72, df = 47 (P < 0.00001); I² = 53%
Test for overall effect: Z = 0.55 (P = 0.58)

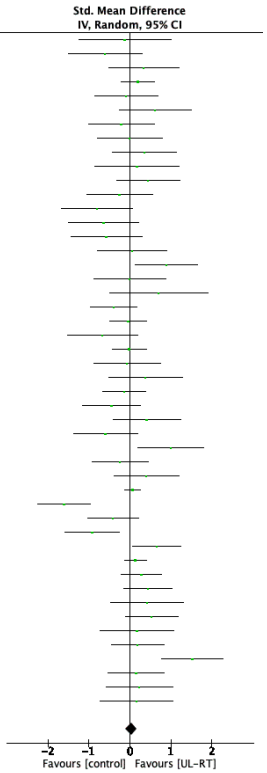


Figure 1b. Effects of UL-RTs on outcome of UL-capacity.

Study or Subgroup	UL-RT Mean	UL-RT SD	UL-RT Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Fasoli 2004	6.8	3.29	30	4.9	4.59	26	3.6%	0.47 [−0.06, 1.01]	2004
Hesse 2005	21.8	10.5	21	6.8	8.3	22	3.2%	1.56 [0.87, 2.25]	2005
Lum 2006 – uni	48.8	4.8	9	48.3	4.8	2	1.4%	0.10 [−1.44, 1.63]	2006
Lum 2006 – bi	44	8.1	5	48.3	4.8	2	1.3%	−0.48 [−2.16, 1.20]	2006
Lum 2006 – co	38.6	5.1	10	48.3	4.8	2	1.2%	−1.77 [−3.51, −0.02]	2006
Volpe 2008	35.45	13.6	11	33.7	8.54	10	2.7%	0.15 [−0.71, 1.00]	2008
Rabadi 2008	18.93	11.76	10	15.74	12.74	10	2.7%	0.25 [−0.63, 1.13]	2008
Housman 2009	9	5.08	15	5	3.78	16	3.0%	0.87 [0.13, 1.62]	2009
Burgar 2011 – lo	41.6	20.92	19	40.3	17.82	9	2.9%	0.06 [−0.73, 0.86]	2011
Hsieh 2011 – hi	3.81	0.55	6	3.33	0.69	3	1.5%	0.72 [−0.74, 2.17]	2011
Hsieh 2011 – lo	3.25	0.5	6	3.33	0.69	3	1.6%	−0.13 [−1.51, 1.26]	2011
Burgar 2011 – hi	37.5	17.32	17	40.3	17.82	9	2.8%	−0.16 [−0.96, 0.65]	2011
Hwang 2012	16.2	10.1	9	13.5	8.2	8	2.5%	0.28 [−0.68, 1.23]	2012
Yang 2012 – bi	3.7	0.6	7	3.7	0.9	3	1.7%	0.00 [−1.35, 1.35]	2012
Yang 2012 – uni	3.6	0.6	7	3.7	0.9	4	1.9%	−0.13 [−1.36, 1.10]	2012
Reinkensmeyer 2012	3.9	3.2	13	4.1	4.4	13	3.0%	−0.05 [−0.82, 0.72]	2012
Yoo 2013	8.5	5.8	11	5.1	2.3	11	2.7%	0.74 [−0.13, 1.61]	2013
Byl 2013 – bi	143	43.8	5	104.3	47.06	3	1.4%	0.75 [−0.77, 2.27]	2013
Byl 2013 – uni	148.1	53.32	5	104.3	47.06	2	1.2%	0.71 [−1.03, 2.44]	2013
Sale 2014 (II)	57.77	24.22	26	39.56	35.1	27	3.6%	0.59 [0.04, 1.14]	2014
Sale 2014 (I)	55.64	30.33	11	75.63	17.52	9	2.6%	−0.75 [−1.67, 0.17]	2014
Hesse 2014	15.8	11.1	25	17	12	25	3.6%	−0.10 [−0.66, 0.45]	2014
Klamroth-Marganska 2014	11.36	8	38	13.56	7.6	35	3.8%	−0.28 [−0.74, 0.18]	2014
Taveggia 2016	54.7	22.2	27	50.6	16.4	27	3.6%	0.21 [−0.33, 0.74]	2016
Lee KW 2016 and 2017	16.48	1.89	25	16.4	1.59	25	3.6%	0.05 [−0.51, 0.60]	2016
Takahashi 2016	62.23	17.08	30	62.88	19.78	26	3.7%	−0.03 [−0.56, 0.49]	2016
Hsieh 2017	8.73	4.93	16	6.99	5.86	15	3.1%	0.31 [−0.40, 1.02]	2017
Vanoglio 2017	60.4	25.7	14	33.2	27.5	13	2.9%	0.99 [0.18, 1.80]	2017
Villafañe 2018	55	19.6	16	51.1	36.6	16	3.2%	0.13 [−0.56, 0.82]	2018
Hung 2019 – BMT	4.05	0.93	10	2.64	0.93	5	1.9%	1.43 [0.20, 2.65]	2019
Hung 2019 – IMT	2.65	1.07	10	2.64	0.93	5	2.2%	0.01 [−1.06, 1.08]	2019
Serrezuela 2020	3.65	0.74	8	2.25	0.46	8	1.8%	2.15 [0.85, 3.45]	2020
Ambrosini 2021	61.3	15.5	32	58.3	18	32	3.8%	0.18 [−0.31, 0.67]	2021
Jiang 2021	65.22	9.31	23	58.95	9.33	22	3.4%	0.66 [0.06, 1.26]	2021
Kim 2021	61.52	29.59	23	38.92	31.88	24	3.5%	0.72 [0.13, 1.31]	2021
Abd El-Kafy 2022	39.29	1.16	18	33.78	1.16	18	1.8%	4.64 [3.33, 5.96]	2022
Bayindir 2022	17.33	9.63	16	14	7.41	17	3.2%	0.38 [−0.31, 1.07]	2022
Coskunsu 2022	27.21	28.23	11	20.47	7	9	2.6%	0.30 [−0.59, 1.19]	2022
Total (95% CI)			595			516	100.0%	0.39 [0.16, 0.61]	

