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

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The mechanisms and principles of the Rehabilitation Gaming System (RGS)

The RGS is a VR-based tool for rehabilitation. A number of studies suggest the effectivity of RGS protocols for overcoming upper limb deficits (2–5, 7). These protocols rest on principles that are derived from the Distributed Adaptive Control theory of mind and brain (14), which places functional recovery in the context of the acquisition and expression of embodied goal-oriented voluntary behavior driven by perception, memory, value and goals and the optimization of perceptual and behavioral prediction. Through these mechanisms, RGS promotes neuronal and functional reorganization by engaging primary and secondary motor areas through non-invasive exposure to multisensory stimulation (4, 12). Specifically, RGS combines embodied goal-oriented action execution with a first-person observation of the corresponding movement in VR (Figure S1).

RGS individualizes training, adjusting the difficulty of the task to the capabilities of the user through machine-learning techniques (11). The task, Spheroids, consists of reaching towards, grasping, and releasing spheres into color-matched boxes (6) (Figure S1). The task comprises three subtasks that are structured in time, and progress from proximal to distal movements. This design introduces task variability during the training sessions and provides a practice schedule that is structured, including rest periods, goal-oriented and embodied. These components have shown to optimize the acquisition, retention, and generalization of motor skills (9, 15). To promote the usage of the affected limb, the RGS contains contextual restrictions that limit both the overuse of the non-affected arm and compensatory movements (e.g., trunk movements controlling hand displacements), thus supporting the recovery of body function and structure. Moreover, the patient receives implicit and explicit feedback, including both information about performance and results, thus reinforcing the execution of appropriate successful goal-oriented movements and maximizing long-term retention (1).

Overall, the RGS training protocols integrate five main principles for motor improvement: 1) provide self-paced individualized intense practice, in ecologically valid settings, 2) limit overcompensation, 3) promote goal-oriented tasks that are structured in time, 4) facilitate motor imagery though embodied training, and 5) provide multimodal feedback. A recent systematic review has identified a set of effective principles of neurorehabilitation that overlap with those guiding the design of RGS protocols, in particular: massed practice, dosage, rest, task-specific and variable practice, multisensory stimulation, adapted and scheduled difficulty, explicit and implicit feedback, avatar representation, and paretic limb use promotion (10). These principles do overlap with the principles that guided the design

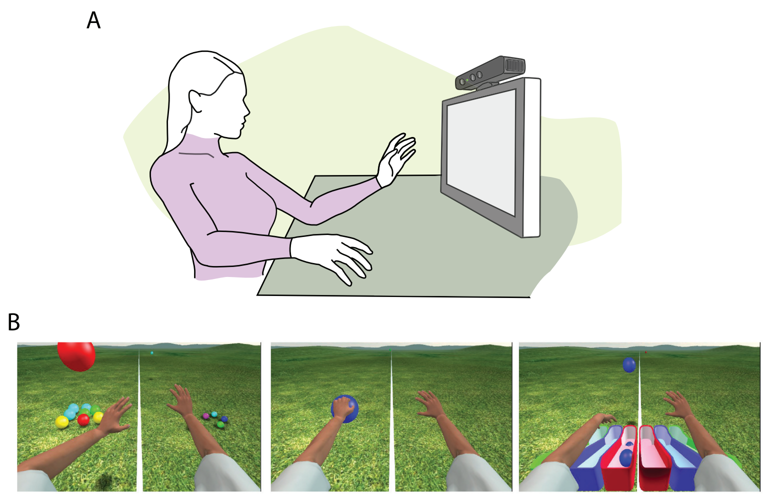

Figure 1. Illustration of the Rehabilitation Gaming System (RGS). A: The system consists of a PC, a 17 inch LCD display, a vision-based motion capture device (Kinect 360, Microsoft, Seatle USA) positioned on top of the screen. The virtual tasks logic and graphics were implemented using the Unity 3D (Unity Technologies, San Francisco, USA) and Torque (Garage Games, Las Vegas, NV, USA) computer game engines. The vision-based motion tracking device and data gloves capture the joint movements of the user's torso, shoulders, elbows, and fingers, and map them onto an avatar through a biomechanical model, thus mimicking the movements of the user. Arm and finger movements are displayed on a screen in a first-person perspective, realizing a paradigm that combines goal-oriented action execution, motor imagery, and action observation. B: the Spheroids task follows a proximal to distal training progression where the users are asked to intercept spheres that move towards them (left), followed by grasping (middle), and placing the spheroids in color matched fashion (right). The scenario is adapted to the performance of the user by controlling the difficulty of the task as defined by the frequency, the speed and the horizontal range of the spheres.

