A critical time window for recovery extends beyond one-year post-stroke

Belén Rubio Ballester[1], Martina Maier [1], Armin Duff [1], Mónica Cameirão [2], Sergi Bermúdez [2], Esther Duarte [3], Ampar Cuxart [4], Susana Rodríguez [4], Rosa María San Segundo Mozo[5], and Paul F.M.J. Verschure [1,6,*]

[1]Laboratory of Synthetic Perceptive, Emotive and Cognitive Systems, Institute for Bioengineering of Catalonia (IBEC), Barcelona, Spain.
[2]Madeira Interactive Technologies Institute and Universidade da Madeira, Campus universitário da Penteada, Funchal, Portugal.
[3]Servei de Medicina Física i Rehabilitació, Hospitals del Mar i l'Esperança, Institut Hospital del Mar d'Investigacions Mèdiques, Barcelona, Spain.
[4]Servei de Medicina Física i Rehabilitació, Hospital Universitari Vall d'Hebron, Barcelona, Spain.
[5]Servei de Medicina Física i Rehabilitació, Hospital Joan XIII, Tarragona, Spain.
[6]ICREA, Institució Catalana de Recerca i Estudis Avançats, Passeig Lluís Companys, Barcelona, Spain.
*Corresponding author: brubio@ibecbarcelona.eu (Belén Rubio Ballester)

Abstract

The impact of rehabilitation on post-stroke motor recovery and its dependency on the patient's chronicity remain unclear. The field has widely accepted the notion of a proportional recovery rule with a 'critical window for recovery' within the first 3-6 months post-stroke. This hypothesis justifies the general cessation of physical therapy at chronic stages. However, the limits of this critical window have, so far, been poorly defined. In this analysis, we address this question, and we further explore the temporal structure of motor recovery using individual patient data from a homogeneous sample of 219 individuals with mild to moderate upper-limb hemiparesis. We observed that improvement in body function and structure was possible even at late chronic stages. A bootstrapping analysis revealed a gradient of enhanced sensitivity to treatment that extended beyond 12 months post-stroke. Clinical guidelines for rehabilitation should be revised in the context of this temporal structure.

Key words

Neuroplasticity, Stroke Recovery, Neurorehabilitation, Virtual Reality, Motor Recovery

New and Noteworthy

Previous studies on humans suggest that there is a 3-6 months 'critical window' of heightened neuroplasticity post-stroke. We analyze the temporal structure of recovery in patients with hemiparesis and uncover a precise gradient of enhanced sensitivity to treatment that expands far beyond the limits of the so-called 'critical window'. These findings highlight the need for providing therapy to patients at the chronic and late chronic stages.

Introduction

The absolute incidence of stroke will continue to rise globally with a predicted 12 million stroke deaths in 2030 and 60 million stroke survivors worldwide (15). Stroke leads to focal lesions in the brain due to cell death following hypoxia and inflammation, affecting both gray and white matter tracts (8). After a stroke, a wide range of deficits can occur with varying onset latencies such as hemiparesis, abnormal posture, spatial hemineglect, aphasia, and spasticity, along with affective and cognitive deficits, chronic pain and depression (34). Due to improved treatment procedures during the acute stage of stroke (e.g. thrombolysis and thrombectomy), the associated reduction in stroke mortality has led to a greater proportion of patients facing impairments and needing long-term care and rehabilitation. However, prevention, diagnostics, rehabilitation and prognostics of stroke recovery have not kept pace (35).

Motor recovery after stroke has been widely operationalized as the individual's change in two domains: 1) body function and structure (38), whose improvement has been called "true recovery" (5) and refers to the restitution of a movement repertoire that the individual had before the injury, and 2) the ability to successfully perform the activities of daily living (24). While the former is mainly due to the interaction of post-stroke plasticity mechanisms and sensorimotor training, the latter is also influenced by the use of explicit and implicit compensatory strategies (5, 22). The most accepted measure for recovery of body function and structure is the change in UE-FM scores (Kwakkel et al., 2017), while other clinical scales focus on the assessment of activities, such as the Chedoke Arm and Hand Activity Inventory (CAHAI) (3) or the Barthel Index for Activities of Daily Living (BI) (16).

Post-stroke motor recovery mostly follows a non-linear trajectory that reaches asymptotic levels a few months after the injury (21). This model suggests the existence of a period of heightened plasticity in which the patient seems to be more responsive to treatment, the so-called 'critical window' for recovery. Aiming at characterizing the temporal structure of recovery, animal models and clinical research have identified a combination of mechanisms underlying neurological repair that seems to be unique to the injured brain, including neurogenesis, gliogenesis, axonal sprouting, and the rebalancing of excitation and inhibition in cortical networks (36). This state of enhanced plasticity seems to be transient and interacts closely with sensorimotor training to facilitate the recovery of motor function (40). However, there is no clear evidence of the exact temporal structure of enhanced responsiveness to treatment in humans, and as a result, the optimal timing and intensity of treatment remain unclear. A systematic review of 14 studies suggested that, in average, recovery reaches plateau at 15 weeks post-stroke for patients with severe hemiparesis and at 6.5 weeks for patients with mild hemiparesis (17). This study however failed to conduct a meta-analysis due to substantial heterogeneity of the sample and protocols. Currently, an ongoing clinical

trial is investigating the existence and the duration of a 'critical window' of enhanced neuroplasticity in humans following ischaemic stroke (27). Based on the assumption of the existence of this critical period, the SMARTS 2 trial (NCT02292251)(20) is currently investigating the effect of early and intensive therapy on upper extremity motor recovery. Sharing the same research question, the Critical Periods After Stroke Study (CPASS) is a large ongoing randomized controlled trial that focuses on determining the optimal time after stroke for intensive motor training (10). To contribute to the delineation of a temporal structure of stroke recovery in humans, we perform an analysis of individual patient clinical data from 219 subjects with upper-limb hemiparesis, who followed occupational therapy (OT) or a VR-based training protocol using the Rehabilitation Gaming System (RGS) (7) (Figure S1 in Supplementary Material [DOI: 10.5281/zenodo.2611949]). We show that physical therapy has a significant impact on the function of the upper extremity (UE) at all periods post-stroke considered, uncovering a gradient of responsiveness to treatment that extends more than 12 months post-stroke.