Heterogeneity: Tau² = 0.28; Chi² = 103.75, df = 37 (P < 0.00001); I² = 64%
Test for overall effect: Z = 3.42 (P = 0.0006)

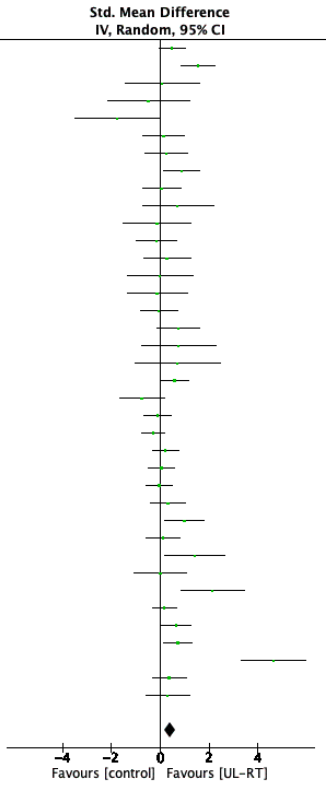


Figure 1c. Effects of UL-RTs on outcome of UL-muscle power.

Quantitative analysis

Eighty-six (N=4,240) out of the 90 included RCTs were found suitable for quantitative analysis. Pooling of data for subgroup or sensitivity analyses was not possible when only one study per subgroup was available. Four trials were excluded from pooling due to a lack of point measures and/or estimates of variability [34,38-40].

Figures 1a-c show the forest plots for muscle synergies (measured with Fugl-Meyer Assessment of the Upper Limb – FM-UL), UL-capacity, and muscle power respectively. The relevant results of the overall analyses are available in the published report [26].

A significant homogeneous Effect-Size summary ($ES_{summary}$) was found for muscle synergies, reflecting an average between-group difference of 2.23 [1.11–3.35] out of 66 points on the FM-UL Similarly, non-homogeneous statistically significant SMDs were found for UL muscle power, with an SMD of 0.39 [0.16–0.61] and for basic ADLs with an SMD of 0.28 [0.10–0.45]. A homogeneous statistically significant SMD of 0.11 [0.00–0.21] was found for performance measures. A non-significant heterogeneous $ES_{summary}$ was found for UL-capacity (SMD 0.04 [-0.10-0.18]). We found no evidence for publication bias and obtained symmetric funnel plots between trial ESs and Standard Error.

We found a positive, significant correlation coefficient between the baseline SD value of FM-UL of each trial that reported these data and the ES for FM-UL (Pearson's r=0.276; p=0.024) and for UL-capacity (Spearman's r=0.339; p=0.03). Higher $ES_{summary}$ values for muscle synergies significantly correlated with PEDro scores (Spearman's r=0·26; p=0·031) and time spent training in each session (Spearman's r=-0·251; p=0·04). Trials that used exoskeletons showed a significant correlation with higher $ES_{summary}$ for UL-capacity (Mann-Whitney U-test; z=2·89; p=0·004) and muscle power (Mann-Whitney U-test z=2·24; p=0·025). Higher $ES_{summary}$ values for muscle power also significantly correlated with restriction of trunk compensations during UL-RT training (Mann-Whitney U-test z=-2·36; p=0·017). However, meta-regression showed no significant association between on the one hand, muscle synergies (i.e., FM-UL scores), muscle strength, and UL-capacity and, on the other hand, trials' ESs with respect to: publication year; total number of subjects included in the trial; methodological quality of the trial; proximal (shoulder–elbow) and/or distal (wrist–hand) UL-RT focus of intervention; degrees of freedom that are controlled by the UL-RT; gravity support (yes/no); simultaneous virtual gaming during UL-RT (yes/no); dosing of therapy in terms of total duration of the intervention and number of repetitions; and competing interests declared by the authors.