Table 1. Illustration of different Risk Of Bias In Non-randomized Studies of Interventions judgments (ROBINS-I) for each study.

Domain	**1**	**2**	**3**	**4**	**5**	**6**
Confounding	Low	Moderate	Low	Low	Low	Low
Participants selection	Low	Moderate	Low	Low	Low	Moderate
Classification of interventions	Low	Low	Low	Low	Low	Low
Deviations from interventions	Moderate	Moderate	Moderate	Moderate	Moderate	Severe
Missing data	Low	Low	Low	Low	Moderate	Moderate
Measurement of outcomes	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Reported result	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Overall	Moderate	Moderate	Moderate	Moderate	Moderate	Severe

Low= ● Moderate= ● Severe= ● Critical= ●

[1] (7), [2] (8, 13), [3] (8), [4] (5), [5] (3), [6] (4)

of RGS training protocols.

Supplementary Figures and Tables

References

1. Mitsunari Abe, Heidi Schambra, Eric M Wassermann, Dave Luckenbaugh, Nicolas Schweighofer, and Leonardo G Cohen. Reward improves long-term retention of a motor memory through induction of offline memory gains. *Current Biology*, 21(7): 557–562, 2011.

2. Belén Rubio Ballester, Jens Nirme, Esther Duarte, Ampar Cuxart, Susana Rodriguez, Paul F.M.J. Verschure, and Armin Duff. The visual amplification of goal-oriented movements counteracts acquired non-use in hemiparetic stroke patients. *Journal of*

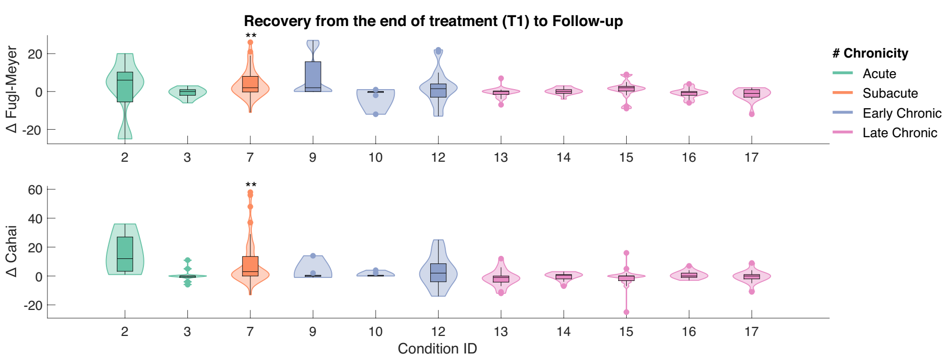

Figure 2. Retention of improvements in the Rehabilitation Gaming System (RGS) group. Impact measured on upper limb motor function (UE-FM) (Top) and performance in iADLs (CAHAI) (Bottom). The effect represents a change in each scale from the end of treatment to follow-up evaluation. Notice that the horizontal axis refers to the RGS conditions listed in Table 1 in the main file and Table S2 in Supplementary Material. Shaded areas indicate the data distribution color coded according to the chronicity of stroke patients participating in each study: acute (green), subacute (orange), early (blue) and late (purple) chronic stage. ** for p-value < 0.01.