Materials and Methods

Data Sets

In this analysis, we included individual patient data from a set of protocols for the recovery of upper extremity function. These protocols included interventions combining occupational therapy (OT) and a specific VR training protocol (RGS) (Section 1 in Supplementary Material [DOI: 10.5281/zenodo.2611949]). Participants met the following inclusion criteria: 1) ischemic strokes (Middle cerebral artery territory) or hemorrhagic strokes (intracerebral), 2) mild-to-moderate upper limb hemiparesis (Medical Research Council scale for proximal muscles > 2) after a first-ever stroke, 3) age between 45 and 85 years old, 4) the absence of any significant cognitive impairment (Mini-Mental State Evaluation > 22). All research on human subjects reported in this manuscript was prospectively approved by the Institutional Review Board of Hospital Joan XXIII, Hospital Vall d'Hebron and Hospital del Mar i l'Esperança from Catalonia, and all participants provided written informed consent.

The datasets were divided into 17 conditions depending on the specific characteristics of the patients and the requirements of the treatment provided (Table 1). Most of the RGS conditions included in this analysis have an identical design based on the same set of neurorehabilitation principles (25) (see Supplementary Material for a full description of the system and its mechanisms [DOI: 10.5281/zenodo.2611949]). However, two relevant design differences should be noticed. First, in four protocols used with acute patients the dosage was three days a week instead of five (conditions 2, 4, 5, and 6, in Table 1). Second, in one study the implicit feedback is augmented through haptic actuators (condition 14 in Table 1, RGS Haptics).

Furthermore, all RGS protocols used by acute and subacute patients, combined RGS-based training with supervised OT, while condition 13 tested the application of RGS in a domiciliary setting. Despite these differences, in all RGS conditions the same protocol was used. A formal risk of bias analysis on the primary outcome (i.e., change in the Fugl-Meyer Assessment of the upper extremity) was performed using ROBINS-I tool (Table S1 in Supplementary Material [DOI: 10.5281/zenodo.2611949.]), covering the evaluation of

Table 1. Overview of the therapy conditions.

ID	Group	Average Chronicity	Intervention	N	Age Mean(SD)	TSO (days)	HA (%left)	Sex (%male)	Oxf.Class.	Reference
1	Control	Acute	12w;5d/w;20min;	5	69(19)	9(15)	40	80	2/1/0/1/1	(12)
2	RGS	Acute	3w;5d/w;20min;	5	70(22)	11(4)	60	20	1/2/0/1/1	(12, 32)
3	RGS	Acute	12w;3d/w;20min;	10	63.5(29)	11(17)	40	30	2/2/2/3/1	(9, 12)
4	Control	Acute	3w;5d/w;20min;	5	64(16)	13(5)	60	60	2/2/0/0/1	(12, 32)
5	Control	Acute	12w;3d/w;20min;NSG	4	65(28)	13(12)	75	50	1/0/1/1/1	(9)
6	Control	Acute	12w;3d/w;20min;IOT	5	56(27)	15(11)	40	40	1/1/2/0/1	(9)
7	RGS	Subacute	3w;5d/w;20min;	49	61(43)	70(375)	30.6	30.6	11/9/13/1/15	- (see Supplementary Material)
8	Control	Subacute	3w;5d/w;20min	4	57(17)	90(226)	0	50	4/0/0/0/0	- (see Supplementary Material)
9	RGS	Chronic	6w;5d/w;30min;+AM	9	63(31)	400(5805)	33.3	33.3	-	(1)
10	RGS	Chronic	6w;5d/w;30min	9	57(36)	735(4471)	11.1	55.6	-	(1)
11	Control	Chronic	3w;5d/w;20min;domiciliary	18	68.5(40)	751(1536)	33.3	50	6/2/4/0/6	(2, 29)
12	RGS	Chronic	3w;5d/w;20min;+OT	20	64.5(37)	770(2789)	40	30	7/0/4/0/9	(11)
13	RGS	Late Chronic	3w;5d/w;20min;domiciliary	17	61.5(43)	997(2987)	47.1	35.3	4/3/4/0/6	(2, 29)
14	RGS	Late Chronic	4w;5d/w;30min;haptics	14	63(45)	1051(3250)	50	57.1	6/0/4/1/3	(6)
15	RGS	Late Chronic	3w;5d/w;30min	15	58(60)	1261(2041)	33.3	46.7	0/1/2/0/12	(11)
16	RGS	Late Chronic	4w;5d/w;30min	16	69.5(46)	1536(3891)	43.8	62.5	6/4/5/0/1	(6)
17	RGS	Late Chronic	4w;5d/w;30min;exoskeleton	14	60(32)	1758(2880)	35.7	71.4	3/1/4/1/5	(6)

Intervention: duration of included protocols indicated per number of weeks (w), days per week (d/w), and minutes (min) of occupational therapy (OT) and VR-based therapy per day. N: sample size in the experimental group. TSO: median(maximum - minimum) days since the stroke. NSG: protocol based on non-specific gaming system (i.e., Nintendo Wii). IOT: condition including intensive occupational therapy. AM: condition including the amplification of movements in VR. Haptics: condition including delivery of haptic feedback during training. HA: percentage of patients with left hemisphere affected. Sex: percentage of males. Oxf. Class: Count of stroke types (lacunar stroke (LACS) / partial anterior circulation stroke (PACS) / total anterior circulation stroke (TACS) / or posterior circulation stroke (POCS)) according to the Oxford Stroke Classification scale. Colored rows indicate the chronicity of stroke patients participating in each study: acute (green), subacute (orange), early (blue) and late (purple) chronic stage.

confounding variables, recruitment for participants, intervention classification, deviations from intended interventions, missing data, measurement of outcomes and selection of reported results.