Discussion

Upper limb rehabilitation encompasses task-specific training in an intensive way after stroke [23]. Commercial UL-RTs, serving both pillars may serve as an effective therapy to achieve clinically meaningful improvements post stroke. However, in the present research synthesis [26], we found small, but significant mean difference of about 3.4% on FM-UE scores *without* clinically meaningful effects at level of UL-capacity. Our meta-regression confirms that selected subjects with some potential of UL-recovery may benefit most from therapy such as UL-RT, especially when applied in the first 3 months after stroke onset [1,2]. The robustness and consistency of our findings challenges the selling of commercial UL-RTs for the clinical field and rather indicate that a better mechanistic understanding about assumed underlying interaction effects between motor recovery and motor learning is needed. Importantly, our results show almost the same between group difference of 2.27 points for FM-UE and no differences for outcome UL-capacity in the only phase IV, RATULS trial involving 770 subjects poststroke [41]. Also, the same significant, homogeneous mean difference (MD) of about 2.15 points (CI95%: 0.73 -3.57) on outcome of FM-UE scores (~3.2%) without significant effects on UL-capacity after stroke (i.e., 0.04; 95%CI: -0.12, 0.19) [27], were found after pooling 38 trials (N=1206) in 2017 as well as after pooling 10 small-sampled phase II trials (N=218) in 2008 [42]. Obviously, despite the fast-growing technology with respect to software and hardware for manufacturing UL-RTs, the overall effect-size remained the same following FM-UE without effects on UL-capacity [26]. Considering the robustness and consistency of neutral effects, we did recommend in our manuscript to *stop* with swamping health care services with new commercially available UL-RT devices. Instead, we propose the UL-RT-industry to go back to the drawing table and develop a better theoretical framework for designing the next generation of UL-RT devices post stroke. In contrast to pharmacodynamics, the fundamental step in making assumptions about *what* and *how* stroke subjects learn to improve their quality of movement when performing upper limb multi-joint tasks after stroke, seems to be skipped in this research pipeline when designing UL-RTs.

Cost-effectiveness

Despite the lack of evidence and proper theoretical framework that targets the dynamic interaction between motor control and motor learning during stroke recovery, a commonly raised argument is that UL-RTs may serve as a cost-effective alternative replacement for usual care offered by a physical and/or occupational therapist [43,44]. However, the cost-effectiveness is not supported in the literature. Analysis of Health Technology Assessment in the only phase IV RATULS trial showed that using the MIT-manus robot is accompanied with higher costs when compared to usual care given by therapists [45,46]. In a previous Cochrane review, Mehrholz and colleagues suggested that electromechanical and robot-assisted training could create additional costs of rehabilitation after stroke [47]. The complete analysis of the costs would consider the initial investments, operational costs, and disposal costs. The initial investment includes the cost of the

device and its installation and may vary a lot depending on the complexity of the device (e.g., 50K - 60K € circa for end-effectors such as the MIT-manus [45], to 150k €+ for complex exoskeletons). Operational costs include maintenance and repair, training and specialized staffing, software updates and licensing. Unfortunately, no data are currently available for operational costs, whereas disposal costs have not been quantified to date. Despite the lack of these data that would increase the cost/effect ratio, the amount of quality evidence produced over the years shows the lack of cost-effectiveness for commercial UL-RTs.

What is needed?

In our opinion, to understand the dynamics of motor *recovery* early post stroke, it is important to acknowledge the non-linear time course of intrinsic, spontaneous neurobiological recovery and the need to delineate between behavioral restitution at level of body function and compensation [23,48]. As suggested, the time course of behavioral restitution of impairments is non-linear and plateauing within 5 to 8 weeks post stroke, suggesting that selection of subjects at baseline and timing to achieve recovery is paramount in designing trials [1,2].

Second, fine-grained, serial biomechanical measures of movement quality in skill acquisition indicate that therapy-induced improvements are mainly caused by an *adaptive* control in which the same multi-joint movement, is controlled in a different way with to a less efficient performance when compared to the movement quality seen in healthy age and gender-matched subjects [2,21,49]. As already shown by Bernstein in the sixties, to achieve optimization in performance, subjects need variability in practice in its own preferred context allowing to use different task parameters such as speed distance and difficulty to achieve long-term retention [50]. Importantly, 'normal movement' seen before stroke, or when compared to age- and gender-matched healthy subjects may *not* serve as an adequate reference to understand the adaptive ways how stroke subjects control their multi-joint movement when performing a meaningful task after stroke. In addition, just increasing the intensity of practice by performing more repetitions of the *same* movement without variation, does not lead to motor learning and, with that, a better quality of movement [26,51].

