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The Combined Impact of Virtual Reality Neurorehabilitation and Its Interfaces on Upper Extremity Functional Recovery in Patients With Chronic Stroke

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Background and Purpose—Although there is strong evidence on the beneficial effects of virtual reality (VR)-based rehabilitation, it is not yet well understood how the different aspects of these systems affect recovery. Consequently, we do not exactly know what features of VR neurorehabilitation systems are decisive in conveying their beneficial effects.

Methods—To specifically address this issue, we developed 3 different configurations of the same VR-based rehabilitation system, the Rehabilitation Gaming System, using 3 different interface technologies: vision-based tracking, haptics, and a passive exoskeleton. Forty-four patients with chronic stroke were randomly allocated to one of the configurations and used the system for 35 minutes a day for 5 days a week during 4 weeks.

Results—Our results revealed significant within-subject improvements at most of the standard clinical evaluation scales for all groups. Specifically we observe that the beneficial effects of VR-based training are modulated by the use/nonuse of compensatory movement strategies and the specific sensorimotor contingencies presented to the user, that is, visual feedback versus combined visual haptic feedback.

Conclusions—Our findings suggest that the beneficial effects of VR-based neurorehabilitation systems such as the Rehabilitation Gaming System for the treatment of chronic stroke depend on the specific interface systems used. These results have strong implications for the design of future VR rehabilitation strategies that aim at maximizing functional outcomes and their retention.

Clinical Trial Registration—This trial was not registered because it is a small clinical study that evaluates the feasibility of prototype devices.

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Key Words: action execution and observation ■ rehabilitation ■ Rehabilitation Gaming System ■ virtual reality ■ chronic stroke

Virtual reality (VR) is a promising tool to induce functional recovery after lesions to the nervous system, and in the last decade, extraordinary improvements have been made regarding the development of these systems for neurorehabilitation with particular emphasis on stroke.[1,2] However, there is the need to further understand the relation between the detailed characteristics of these systems and the impact on the recovery of their users. The aim of this study is to assess the impact of a VR task for upper limb rehabilitation on stroke neurorehabilitation when performed with different interface technologies using as a basis the Rehabilitation Gaming System (RGS).[3,4] The main hypothesis of the RGS is that bimanual task-oriented action execution combined with the first person observation of virtual limbs that reproduce the executed movements creates the conditions that facilitate the functional reorganization of the motor and premotor systems affected by stroke by recruiting the mirror neuron system.[5] We hypothesize that RGS drives the mirror neuron system by enhancing the observation of goal-oriented movements through a virtual representation of the body and thus accesses the motor and premotor systems through this route.

RGS proposes a multimodal and task-specific VR-based training that includes online adjustment of task difficulty based on a number of principles.[3] The individualized training provided by RGS has already been shown to have an impact on functional recovery in the acute phase of stroke.[4] Patients

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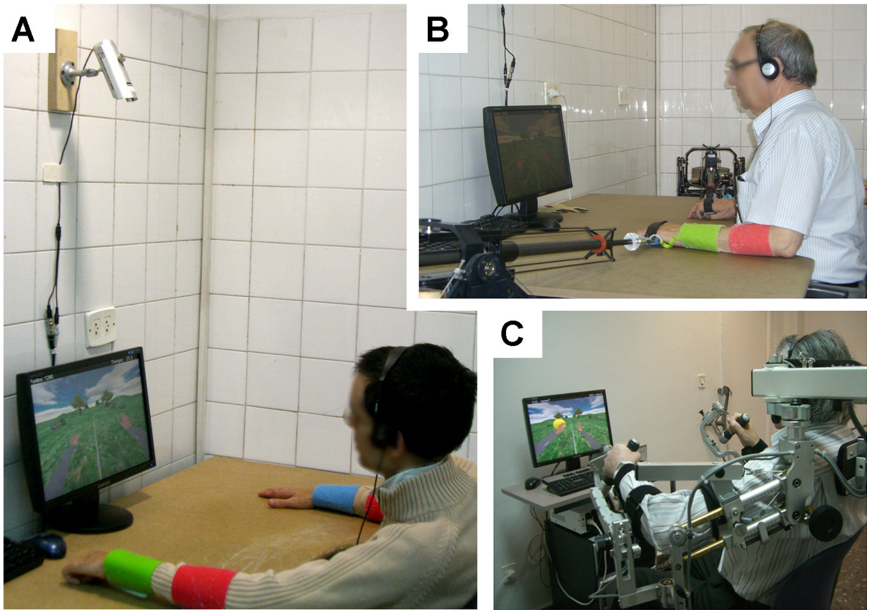