Outcome Measures

The primary outcome considered in this analysis was the UE motor impairment and activity at the end of therapy, as measured by two standardized clinical scales: the Fugl-Meyer Assessment of the upper extremity (UE-FM) and Chedoke Arm and Hand Activity Inventory (CAHAI)(3) scales. Previous studies have shown that the UE-FM shows excellent reliability, responsiveness and validity properties (37). Secondly, the CAHAI evaluates the UE bilateral function in the performance of specific iADLs (3). Score changes in the UE-FM and CAHAI were used as measures of motor improvement (body function and structure) and performance in iADLs respectively. In addition, the Barthel Index (16) was considered a secondary outcome for the assessment of the patient's level of independence.

Statistical Analysis

We performed two analyses. Firstly, we explored recovery measures independently within each of the 17 conditions. In this analysis, we examined recovery measures using the UE-FM and CAHAI in absolute terms. Here we quantified improvement using mean differences and 95% confidence intervals (CI). Secondly, we analyzed the temporal structure of recovery post-stroke by merging all the conditions (178 patients performing RGS-based training and 368 follow-up measures) and bootstrapping our data using the Efron and Tib method (13) to evaluate the effects of the therapy across the patients' chronicity (subacute, early chronic, and late chronic). This method overcomes the high inter-subject variability and provides a superior statistical power (13). The homogenized data was generated by separating improvement measures at different time intervals and allocating them to

either being an RGS-based training, OT based-training, or follow-up (i.e., no-therapy). We then calculated the improvement rate per week-normalized within-subjects according to their respective recovery potential. This metric therefore captures the improvement observed normalized to the total amount that each patient can gain given their baseline in standardized clinical scales. The normalized improvement (NI) on scale i at time t, was defined as:

$$NI(i,t) = \left(\frac{X_i(t) - X_i(t=0)}{MaxScore_i - X_i(t=0)} \right) * 100. \quad (1)$$

where $X_i(t=0)$ refers to the corresponding baseline score. According to this normalization method, a patient with a baseline score of 16 in UE-FM will have 50 points of potential improvement since the UE-FM has a maximum score of 66 (9). In case this patient would recover 10 points, reaching a score of 26 points in the scale at T1, this would be equal to 20% (i.e., 10/50) of Normalized Improvement (NI). Note that this value may depend on the time lapsed between baseline measurement and subsequent assessments. We overcome this bias by dividing the NI by the number of weeks between both measurement time-points, therefore obtaining an estimate of NI per week. This normalization method allowed us to bundle the data of the different conditions while overcoming the risk of bias due to the variation in treatment intensity and response rates among protocols (26, 28, 33). We computed a NI value for three-time intervals: pre-, post-assessments, and long-term follow-up. For example, for a patient who followed RGS training with a baseline, end of the treatment, and follow-up assessment, we calculated the NI per week for two periods: baseline to end of the treatment and end of the treatment to long-term follow-up. The measured change from baseline to the end of the treatment was allocated to the RGS or the OT group, while the change from the end of the treatment to follow-up was assigned to the follow-up group. If a patient had multiple follow-up assessments at different time points, all the follow-up measures were assigned to the follow-up group.

For all tests, statistical significance levels were set at $p < .05$. Average and dispersion values are reported in medians $\pm$ median absolute deviation (MAD) or means $\pm$ standard deviation (SD) according to results from normality assessments (Kolmogorov–Smirnov normality test). To facilitate the exploration and replication of our findings, we published the complete dataset and analysis source-code as freely available and open, accessible at DOI: 10.5281/zenodo.2611949.

Results

Impact assessment of individual conditions

The complete dataset includes 219 stroke survivors assigned to 17 rehabilitation conditions (Table 1) at different stages post-stroke: acute ($<$ 3 weeks), subacute (3 weeks to 6 months), early chronic (6-18 months), and late chronic ($>$ 18 months). We observed significant gains in body function and structure after treatment, both in acute (median 20.0 ± 7.9 MAD, $p < .01$) and subacute patients (median 8.0 ± 5.6 MAD, $p < .01$), as measured by UE-FM (Figure 1 A, Table S1 in Supplementary Material [DOI: 10.5281/zenodo.2611949]). These gains were accompanied by an improved performance in iADLs in both acute (median 42.5 ± 14.1 MAD, $p < .01$) and subacute groups (median 7.0 ± 10.5 MAD, p

$< .01$)(Figure 1 B, Table S2 in Supplementary Material [DOI: 10.5281/zenodo.2611949]). More interestingly, at the chronic and late chronic stage, the therapy showed overall effectiveness in facilitating improvements in UE-FM (ranging from median 2.7 ± 3.8 MAD to median 7.0 ± 3.6 MAD, $p < .05$) and CAHAI (median 1.0 ± 3.8 MAD to median 8.0 ± 5.6 MAD, $p < .05$). The application of the RGS at-home showed no significant effects in UE-FM but induced statistically significant gains in the execution of iADLs (median 1.0 ± 1.6 MAD, $p < .01$). Surprisingly, a dosage-matched RGS study conducted in the clinic on late chronic patients had an impact on UE-FM (condition 15 in Table 1, median 3.0 ± 4.1 MAD, $p < .01$; Figure 1 A and B, condition Late Chronic 3w). Furthermore, we observed a clear dependency between the number of days post-stroke before the start of the RGS therapy and the improvements in motor function as measured by UE-FM and CAHAI ($p < .001$, Spearman correlation).