Third, longitudinal biomechanical studies are needed in which behavioral restitution is distinguished from compensation allowing to understand *what* patients learn by an intervention when they improve in their upper limb capacity and QoM after stroke [2]. However, after reviewing 32 longitudinal studies reporting 46 different kinematic metrics none of these studies did explicitly addressed the distinction between behavioral restitution and compensation [2]. Recently, we achieved consensus in the International Stroke Recovery and Rehabilitation Alliance (ISRRA) how to measure QoM post stroke in terms of behavioral restitution and compensation based on using high-fidelity systems to capture movement, by defining four 'performance assays', in which behavioral compensation is prevented and healthy age- and gender-matched controls are used as a comparator [3].

Fourth, none of the designers of commercial UL-RTs did publish a peer reviewed paper describing how to measure changes in QoM, but rather choose a common motor impairment scale, such as FM-UE scores. FM-UE reflecting muscle synergies and with that, strongly associated with the DoF that patients can control for are mainly defined at the level of body function. However, improvements in FM-UE scores are also flawed by the 8% improvements in muscle strength, as seen in our research synthesis and UL-RT [26] and not reflecting a pure assessment of ability of dissociation post stroke. Therefore, FM-UE scores that plateaus within 8 weeks might be not the ideal primary measurement of outcome for capturing adaptive motor learning in UL-RT trials. It is more straightforward to measure the impact on compensation strategies to improve UL-capacity and search for possible interaction effects of motor learning with QoM [23,52].

Fifth, none of the designers made hypotheses about how the UL-RT targets the interaction between motor control and motor learning during stroke recovery and with that, none of designers of commercial UL-RTs made assumptions about how the device can align with the preferred compensatory movement of the subject when performing a meaningful task. Based on principles of practice makes perfect in neurorehabilitation and increasing intensity of practice by repetition without repetition, there is a fundamental need for insight in the neurobiological assumptions of manufactured UL-RTs. At least these assumptions should address how the UL-RT interface interact between motor control and motor learning and deals with the redundancy (or abundancy) in the number of DoF in multi-joint movements like reaching in a patient-specific, natural way [26,53-55].

Sixth, most UL-RTs using haptic, force, electromyographical, proprioceptive, visual and/or auditory ways of feedback for movement correction. However, the chosen feedback, i.e., the form of perception provided, determines different forms of 'resistance' to the preferred movement that the patient would perform in a goal-directed multi-joint movement, i.e., the 'action'. Whether these different modalities of action-perception mismatch have different effects on adaptive 'motor learning' is unclear. The control by the end-user should be continuous, shared when optimizing a preferred adaptive movement and assisted only if needed. Several mathematical models have been created to try to describe how the central nervous system (CNS) deals with the behavioral dynamics, such as the minimum-jerk model [56], the threshold-position control model [50] or the minimum torque-change model [57]. However, all these theoretical models are insufficiently considered for their pros and cons in perspective motor control and motor learning when improving in QoM after stroke.

In sum, the current knowledge gap that links the non-linear relationship between body (UL) and machine (RT) in a real-world environment during stroke recovery, is still a 'black box', that raises questions such as "*Who is in charge and who is adapting when performing a multi-joint goal-directed movement such as reaching?" "Is it the UL-robot to the subject or the subject with the impaired arm to the robot?"* These fundamental dilemmas need to be addressed before making assumptions about interfacing robot and machine. Subjects with compromised control in their degrees of freedom after stroke, need to be able to explore their multi-joint task by themselves within their own symptom-specific constraints, and not just follow the haptic corrected guidance. Therefore, questions about 'who is in charge in goal-directed multi-joint movements, need to be addressed first in designing new UL-RTs.

In this 'two-learners problem' [58,59] in which on both sides, the subject and the robot, need to co-adapt in their performance making the movement in the most effective and efficient way [59,59], greater authority should be given to the user of the device than the programmed control of the device self. Recently, Kang and colleagues suggested that Artificial intelligence (AI) or deep learning techniques may be a better way to optimize the real time interaction between body and device in a patient preferred, task-specific way [60].

What is next? – directions for future research

As emphasized in our research synthesis [26], it is significant to note, that the aim of UL-RTs designed to support adaptive motor learning, should not be confused with robot-devices that are able to '*replace*' or '*take over*' parts of the affected limb, such as a bionic limbs or devices designed to bypass the CST using Brain-Computer Interfaces (BCI) or Brain-Machine Interfaces (BMI) [61]. At the same moment, we need to acknowledge that advances in technology constantly stay ahead of the research (which takes years to conduct and refine). Being optimistic about UL-RTs and certainly not closing the door as emphasized in the discussion of our review [26], there are several basic steps needed to follow first in this field.

First, in line with the vision of the International Stroke Recovery and Rehabilitation Alliance (ISRRA), there is an urgent need to give a set of definitions and recommendations about, respectively the used taxonomy and underlying assumptions of the UL-RT. Even a consensus-based definition of UL-RT is lacking. In line with other interventions and outcomes, the International Classification of Functioning and Disability model (ICF) may start as a framework and the taxonomy should be aligned with those of movement, neuro- and rehabilitation sciences.