Figure 1. The 3 RGS configurations. **A**, RGS: patients work on a cutout table top facing a computer screen. The tracking system AnTS uses color detection to capture the movements of color patches located on the arms and map these onto the movements of the virtual arms. See Cameirao et al[3] for details. **B**, RGS-H: in addition to RGS, 2 mechanical arms provide force-feedback by means of 2 handles that the patient has to grasp during training. **C**, RGS-E: a bimanual adjustable exoskeleton provides support against gravity during the performance of the task. RGS indicates Rehabilitation Gaming System; RCS-E, Rehabilitation Gaming System-Exoskeleton; RCS-H, Rehabilitation Gaming System-Haptics.

who used the RGS during 12 weeks in addition to conventional therapy displayed a faster and significant improvement in motor and functional performance in comparison to a control group that underwent intense occupational therapy or nonspecific interactive gaming. Given this outcome, we want to now investigate the generalization to patients with chronic stroke and in particular study how recovery is affected by different interface systems, that is, haptic feedback and a passive exoskeleton providing orthosis. Augmenting the visual and auditory feedback of the VR interaction with haptic feedback on touching virtual objects together enhances the salience of interaction events and the ecological validity of the task.[6] More specifically, one could argue that the plastic brain is largely driven by the statistics of the inputs it is exposed to and thus enhancing multimodal feedback will lead to an improved ability to classify and process information.[7] In case of RGS, this would translate into a more effective drive onto the mirror neuron system and thus, indirectly, the motor planning and execution system. Including an exoskeleton for orthosis addresses a typical problem faced in the rehabilitation of patients with stroke that the paretic arm cannot act against gravity. Exoskeletons facilitate the movements of the impaired arm by supporting the weight of the arm against gravity at the same time as preventing the use of compensatory movement strategies.[8] Indeed, it has been suggested that task-specific training with constrained kinematics may allow for a more effective movement recovery.[9,10]

The main purpose of this study is not to investigate whether RGS-based training is beneficial for patients with chronic stroke as compared with patients receiving standard rehabilitation. Rather it addresses the specifics of VR-based systems to understand in which way this technology can be deployed to maximally exploit the neuronal mechanisms of recovery and compensation. Hence, to compare the impact of RGS-based training with these 2 different types of interface systems, we used the RGS coupled with a vision-based tracking system (its standard configuration[3]), a haptic feedback system,[11] and a passive exoskeleton,[8] each of these interfaces providing a new feature to the existing system. In the context of RGS, we hypothesize that the addition of these interface systems may further support the sensorimotor contingencies that underlie the training by adding additional sources of (haptic) information or in case of the exoskeleton further facilitate the training of the specific movements that are the objective of rehabilitation reducing the impact of compensatory movements.

In this study, we show that the VR-based RGS paradigm induces functional recovery in the group of patients with chronic stroke independent of the specifics of the interface used. However, the details of the interface technology used modulate the amount of improvement observed and its retention. We discuss how the different interface systems considered can influence the specific pattern of improvements we observed and argue that the interface-specific modulation is consistent with the learning principles underlying RGS.