The analysis of follow-up measures illustrates that improvements were retained in all groups.The subacute group training with RGS exhibited a significant improvement during the follow-up period (3 months after the end of treatment) both in UE-FM (median 2.0 ± 5.3 MAD, $p < .01$) and CAHAI (median 3.0 ± 11.7 MAD, $p < .01$) (Figure S3 A and B in Supplementary Material [DOI: 10.5281/zenodo.2611949.]). The acute groups, however, showed higher inter-individual variability and non-significant gains from the end of the therapy to the follow-up.

Revealing an extended critical window for recovery

To study the temporal structure of recovery after stroke, we now combine the impact of all the conditions and examine the effects of chronicity on the patients' normalized improvement (NI, see Eq. 1 in Methods). In the group receiving therapy (RGS), we observe a mean UE-FM NI per week of 5.2 ± 1.0 SD % in subacute (median 10.3 weeks), and 2.7 ± 0.6 SD % and 1.4 ± 0.3 SD % in early chronic (median 12.0 months) and late chronic (median 3.9 years) patients respectively (Figure 2 top-left). The change on the CAHAI scale shows a mean NI per week of 3.4 ± 0.7 SD % in subacute, and 1.9 ± 0.4 SD % and 1.1 ± 0.2 SD % in early and late chronic patients respectively (Figure 2 bottom-left). We found statistically significant differences between subacute and early chronic patients, even during the follow-up period ($p < .01$, Wilcoxon Rank-Sum). Those patients at the subacute phase showed higher NI per week. However, only in the RGS group, the early chronic group (6-18 months) showed higher recovery rates than the late chronic group (> 18 months) ($p < .05$, Wilcoxon Rank-Sum). This analysis reveals a long-lasting gradient of sensitivity to treatment that remains visible across the first 18 months post-stroke (Figure 2 right). This effect was not present in the follow-up measures, a period in which no-therapy was administered. Due to the low number of chronic patients in the OT group, we could not apply the bootstrapping method to this sample for comparison. Despite this, we display the full data to allow for visual inspection.

The patient's age could not explain the gradient of sensitivity to treatment found in the RGS group even at early and late chronic stages (Spearman's correlation $r < 0.003$, $p > .96$) and neither by the patient's baseline impairment score (Spearman's correlation $r < 0.052$, $p > .43$ for FM; $r < 0.006$, $p > .93$ for CAHAI). Notice that the design of this analysis controls for additional confounding variables since all patients were recruited according to standard inclusion and exclusion criteria concerning age, motor

impairment severity, cognitive impairment severity, type of stroke (Oxford Classification), hand dominance, the absence of a second stroke, and gender. None of these variables correlate with the patients' chronicity, and therefore none of them can explain the uncovered gradient. The homogeneity of the demographics of these patients in combination with highly heterogeneous chronicity highlights the peculiarity of this data sample.

Finally, we analyzed the co-variation of the recovery measures of the different clinical scales. We observed a distinct effect of the patient's chronicity on the association of Δ UE-FM, Δ CAHAI, and Δ BI scores. While at the acute/subacute stages these recovery measures correlate, they do progressively dissociate as the patient advances towards the late chronic stage (Figure 3).

Discussion

In opposition to compensation, recovery of body function and structure (24) (i.e., 'true recovery' according to (5)) refers to the partial or complete restoration of the repertoire of behaviors that was available before injury (5, 39). In the absence of a precise assessment of kinematic and kinetic measures, recovery of body function and structure has been operationalized as the change in UE-FM scores (22). Previous studies on humans have identified a 3-6 months period of enhanced neuroplasticity mechanisms triggered by the injury (17, 19). Here, by analyzing clinical recovery scores from stroke patients with variable chronicity but comparable baseline impairment levels, we are able to detect a smooth decrease in the sensitivity to treatment (i.e., critical window for recovery) that extends beyond 12 months post-stroke. These results suggest that there is a long-lasting critical period of enhanced neuroplasticity post-stroke that enables improvement in body function and structure even at late chronic stages. This is the first time that such an extended critical period of recovery is reported. Capturing this effect may require large homogeneous data sets and analytical methods with enhanced accuracy such as the bootstrapping technique we apply here.

In line with the previous literature, our data illustrate the correlation of Δ UE-FM with Δ CAHAI and Δ BI scores at acute stages (4, 31). However, we found that at chronic stages these scales dissociate, possibly due to the introduction of compensatory mechanisms (31). Altogether, our data support the interpretation of UE-FM as an assessment of recovery of body function and structure that is independent of improvement in the performance of iADLs and closely associated with true neurological repair (22).

The results presented in this study do require further investigation for a number of reasons. The clinical importance of the detected improvements is marginal at late chronic stages. It is relevant to notice however that the UE-FM minimal clinically important difference (MCID) is derived from the chronicity-dependent variability in the UE-FM's measurement error and the patient's perceived improvement thresholds (30). According to previous studies, the UE-FM MCID ranges from 16 % to 30 % of the scale's maximum value at acute stages ($<$30 days post-stroke) (23), and 7.2% to 11.0% at chronic stages ($>$ 4 months post-stroke)(30). In the case of CAHAI, MCID thresholds have been established above 7% of the scale range (6.3 points) for 'stable patients' within the first year post-stroke (3). If the reduction of the sensitivity to treatment revealed by our analysis exists and extends beyond 12 months post-stroke, these MCID estimates could be better described as

a continuous function of chronicity and should differentiate between late chronic and early chronic patients. Future studies should explore this relationship to delineate more accurate MCID thresholds.

It is important to note that the uncovered gradient of sensitivity to therapy may not be specific to VR-based interventions. However, due to the low number of chronic patients in the Occupational Therapy group, we could not perform a bootstrapping analysis in this sample, and we were thus not able to evaluate the limits of the critical window in these patients. Therefore, the generalization of our findings to therapies based on different rehabilitation methods (e.g., Constraint-Induced Movement Therapy) needs to be investigated. The factors determining the duration of this critical window and the decay rate of the patient's responsiveness to treatment deserve further investigation.