Second, to improve the efficiency in this translational and transdisciplinary research pipeline in designing UL-RT, we suggest improving the transparency of the theoretical rationale and fundamental assumptions of newly designed UL-RTs [26]. At least, the neurobiological and technical assumptions about the working of UL-RT how motor control and motor learning may interact with dynamics of motor recovery, should be clear, which is not different from knowledge about pharmacodynamics of a medication and testing before prescribing commercial available pills [26].

Third, to improve the trial methodology including stratification of underpowered UL-RT studies acknowledging the problem of heterogeneity of spontaneous motor recovery and need for selecting patients with some potential for recovery. The positive association between baseline FM-UE score and RT-induced improvement in UL-capacity is in line with prognostic research showing that about 20% to 30% of subjects with FM-UE scores of 18 points or lower fail to show spontaneous neurobiological recovery at all [8,52].

Fourth, there is a need for longitudinal studies investigating *how* UL-RTs may influence adaptive learning by measuring QoM during stroke recovery, rather than the question if we can change FM-UE scores at impairment level [62]. Preferably, these aims should be in line with the recommendations on how to monitor behavioral restitution and compensation post stroke [3,63].

Fifth, longitudinal studies have shown that about 60% of these improvements are defined by recovery of the hand and less by the transport of the hand (i.e., arm and trunk) [2,64]. However, proof-of-concept trials investigating the effects of hand-robots on improving dexterity are still in their infancy.

Finally, fundamental research is needed about the parallelism between spontaneous motor recovery and 'motor learning' and address questions how neural restitution and substitution are longitudinally associated with behavioural restitution and compensation post stroke [65,66]. This delineation is not imperative for improving UL-RT trials but also for allowing proper interpretation of neuroimaging studies to investigate how UL-RT-induced brain plasticity, may contribute to stroke recovery [3].

Limitations

The current research synthesis has some limitations. First, our effort is compromised by the lack of an appropriate comparator in current trials. The heterogeneity of the control interventions across different trials can make pooling of data in one meta-analysis questionable and reduce the reliability of the results [67,68]. Therefore, further classification of 'usual' or 'control care' as a comparator is required at this point. Second, the present findings focus on UL-RTs designed as a training device in support of rehabilitation services. This restriction does not mean that other robot types are ineffective from the perspective of regaining UL-capacity. Depending on the definition that is used, UL robots could be perfectly able to 'take over' pre-programmed activities of the paretic limb. Finally, the conclusions in the present meta-analyses are

based at group level of RCTs and not at an individual level in which the numbers and characteristics of responders and non-responders of clinical meaning full effects on UL-muscle synergies and UL-capacity can be identified.