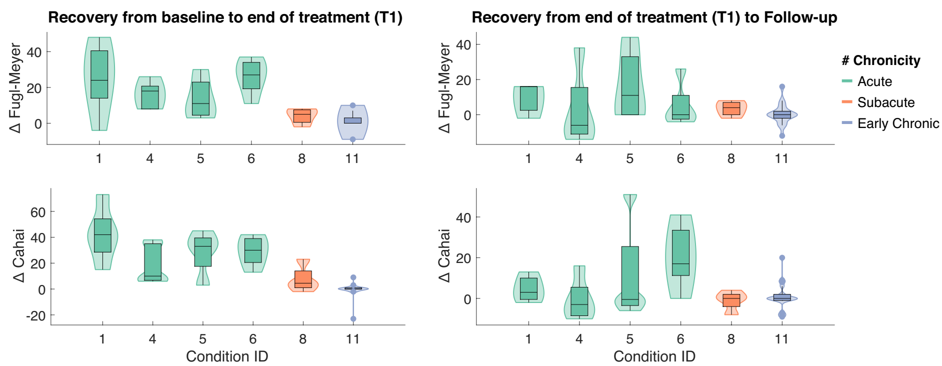

Figure 3. Effect of occupational therapy (OT) from the start to the end of the treatment (T1) (Left), and the retention of improvements during the follow-up (Right). Box-plots indicate the change in UE-FM (Top) and CAHAI (bottom). Notice that the horizontal axis refers to the OT conditions listed in Table 1 in the main file and in Table S2 in Supplementary Material. Shaded areas indicate the data distribution color coded according to the chronicity of stroke patients participating in each study: acute (green), subacute (orange), and early chronic stage (blue).

Table 2. Impact on recovery at the end of the therapy (T1) and during the follow-up by treatment condition.

	Change from Baseline to T1				Change from T1 to Follow-Up			
ID	Median FM ± MAD	Median CAHAI ± MAD	p-value (FM)	p-value (CAHAI)	Median FM ± MAD	Median CAHAI ± MAD	p-value (FM)	p-value (CAHAI)
1	24.000 ± 14.240	42.000 ± 14.640	-	-	8.00 ± 3.60	3.00 ± 5.12	-	-
2	9.000 ± 8.560	13.000 ± 19.840	-	-	6.00 ± 11.04	12.00 ± 11.68	-	-
3	20.000 ± 7.900	42.500 ± 14.080	**.002**	**.002**	0.00 ± 2.04	0.00 ± 3.00	.421†	.743†
4	18.000 ± 6.240	10.000 ± 13.600	-	-	-3.00 ± 7.92	-3.00 ± 7.68	-	-
5	11.000 ± 9.250	33.000 ± 12.750	-	-	5.50 ± 8.25	-0.50 ± 20.00	-	-
6	27.000 ± 7.600	30.000 ± 8.960	-	-	0.00 ± 4.32	17.00 ± 12.16	-	-
7	8.000 ± 5.556	7.000 ± 10.518	**<.001**	**<.001**	2.00 ± 5.31	3.00 ± 11.71	**<.001**	**<.001**
8	5.000 ± 3.500	4.500 ± 7.750	-	-	2.00 ± 1.75	0.00 ± 3.50	-	-
9	4.000 ± 4.667	0.000 ± 1.111	**.008**	.125	2.00 ± 8.96	0.00 ± 2.86	.063	.354†
10	7.000 ± 3.630	0.000 ± 1.407	**.008**	0.293†	0.00 ± 2.47	0.00 ± 1.04	.314†	.500
11	0.000 ± 2.519	0.000 ± 2.815	.148	.647†	.00 ± 1.91	0.00 ± 4.38	.816†	.490†
12	2.500 ± 3.830	8.000 ± 5.620	**.010**	**.001**	1.50 ± 6.20	2.00 ± 8.30	.395	.243
13	0.000 ± 1.045	1.000 ± 1.619	.426	**.008**	0.00 ± 1.86	-1.00 ± 4.03	.459†	.209
14	2.750 ± 2.061	4.250 ± 4.235	**<.001**	**.001**	0.00 ± 1.33	0.50 ± 2.06	.566†	.853†
15	3.000 ± 4.098	1.000 ± 3.467	**.003**	**.005**	2.00 ± 3.25	0.00 ± 4.69	.168	.586†
16	3.000 ± 2.441	1.750 ± 3.477	**<.001**	**.044**	-0.50 ± 1.94	0.00 ± 1.97	.291	.313
17	2.750 ± 2.929	1.000 ± 3.806	**.010**	**.031**	-1.00 ± 2.41	0.00 ± 3.14	.191	.573

The IDs per row refer to the numeric identifiers of treatment conditions listed in Table 1 on the main file. Colored rows indicate the chronicity of stroke patients participating in each study: acute (green), subacute (orange), early (blue) and late (purple) chronic stage. P-values computed with non-parametric statistical tests (Wilcoxon Signed-Rank Test), except for those samples marked with †for which we could confirm normal distribution (Kolmogorov–Smirnov normality test) and perform parametric tests (t-test).