Our results suggest that, as during ontogenesis, the re-acquisition of function after stroke might have to be seen as a process that must satisfy distinct dependencies. Multiple sensitive periods for the acquisition of motor and cognitive function may be structured according to specific dependencies. For instance, in postnatal stages, the development of neural pathways for sensory processing precedes those of language and motor functioning (18). Based on our results, we speculate that the temporal structure of recovery post-stroke may also comprise such a cascade of domain-specific stages or critical periods. Clinical protocols for rehabilitation should be evaluated in this new context.

Conclusion

We have investigated the distinct dynamics of post-stroke recovery and the sensitivity to treatment. By unifying results from eleven rehabilitation pilot studies, we observed improvement in function over at all stages post-stroke. This effect displayed a specific gradient of recovery that faded out exponentially and reached asymptotic levels after one year and a half post-stroke. These findings call for an urgent scientific effort to reassess the 'critical window for recovery' and highlight the need for both providing early therapy and extending it to patients in the chronic stages post-stroke.

Funding source

This study was supported by the Rehabilitation Gaming System, AAL Joint Program 2008-1, European Commission, the European Research Council under grant agreement 341196 (CDAC), EC H2020 project socSMCs (H2020EU.1.2.2. 641321) and MINECO project SANAR (Gobierno de España) under agreement TIN201344200REC.

Conflict of Interest Statement

PV leads the research group SPECS that developed RGS, and the CEO/founder of the spin-off company Eodyne Systems SL, which commercializes RGS with the goal to achieve a large-scale distribution of low-cost science-based rehabilitation technologies.

Author Contributions

Conception and design of the study: BRB, MM, AD, MC, SB, EDO, AC, SR, RMSM, and PV; implementation: BRB, MM and AD; data acquisition: BRB, MM, MC, SB; analysis and interpretation: BRB, MM, AD, MC, SB, EDO, AC, SR, RMSM, and PV; and manuscript preparation: BRB, MM, AD, MC, SB, EDO, AC, SR, RMSM, and PV.

Funding

This study was supported by the Rehabilitation Gaming System, AAL Joint Program 2008-1, European Commission, the European Research Council under grant agreement 341196 (CDAC), EC H2020 project socSMCs (H2020EU.1.2.2. 641321) and MINECO project SANAR (Gobierno de España) under agreement TIN201344200REC.

Acknowledgments

The authors gratefully acknowledge the participation of the patients. We would like to especially thank Irene Camacho, Estefanía Montiel, Leonor Vidal, and María José Aboy, for their assistance in the collection of data.

Data Availability Statement

The complete dataset and analysis source-code is open and freely accessible at DOI: 10.5281/zenodo.2611949. This resource contains the following datasets:

Dataset D1. [DOI: 10.5281/zenodo.2611949] "PatientsDemographicsAndClinicalScreening.xlxl": Demographical data and clinical screening information (age, gender, chronicity, center ID, stroke type, oxford classification, affected arm, arm dominance, presence of aphasia, days after stroke).

Dataset D2. [DOI: 10.5281/zenodo.2611949] "ClinicalScalesAll.csv": Recovery scores from 219 hemiparetic stroke patients evaluated using the Upper Extremity section of the Fugl-Meyer, CAHAI, and BI clinical scales at multiple time points (baseline, end of the treatment, and follow-up periods).

References

1. Ballester B. R., Maier M., San Segundo-Mozo R. M., Castañeda V., Duff A., and Verschure P F M J. Counteracting learned non-use in chronic stroke patients with reinforcement-induced movement therapy. *Journal of NeuroEngineering and Rehabilitation*, 13(1):74, 2016.

2. Ballester B.R., Nirme J., Camacho C., Duarte E., Rodriguez S., Cuxart A., Duff A. and Verschure, PFMJ. Domiciliary VR-Based Therapy for Functional Recovery and Cortical Reorganization : Randomized Controlled Trial in Participants at the Chronic Stage Post Stroke. *JMIR*, 5(3):1–12, 2017. doi: 10.2196/games.6773.

3. Barreca SR., Stratford PW., Lambert CL., Masters LM., and Streiner DL. Test-Retest reliability, validity, and sensitivity of the chedoke arm and hand activity inventory: A new measure of upper-limb function for survivors of stroke. *Archives of Physical*

Medicine and Rehabilitation, 86(8):1616–1622, 2005. ISSN 00039993. doi: 10.1016/j.apmr.2005.03.017.

4. Beebe JA. and Lang CE. Relationships and responsiveness of six upper extremity function tests during the first 6 months of recovery after stroke. *Journal of neurologic physical therapy: JNPT*, 33(2):96, 2009.

5. Bernhardt J., Hayward K.S., Kwakkel G., Ward NS., Wolf SL., Borschmann K., Krakauer JW., Boyd LA., Carmichael ST., Corbett D., and Cramer SC. Agreed definitions and a shared vision for new standards in stroke recovery research: the stroke recovery and rehabilitation roundtable taskforce. *International Journal of Stroke*, 12(5):444–450, 2017.

6. Cameirão M. S. , Badia S. B., Duarte E., Frisoli A., and Verschure PFMJ. The Combined Impact of Virtual Reality Neurorehabilitation and Its Interfaces on Upper Extremity Functional Recovery in Patients With Chronic Stroke. *Stroke*, 43(10):2720–2728, oct 2012. ISSN 0039-2499. doi: 10.1161/STROKEAHA.112.653196. URL http://stroke.ahajournals.org/cgi/doi/10.1161/STROKEAHA.112.653196.