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References

1. Langhorne P, Bernhardt J, Kwakkel G. Stroke rehabilitation. Lancet. 2011 May 14;377(9778):1693-702.
2. Saes M, Mohamed Refai MI, van Beijnum BJF, Bussmann JBJ, Jansma EP, Veltink PH, et al. Quantifying Quality of Reaching Movements Longitudinally Post-Stroke: A Systematic Review. Neurorehabil Neural Repair. 2022 Mar;36(3):183-207.
3. Kwakkel G, Van Wegen E, Burridge JH, Winstein CJ, van Dokkum L, Alt Murphy M, et al. Standardized measurement of quality of upper limb movement after stroke: Consensus-based core recommendations from the Second Stroke Recovery and Rehabilitation Roundtable. Int J Stroke. 2019 Oct;14(8):783-791.
4. Saes M, Mohamed Refai MI, van Kordelaar J, Scheltinga BL, van Beijnum BF, Bussmann JBJ, et al. Smoothness metric during reach-to-grasp after stroke: part 2. longitudinal association with motor impairment. J Neuroeng Rehabil. 2021 Sep 24;18(1):144.
5. Ekstrand E, Rylander L, Lexell J, Brogårdh C. Perceived ability to perform daily hand activities after stroke and associated factors: a cross-sectional study. BMC Neurol. 2016 Nov 2;16(1):208.
6. Meyer S, Karttunen AH, Thijs V, Feys H, Verheyden G. How do somatosensory deficits in the arm and hand relate to upper limb impairment, activity, and participation problems after stroke? A systematic review. Phys Ther. 2014 Sep;94(9):1220-31.
7. Lieshout ECCV, van de Port IG, Dijkhuizen RM, Visser-Meily JMA. Does upper limb strength play a prominent role in health-related quality of life in stroke patients discharged from inpatient rehabilitation? Top Stroke Rehabil. 2020 Oct;27(7):525-33.
8. van der Vliet R, Selles RW, Andrinopoulou ER, Nijland R, Ribbers GM, Frens MA, et al. Predicting Upper Limb Motor Impairment Recovery after Stroke: A Mixture Model. Ann Neurol. 2020 Mar;87(3):383-93.
9. Goldsmith J, Kitago T, Garcia de la Garza A, Kundert R, Luft A, Stinear C, et al. Arguments for the biological and predictive relevance of the proportional recovery rule. Elife. 2022 Oct 18;11:e80458.
10. van Kordelaar J, van Wegen EE, Nijland RH, Daffertshofer A, Kwakkel G. Understanding adaptive motor control of the paretic upper limb early poststroke: the EXPLICIT-stroke program. Neurorehabil Neural Repair. 2013 Nov-Dec;27(9):854-63.
11. Saes M, Zandvliet SB, Andringa AS, Daffertshofer A, Twisk JWR, Meskers CGM, et al. Is Resting-State EEG Longitudinally Associated With Recovery of Clinical Neurological Impairments Early Poststroke? A Prospective Cohort Study. Neurorehabil Neural Repair. 2020 May;34(5):389-402.
12. Kwakkel G, Winters C, van Wegen EE, Nijland RH, van Kuijk AA, Visser-Meily A, et al. Effects of Unilateral Upper Limb Training in Two Distinct Prognostic Groups Early After Stroke: The EXPLICIT-Stroke Randomized Clinical Trial. Neurorehabil Neural Repair. 2016 Oct;30(9):804-16.
13. Lo AC, Guarino PD, Richards LG, Haselkorn JK, Wittenberg GF, Federman DG, et al. Robot-assisted therapy for long-term upper-limb impairment after stroke. N Engl J Med. 2010 May 13;362(19):1772-83.
14. Buurke JH, Nene AV, Kwakkel G, Erren-Wolters V, Ijzerman MJ, Hermens HJ. Recovery of gait after stroke: what changes? Neurorehabil Neural Repair. 2008 Nov-Dec;22(6):676-83.
15. Schröder J, Saeys W, Embrechts E, Hallemans A, Yperzeele L, Truijen S, et al. Recovery of Quiet Standing Balance and Lower Limb Motor Impairment Early Poststroke: How Are They Related? Neurorehabil Neural Repair. 2023 Aug;37(8):530-44.
16. Nijboer TC, Kollen BJ, Kwakkel G. Time course of visuospatial neglect early after stroke: a longitudinal cohort study. Cortex. 2013 Sep;49(8):2021-7.
17. Overman MJ, Binns E, Milosevich ET, Demeyere N. Recovery of Visuospatial Neglect With Standard Treatment: A Systematic Review and Meta-Analysis. Stroke. 2024 Sep;55(9):2325-39.
18. Lazar RM, Minzer B, Antoniello D, Festa JR, Krakauer JW, Marshall RS. Improvement in aphasia scores after stroke is well predicted by initial severity. Stroke. 2010 Jul;41(7):1485-8.
19. Brady MC, Ali M, VandenBerg K, Williams LJ, Williams LR, Abo M, et al. Precision rehabilitation for aphasia by patient age, sex, aphasia severity, and time since stroke? A prespecified, systematic review-based, individual participant data, network, subgroup meta-analysis. Int J Stroke. 2022 Dec;17(10):1067-77.
20. Zandvliet SB, Kwakkel G, Nijland RHM, van Wegen EEH, Meskers CGM. Is Recovery of Somatosensory Impairment Conditional for Upper-Limb Motor Recovery Early After Stroke? Neurorehabil Neural Repair. 2020 May;34(5):403-16.
21. Kwakkel G, Kollen B, Lindeman E. Understanding the pattern of functional recovery after stroke: facts and theories. Restor Neurol Neurosci. 2004;22(3-5):281-99.
22. Buma F, Kwakkel G, Ramsey N. Understanding upper limb recovery after stroke. Restor Neurol Neurosci. 2013;31(6):707-22.
23. Kwakkel G, Stinear C, Essers B, Munoz-Novoa M, Branscheidt M, Cabanas-Valdés R, et al. Motor rehabilitation after stroke: European Stroke Organisation (ESO) consensus-based definition and guiding framework. Eur Stroke J. 2023 Dec;8(4):880-894.
24. Dromerick AW, Geed S, Barth J, Brady K, Giannetti ML, Mitchell A, et al. Critical Period After Stroke Study (CPASS): A phase II clinical trial testing an optimal time for motor recovery after stroke in humans. Proc Natl Acad Sci U S A. 2021 Sep 28;118(39):e2026676118.

25. Hofmeijer J, Ham F, Kwakkel G. Evidence of rTMS for Motor or Cognitive Stroke Recovery: Hype or Hope? Stroke. 2023 Oct;54(10):2500-11.

26. De Iaco L, Veerbeek JM, Ket JCF, Kwakkel G. Upper Limb Robots for Recovery of Motor Arm Function in Patients With Stroke: A Systematic Review and Meta-Analysis. Neurology. 2024 Jul 23;103(2):e209495.

27. Veerbeek JM, Langbroek-Amersfoort AC, van Wegen EE, Meskers CG, Kwakkel G. Effects of Robot-Assisted Therapy for the Upper Limb After Stroke. Neurorehabil Neural Repair. 2017 Feb;31(2):107-121.

28. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009 Jul 21;6(7):e1000097.

29. Verhagen AP, de Vet HC, de Bie RA, Kessels AG, Boers M, Bouter LM, et al. The Delphi list: a criteria list for quality assessment of randomized clinical trials for conducting systematic reviews developed by Delphi consensus. J Clin Epidemiol. 1998 Dec;51(12):1235-41.

30. Lugtmeijer S, Lammers NA, de Haan EHF, de Leeuw FE, Kessels RPC. Post-Stroke Working Memory Dysfunction: A Meta-Analysis and Systematic Review. Neuropsychol Rev. 2021 Mar;31(1):202-19.

31. Tenberg S, Mueller S, Vogt L, Roth C, Happ K, Scherer M, et al. Comparative Effectiveness of Upper Limb Exercise Interventions in Individuals With Stroke: A Network Meta-Analysis. Stroke. 2023 Jul;54(7):1839-53.

32. Sen S, Yildirim I. A tutorial on how to conduct meta-analysis with IBM SPSS statistics. Psych. 2022 Sep 22;4(4):640-67.

33. Bernhardt J, Hayward KS, Kwakkel G, Ward NS, Wolf SL, Borschmann K, et al. Agreed definitions and a shared vision for new standards in stroke recovery research: the stroke recovery and rehabilitation roundtable taskforce. International Journal of Stroke. 2017 Jul;12(5):444-50.

34. Kahn LE, Zygman ML, Rymer WZ, Reinkensmeyer DJ. Robot-assisted reaching exercise promotes arm movement recovery in chronic hemiparetic stroke: a randomized controlled pilot study. J Neuroeng Rehabil. 2006 Jun 21;3:12.

35. Hsieh YW, Wu CY, Liao WW, Lin KC, Wu KY, Lee CY. Effects of treatment intensity in upper limb robot-assisted therapy for chronic stroke: a pilot randomized controlled trial. Neurorehabil Neural Repair. 2011 Jul-Aug;25(6):503-11.

36. Franceschini M, Mazzoleni S, Goffredo M, Pournajaf S, Galafate D, Criscuolo S, Agosti M, et al. Upper limb robot-assisted rehabilitation versus physical therapy on subacute stroke patients: A follow-up study. J Bodyw Mov Ther. 2020 Jan;24(1):194-98.

37. World Health Organization. Towards a common language for functioning, disability and health: ICF. International Classification of Functioning Disability and Health. Published online 2002. http://www.who.int/classifications/icf/training/icfbeginnersguide.pdf

38. Burgar CG, Lum PS, Shor PC, Machiel Van der Loos HF. Development of robots for rehabilitation therapy: the Palo Alto VA/Stanford experience. J Rehabil Res Dev. 2000 Nov-Dec;37(6):663-73.

39. Kahn LE, Averbuch M, Rymer WZ, Reinkensmeyer DJ. Comparison of robot-assisted reaching to free reaching in promoting recovery from chronic stroke. InProceedings of the international conference on rehabilitation robotics 2001 Apr; 25:39-44.

40. Abdullah HA, Tarry C, Lambert C, Barreca S, Allen BO. Results of clinicians using a therapeutic robotic system in an inpatient stroke rehabilitation unit. J Neuroeng Rehabil. 2011 Aug 26;8:50.

41. Rodgers H, Bosomworth H, Krebs HI, van Wijck F, Howel D, Wilson N, et al. Robot assisted training for the upper limb after stroke (RATULS): a multicentre randomised controlled trial. Lancet. 2019 Jul 6;394(10192):51-62.

42. Kwakkel G, Kollen BJ, Krebs HI. Effects of robot-assisted therapy on upper limb recovery after stroke: a systematic review. Neurorehabil Neural Repair. 2008 Mar-Apr;22(2):111-21.

43. Lo K, Stephenson M, Lockwood C. The economic cost of robotic rehabilitation for adult stroke patients: a systematic review. JBI Database System Rev Implement Rep. 2019 Apr;17(4):520-47.

44. Chien WT, Chong YY, Tse MK, Chien CW, Cheng HY. Robot-assisted therapy for upper-limb rehabilitation in subacute stroke patients: A systematic review and meta-analysis. Brain Behav. 2020 Aug;10(8):e01742.

45. Rodgers H, Bosomworth H, Krebs HI, van Wijck F, Howel D, Wilson N, et al. Robot-assisted training compared with an enhanced upper limb therapy programme and with usual care for upper limb functional limitation after stroke: the RATULS three-group RCT. Health Technol Assess. 2020 Oct;24(54):1-232.

46. Fernandez-Garcia C, Ternent L, Homer TM, Rodgers H, Bosomworth H, Shaw L, et al. Economic evaluation of robot-assisted training versus an enhanced upper limb therapy programme or usual care for patients with moderate or severe upper limb functional limitation due to stroke: results from the RATULS randomised controlled trial. BMJ Open. 2021 May 25;11(5):e042081.