NeuroEngineering and Rehabilitation, 12(1):50, jan 2015. ISSN 1743-0003. doi: 10.1186/s12984-015-0039-z. URL http://www.jneuroengrehab.com/content/12/1/50.

3. Belén Rubio Ballester, Martina Maier, Rosa María San Segundo Mozo, Victoria Castañeda, Armin Duff, and Paul F M J Verschure. Counteracting learned non-use in chronic stroke patients with reinforcement-induced movement therapy. *Journal of NeuroEngineering and Rehabilitation*, 13(1):74, 2016.

4. Belén Rubio Ballester, Jens Nirme, Irene Camacho, and Esther Duarte. Domiciliary VR-Based Therapy for Functional Recovery and Cortical Reorganization : Randomized Controlled Trial in Participants at the Chronic Stage Post Stroke Corresponding Author :. *JMIR*, 5(3):1–12, 2017. doi: 10.2196/games.6773.

5. M. S. Cameirão, S. B. i. Badia, E. Duarte, A. Frisoli, and Paul F.M.J. Verschure. 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.

6. Monica S Cameirão, Sergi Bermudez i Badia, Esther Duarte Oller, and Paul F.M.J. Verschure. 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.

7. M da Silva Cameirão, I Badia S Bermúdez, E Duarte, and Paul F.M.J. Verschure. 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.

8. A Duff, J Nirme, B Rubio, E Duarte, A Cuxart, S Rodriguez, and PFMJ Verschure. 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.

9. Robert E Hanlon. Motor learning following unilateral stroke. *Archives of physical medicine and rehabilitation*, 77(8):811–815, 1996.

10. Martina Maier, Belén Rubio Ballester, Armin Duff, Esther Duarte Oller, and Paul F M J Verschure. Effect of Specific Over Nonspecific VR-Based Rehabilitation on Poststroke Motor Recovery: A Systematic Meta-analysis. *Neurorehabilitation and Neural Repair*, page 1545968318820169, 2019.

11. Jens Nirme, Armin Duff, and Paul F.M.J. Verschure. Adaptive rehabilitation gaming system: on-line individualization of stroke rehabilitation. In *Conference proceedings : Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. Annual Conference*, volume 2011, pages 6749–52. IEEE, 2011. ISBN 9781424441228. doi: 10.1109/IEMBS.2011.6091665. URL http://www.ncbi.nlm.nih.gov/pubmed/22255888.

12. D. Prochnow, S. Bermúdez i Badia, J. Schmidt, A. Duff, S. Brunheim, R. Kleiser, R. J. Seitz, and Paul F.M.J. Verschure. A functional magnetic resonance imaging study of visuomotor processing in a virtual reality-based paradigm: Rehabilitation Gaming System. *European Journal of Neuroscience*, 37(9):1441–1447, may 2013. ISSN 0953816X. doi: 10.1111/ejn.12157. URL http://doi.wiley.com/10.1111/ejn.12157.

13. Susana Rodriguez, Sergi Bermúdez i Badia, Monica D Cameirão, Ampar Cuxart Fina, Esther Duarte, Armin Duff, and Paul Verschure. 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.

14. Paul F.M.J. Verschure. Distributed Adaptive Control: A theory of the Mind, Brain, Body Nexus. *Biologically Inspired Cognitive Architectures*, 1:55–72, 2012. ISSN 2212683X. doi: 10.1016/j.bica.2012.04.005. URL http://linkinghub.elsevier.com/retrieve/pii/S2212683X12000102.

15. Tadashi Yamazaki, Soichi Nagao, William Lennon, and Shigeru Tanaka. Modeling memory consolidation during posttraining periods in cerebellovestibular learning. *Proceedings of the National Academy of Sciences*, 112(11):3541–3546, 2015.