7. Cameirão MS., Bermudez i Badia S., Duarte Oller E., and Verschure P.F.M.J. Neurorehabilitation using the virtual reality based Rehabilitation Gaming System: methodology, design, psychometrics, usability and validation. *Journal of NeuroEngineering and Rehabilitation*, 7(1):48, 2010. ISSN 1743-0003. doi: 10.1186/1743-0003-7-48. URL http://www.jneuroengrehab.com/content/7/1/48.

8. Corbetta M., Ramsey L., Callejas A., Baldassarre A., Hacker C.D., Siegel J.S., Astafiev S.V., Rengachary J., Zinn C., Lang C.E., et al. Common behavioral clusters and subcortical anatomy in stroke. *Neuron*, 85(5):927–941, 2015.

9. Silva Cameirão M., Bermúdez i Badia S., Duarte E., and Verschure P.F.M.J. Virtual reality based rehabilitation speeds up functional recovery of the upper extremities after stroke: a randomized controlled pilot study in the acute phase of stroke using the rehabilitation gaming system. *Restorative Neurology And Neuroscience*, 29(5):287–298, 2011. ISSN 09226028. doi: 10.3233/RNN-2011-0599. URL http://search.ebscohost.com.lib.fontys.nl/login.aspx?direct=true{&}db=mnh{&}AN=21697589{&}site=ehost-live{&}scope=site{%}5Cnhttp://content.iospress.com/download/restorative-neurology-and-neuroscience/rnn599?id=restorative-neurology-and-neuroscience/rnn599.

10. Dromerick A.W., Edwardson M.A., Edwards D.F., Giannetti M.L., Barth J., Brady K.P., Chan E., Tan M.T., Tamboli I., Chia R., Orquiza M., Padilla R.M., Cheema A.K., Mapstone M.E., Fiandaca M.E., Federoff H.J., and Newport E.L. Critical periods after stroke study: translating animal stroke recovery experiments into a clinical trial. *Frontiers in Human Neuroscience*, 9, 2015. ISSN 1662-5161. doi: 10.3389/fnhum.2015.00231. URL http://journal.frontiersin.org/article/10.3389/fnhum.2015.00231/abstract.

11. Duff A., Duarte E., Cuxart A., Rodr′iguez S., Cameirão M., Bermúdez i Badia S, and Verschure P.F.M.J. Rehabilitation Gaming System (rgs): The Impact Of Virtual

Reality Based Training On Upper Limb Recovery In The Acute And Chronic Phase Of Stroke. *Cerebrovascular Diseases*, 31:190, 2011.

12. Duff A., Nirme J., Ballester B.R., Duarte E., Cuxart A., Rodriguez S., and Verschure P.F.M.J. The optimal dosage of the Rehabilitation Gaming System: The impact of a longer period of virtual reality based and standard occupational training on upper limb recovery in the acute phase of stroke. In *Cerebrovascular Diseases*, volume 35, page 146, 2013.

13. Efron B. and Tibshirani R. Bootstrap methods for standard errors, confidence intervals, and other measures of statistical accuracy. *Statistical science*, pages 54–75, 1986.

14. Eilers P.H.C. A perfect smoother. *Analytical chemistry*, 75(14):3631–3636, 2003.

15. Feigin V.L., Forouzanfar M.H., Krishnamurthi R., Mensah G., Connor M., Bennett D., Moran A.E., Sacco R.L., Anderson L., Truelsen T., O'Donnell M., Venketasubramanian N., Barker-Collo S., Lawes C.M.M., Wang W., Shinohara Y., Witt E., Ezzati M., and Naghavi M.. Global and regional burden of stroke during 1990-2010: Findings from the Global Burden of Disease Study 2010. *The Lancet*, 383(9913):245–255, 2014. ISSN 01406736. doi: 10.1016/S0140-6736(13)61953-4.

16. Granger C.V., Albrecht G.L., and Hamilton B.B.. Outcome of comprehensive medical rehabilitation: measurement by PULSES profile and the Barthel Index. *Archives of physical medicine and rehabilitation*, 60(4):145–154, 1979.

17. Hendricks H.T., van Limbeek J., Geurts A.C., and Zwarts M.J. Motor recovery after stroke: a systematic review of the literature. *Archives of physical medicine and rehabilitation*, 83(11):1629–1637, 2002.

18. Hensch T.K. Critical period plasticity in local cortical circuits. *Nature Reviews Neuroscience*, 6(11):877, 2005.

19. Kitago T. and Krakauer J.W. Motor learning principles for neurorehabilitation. In *Handbook of clinical neurology*, volume 110, pages 93–103. Elsevier, 2013.

20. Krakauer J.W. and Cort J.C. A non-task-oriented approach based on high-dose playful movement exploration for rehabilitation of the upper limb early after stroke : A proposal. 43:31–40, 2018. doi: 10.3233/NRE-172411.

21. Kwakkel G., Kollen B., and Lindeman E. Understanding the pattern of functional recovery after stroke: facts and theories. *Restorative Neurology and Neuroscience*, 22 (3-5):281–299, 2004. ISSN 0922-6028. doi: 10.1177/1545968308317972.

22. Kwakkel G., Lannin N.A., Borschmann K., English C., Ali M., Churilov L., Saposnik G., Winstein C., Van Wegen E.E.H., Wolf S.L., Krakauer J.W., and Bernhardt J. Standardized measurement of sensorimotor recovery in stroke trials : Consensus-based core recommendations from the Stroke Recovery and Rehabilitation Roundtable. 12(5):451–461, 2017. doi: 10.1177/1747493017711813.

23. Lang C.E., Edwards D.F., Birkenmeier R.L., and Dromerick A.W. Estimating minimal clinically important differences of upper-extremity measures early after stroke. *Archives of physical medicine and rehabilitation*, 89(9):1693–1700, 2008.

24. Levin M.F., Kleim J.A., and Wolf S.L. What do motor "recovery" and "compensation" mean in patients following stroke? *Neurorehabilitation and neural repair*, 23(4): 313–319, 2009.