47. Mehrholz J, Pohl M, Platz T, Kugler J, Elsner B. Electromechanical and robot-assisted arm training for improving activities of daily living, arm function, and arm muscle strength after stroke. Cochrane Database Syst Rev. 2018 Sep 3;9(9):CD006876.

48. Levin MF, Kleim JA, Wolf SL. What do motor "recovery" and "compensation" mean in patients following stroke? Neurorehabil Neural Repair. 2009 May;23(4):313-9.

49. Roby-Brami A, Jarrassé N, Parry R. Impairment and Compensation in Dexterous Upper-Limb Function After Stroke. From the Direct Consequences of Pyramidal Tract Lesions to Behavioral Involvement of Both Upper-Limbs in Daily Activities. Front Hum Neurosci. 2021 Jun 21;15:662006.

50. Latash ML, Levin MF, Scholz JP, Schöner G. Motor control theories and their applications. Medicina (Kaunas). 2010;46(6):382-92.

51. Krakauer J, Carmichael ST. Broken Movement: The Neurobiology of Motor Recovery after Stroke. Cambridge, MA: The MIT Press; 2017.

52. Winters C, Kwakkel G, van Wegen EEH, Nijland RHM, Veerbeek JM, Meskers CGM. Moving stroke rehabilitation forward: The need to change research. NeuroRehabilitation. 2018;43(1):19-30.

53. van Kordelaar J, van Wegen EE, Kwakkel G. Unraveling the interaction between pathological upper limb synergies and compensatory trunk movements during reach-to-grasp after stroke: a cross-sectional study. Exp Brain Res. 2012 Sep;221(3):251-62.

54. Levin MF. Interjoint coordination during pointing movements is disrupted in spastic hemiparesis. Brain. 1996 Feb;119 (Pt 1):281-93.

55. Levin MF, Michaelsen SM, Cirstea CM, Roby-Brami A. Use of the trunk for reaching targets placed within and beyond the reach in adult hemiparesis. Exp Brain Res. 2002 Mar;143(2):171-80.

56. Flash T, Hogan N. The coordination of arm movements: an experimentally confirmed mathematical model. J Neurosci. 1985 Jul;5(7):1688-703.

57. Uno Y, Kawato M, Suzuki R. Formation and control of optimal trajectory in human multijoint arm movement. Minimum torque-change model. Biol Cybern. 1989;61(2):89-101.

58. Müller JS, Vidaurre C, Schreuder M, Meinecke FC, von Bünau P, Müller KR. A mathematical model for the two-learners problem. J Neural Eng. 2017 Jun;14(3):036005.

59. Wu HN, Wang M. Learning Human Behavior in Shared Control: Adaptive Inverse Differential Game Approach. IEEE Trans Cybern. 2024 Jun;54(6):3705-15.

60. Kang J, Kim SJ, Moon SH, Kim SM, Seo Y, Cha WC, et al. Using Real-Time Interaction Analysis to Explore Human-Robot Interaction. Stud Health Technol Inform. 2023 May 18;302:651-55.

61. Casadio M, Ranganathan R, Mussa-Ivaldi FA. The body-machine interface: a new perspective on an old theme. J Mot Behav. 2012;44(6):419-33.

62. Saes M, Mohamed Refai MI, van Beijnum BJF, Bussmann JBJ, Jansma EP, Veltink PH, et al. Quantifying Quality of Reaching Movements Longitudinally Post-Stroke: A Systematic Review. Neurorehabil Neural Repair. 2022 Mar;36(3):183-207.

63. Kwakkel G, Lannin NA, Borschmann K, English C, Ali M, Churilov L, et al. Standardized measurement of sensorimotor recovery in stroke trials: Consensus-based core recommendations from the Stroke Recovery and Rehabilitation Roundtable. Int J Stroke. 2017 Jul;12(5):451-61.

64. Kwakkel G, Kollen B. Predicting improvement in the upper paretic limb after stroke: a longitudinal prospective study. Restor Neurol Neurosci. 2007;25(5-6):453-60.

65. Joy MT, Carmichael ST. Encouraging an excitable brain state: mechanisms of brain repair in stroke. Nat Rev Neurosci. 2021 Jan;22(1):38-53.

66. Joy MT, Carmichael ST. Learning and Stroke Recovery: Parallelism of Biological Substrates. Semin Neurol. 2021 Apr;41(2):147-56.

67. Hayward KS, Dalton EJ, Barth J, Brady M, Cherney LR, Churilov L, et al. Control intervention design for preclinical and clinical trials: Consensus-based core recommendations from the third Stroke Recovery and Rehabilitation Roundtable. Int J Stroke. 2024 Feb;19(2):169-79.

68. Bernhardt J, Borschmann KN, Kwakkel G, Burridge JH, Eng JJ, Walker MF, et al. SRRR2 Collaboration. Setting the scene for the Second Stroke Recovery and Rehabilitation Roundtable. Int J Stroke. 2019 Jul;14(5):450-6.