Materials and Methods

Setup

The standard version of the RGS is based on a vision-based tracking system (AnTS), capturing the movements of the upper extremities by tracking colored markers positioned at specific points (Figure 1A).[3] The tracked movements are mapped onto the movements of 2 virtual arms embedded within a virtual world. In a second setup, the RGS-Haptics (RGS-H), the RGS was coupled with a haptic interface made of 2 mechanical arms with 6 degrees of freedom (GRAB; Percro–Scuola Superiore Sant'Anna, Pisa, Italy)[11] (Figure 1B). This device provides force-feedback on the end-effectors through the handles that the user has to grasp. This interface allows the subject to receive additional sensory feedback when touching virtual objects. Like in the case of the standard RGS setup, the arm position is tracked by means of the AnTS tracking system (see previously). In the third setup, the RGS-Exoskeleton (RGS-E), the RGS was coupled with a bimanual passive exoskeleton with adjustable arm support (ARMEO; Hocoma, Volketswil, Switzerland; Figure 1C). The standard unimanual ARMEO is based on the T-WREX[8,12] and facilitates movements by supporting the weight of the arms against gravity. For this study, we interfaced a unique bimanual version of this system allowing the use of the 2 arms during the performance of the task. The position of the arms is captured by the exoskeleton and then mapped onto the corresponding angles on the avatar used in the training scenario.

Task

In all conditions, subjects performed a bimanual virtual task called spheroids.[3,13] In all conditions, the subjects that were divided into 3 groups trained with one of 3 different RGS configurations because the main target was to compare the impact of the different technologies and not to assess the impact of VR training in comparison to standard rehabilitation. Spheres with adjustable speed, range of dispersion, and time interval between consecutive spheres move toward the subject and have to be intercepted and grasped. The game parameters are regulated as to generate a difficulty level that is adjusted to the performance of the user. This difficulty level is updated online by a psychometrically validated adaptive controller, or Personalized Training Module. The Personalized Training Module detects the performance of the user and continuously adapts the difficulty of the task individually for each arm during the training session (see Cameirao et al[3] for further details on the spheroids training task and the Personalized Training Module). Spheroids deploy a graded training approach that culminates in the subject grasping and releasing the spheres using data obtained with data gloves. Given the objective of the current study to compare between different interface systems, however, we have removed this specific feature. Here each time a sphere was intercepted by the virtual hand, it was automatically grasped independently of the ability of the subject to actually perform the grasping movement. Nevertheless, the patient was always instructed to try to grasp the spheres at the moment of interception. Before every spheroids session, the patients performed a calibration task in which they were asked to move their arms to 4 fixed numbered positions with different movement ranges in the virtual world.[3] This allowed capturing speed, range of movement, and absolute elbow and shoulder angles and defined the baseline difficulty level for the subsequent training session.

Subjects and Experimental Protocol

The subjects were patients with chronic stroke who in the past had carried out inpatient poststroke rehabilitation in the Physical Medicine and Rehabilitation Unit of the Hospital de L'Esperança in Barcelona. The inclusion criteria were: a minimum of 1 year poststroke at baseline assessment, discharge from rehabilitation since at least 3 months, severe to moderate deficits of the paretic upper extremity (2 ≤proximal Medical Research Council ≤3),[14] age ≤80 years, cooperation, and stability in baseline measures. Exclusion criteria comprised severe to moderate aphasia,[15] and other cognitive and visual deficits that could influence the performance and understanding of the task. Patients had to score at least 22 out of 30 in the Mini-Mental State Examination.[16] A total of 48 patients satisfied the inclusion criteria and were recruited for baseline evaluation. Six patients had mild aphasia (4 Broca and 2 global aphasias)[17] that did not interfere with the understanding and execution of the task.

After giving their informed consent, the patients were randomly assigned to one of the 3 treatment groups: RGS (n=17), RGS-H (n=16), or RGS-E (n=15). The treatment consisted of 5 weekly sessions of 35 minutes. The patients underwent clinical assessment at baseline (evaluated twice with a 1-week interval to ensure stability), at Week 4 (end of treatment), Week 8 (first follow-up), and Week 16 (second follow-up). The study followed accepted guidelines and was approved by the ethics committee of clinical research of the Parc de Salut Mar.