25. Maier M., Ballester B.R., Duff A., Duarte-Oller E., and Verschure P.F.M.J. Effect of Specific Over Nonspecific VR-Based Rehabilitation on Poststroke Motor Recovery: A Systematic Meta-analysis. *Neurorehabilitation and neural repair*, 3(2): 112-129, 2019.

26. Makuch R.W. and Johnson M.F. Dilemmas in the use of active control groups in clinical research. *IRB: Ethics & Human Research*, 11(1):1–5, 1989.

27. McDonnell M.N., Koblar S., Ward N.S., Rothwell J.C., Hordacre B., and Ridding M.C. An investigation of cortical neuroplasticity following stroke in adults: is there evidence for a critical window for rehabilitation? *BMC neurology*, 15(1):109, 2015.

28. Medica E.M., Laver K., George S., Thomas S., and Deutsch J.E. Virtual reality for stroke rehabilitation : an abridged version of a Cochrane Review Eur J Phys Rehabil Med 2015 Jul 09 [Epub ahead of print] EUROPEAN JOURNAL OF PHYSICAL AND REHABILITATION COPYRIGHT © 2015 EDIZIONI MINERVA MEDICA Virtual reality for st. *European Journal of Physical and Rehabilitation Medicine*, Jul 09 [Ep:CD008349, jan 2015. ISSN 1469-493X. doi: 10.1002/14651858.CD008349. pub3.). URL http://www.ncbi.nlm.nih.gov/pubmed/25927099.

29. Nirme J., Ballester B.R., Duff A., Duarte E., Rodriguez S., Cuxart A., and Verschure P.F.M.J. At Home Motor Rehabilitation in the Chronic Phase of Stroke Using the Rehabilitation Gaming System. In *Converging clinical and engineering research on neurorehabilitation*, pages 931–935. Springer, Berlin, Heidelberg, 2013.

30. Page S.J., Fulk J.D., and Boyne P. Clinically important differences for the upper-extremity Fugl-Meyer Scale in people with minimal to moderate impairment due to chronic stroke. *Physical therapy*, 92(6):791–798, 2012.

31. Rabadi M.H. and Rabadi F.M. Comparison of the action research arm test and the Fugl-Meyer assessment as measures of upper-extremity motor weakness after stroke. *Archives of physical medicine and rehabilitation*, 87(7):962–966, 2006.

32. Rodriguez S., Bermúdez i Badia S., Cameirão M., Cuxart-Fina A., Duarte E., Duff A., and Verschure P.F.M.J. Session 225 Effects of Virtual Reality Upper Limb Based Training (Rehabilitation Gaming System) on Spasticity, Shoulder Pain, and Depression After Stroke. *PM&R*, 3(10):S160, 2011.

33. Saposnik G. and Levin M. Virtual Reality in Stroke Rehabilitation: A Meta-Analysis and Implications for Clinicians. *Stroke*, 42(5):1380–1386, may 2011. ISSN 0039-2499. doi: 10.1161/STROKEAHA.110.605451. URL http://stroke.ahajournals.org/cgi/doi/10.1161/STROKEAHA.110.605451.

34. Teasell R.W., Foley N.C., Bhogal S.K., and Speechley M.R. An evidence-based review of stroke rehabilitation. *Topics in stroke Rehabilitation*, 2015.

35. Veerbeek J.M., van Wegen E., van Peppen R., van der Wees P.J., Hendriks E., Rietberg M., and Kwakkel G. What Is the Evidence for Physical Therapy Poststroke? A Systematic Review and Meta-Analysis. *PLoS ONE*, 9(2):e87987, 2014. ISSN 1932-6203. doi: 10.1371/journal.pone.0087987. URL http://dx.plos.org/10.1371/journal.pone.0087987.

36. Ward N.S. Restoring brain function after. *Nature Publishing Group*, 2017. ISSN 1759-4758. doi: 10.1038/nrneurol.2017.34. URL http://dx.doi.org/10.1038/nrneurol.2017.34.

37. Wei X.J., Tong K.Y., and Hu X.L. The responsiveness and correlation between Fugl-Meyer Assessment, Motor Status Scale, and the Action Research Arm Test in chronic stroke with upper-extremity rehabilitation robotic training. *International journal of rehabilitation research. Internationale Zeitschrift für Rehabilitationsforschung. Revue internationale de recherches de réadaptation*, 34(4):349–56, 2011. ISSN 1473-5660. doi: 10.1097/MRR.0b013e32834d330a. URL http://www.ncbi.nlm.nih.gov/pubmed/22044987.

38. WHO. *International classification of functioning, disability and health: ICF*. Geneva: World Health Organization, 2001.

39. Zeiler S.R. and Krakauer J.W. The interaction between training and plasticity in the post-stroke brain. *Current opinion in neurology*, 26(6):609, 2013.

40. Zeiler S.R., Hubbard R., Gibson E.M., Zheng T., Ng K., O'Brien K., and Krakauer J.W. Paradoxical motor recovery from a first stroke after induction of a second stroke: reopening a postischemic sensitive period. *Neurorehabilitation and neural repair*, 30 (8):794–800, 2016.

Figure 1

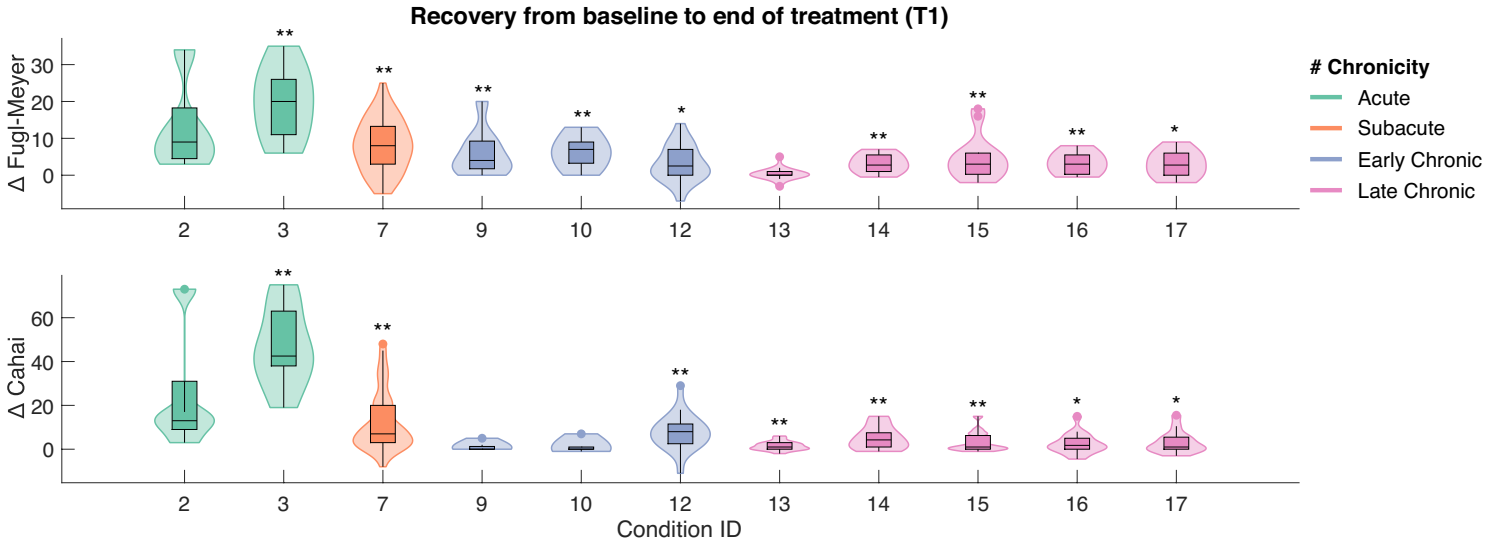

Figure 2

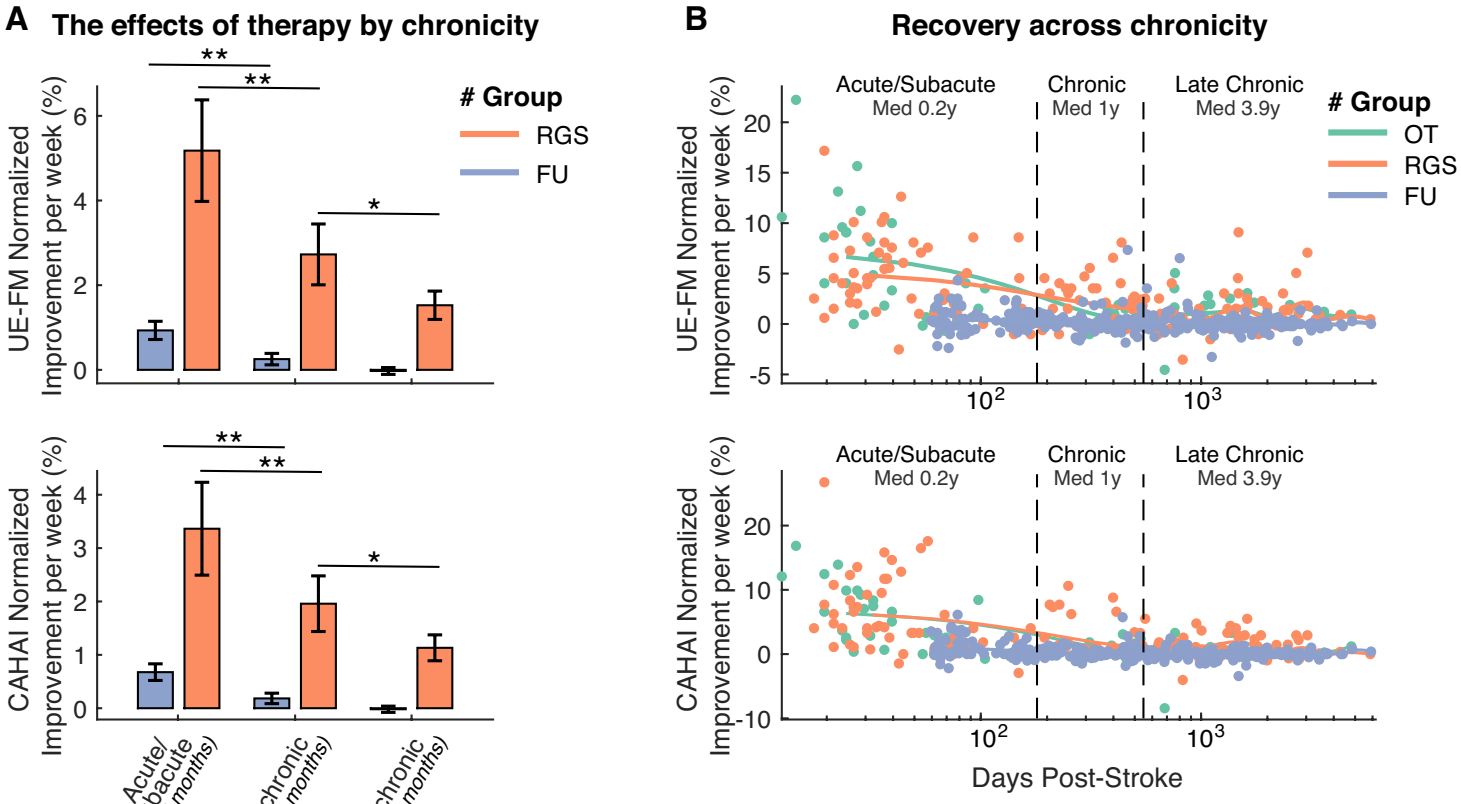

Figure 3