Of the original 48 patients included in the study, 4 dropped out of the study before the end of the treatment (3 due to reasons not related to the treatment and one withdrew) and could therefore not be included in the analysis due to the lack of posttreatment data. For the remaining patients, we have 3 missing evaluations at the first follow-up (Week 8) and 4 at the second follow-up (Week 16) because the patients were not available at the period of evaluation. The 44 patients who completed the entire treatment period had the following types of stroke: 9 hemorrhagic, 22 atherosclerotic, 4 cardioembolic, one small-vessel occlusion, and 8 undetermined.[18] According to the Oxford Stroke Classification,[19] we had 13 total anterior circulation, 5 partial anterior circulation, 15 lacunar, and 2 posterior circulation infarctions. Twenty-eight patients had a lesion in the right hemisphere. See the online-only Data Supplement for extended demographic information per treatment group.

Outcome Measures

An extended clinical assessment was carried out at the different evaluation stages. The evaluator was blind to the group allocation of each individual. Because there is no single measure available to capture the full scope of impairment and functionality, a number of standard clinical evaluation scales were used to assess different abilities: Barthel Index[20,21] for overall independence in activities of daily living, Motricity Index[22] (upper extremities) for muscle strength, Modified Ashworth Scale[23] for spasticity, Fugl-Meyer Assessment test[24] (upper extremities) for synergistic motor patterns, Chedoke Arm and Hand Activity Inventory (CAHAI)[25] for the functional assessment of the recovering arm and hand, Nine Hole Peg Test[26] for finger dexterity (only included as baseline assessment because the number of patients that were able to complete the task was insufficient for further analysis), and Box and Block Test[27] for manual dexterity.

The RGS calibration task allowed us to measure the speed of movement combined with elbow and shoulder joint angles. From the spheroids training session, we extracted information on the difficulty level reached and also on the individual gaming parameters (speed of the spheres, range of dispersion, and time interval between consecutive spheres) for both the paretic and the nonparetic arms.

To assess patients' subjective opinions with respect to a number of aspects of the treatment with RGS, RGS-E, or RGS-H, a 5-point Likert scale self-report questionnaire was used at the end of the treatment (Week 4).

Statistical Analysis

The absolute baseline measures of the clinical scales were statistically compared using the χ^2 test for categorical data and a one-way analysis of variance or a Kruskal-Wallis test for quantitative data. The normality of the distribution was assessed using a single sample Lilliefors hypothesis test of composite normality. To assess the overall within-subject impact of treatment over time, we performed a Friedman test for the clinical scores from baseline up to the different evaluation stages (end, follow-up one, and follow-up 2). For the significant findings at the level of individual groups, we performed pairwise comparisons with respect to baseline using a 2-tailed Wilcoxon signed ranks test. In addition, we computed the absolute change with respect to baseline. The overall effect of group was then assessed using a 2-way analysis of variance in which group and stroke type (ischemic, hemorrhagic) were inserted as independent variables. Between-group comparisons of 2 samples were obtained with a 2-tailed Mann-Whitney test.

For the analysis of the RGS data, we computed the daily maximum difficulty reached during the spheroids task (average of the last 3 trials), separated for both paretic and nonparetic arms, and averaged it over patients for the individual groups. In addition, we also extracted the average speed of the spheres and range of dispersion. The effect of group allocation was assessed using a Kruskal-Wallis test for the daily sessions. From the calibration task, we measured the shoulder adduction and elbow extension at 4 predefined reaching positions for both the paretic and nonparetic arms. This allowed us to quantify the kinematics of the movements at different reaching distances. Subsequently, we computed the average angular mismatch (nonparetic minus paretic) for shoulder and elbow angles over the last 5 sessions of treatment (fourth week), which determines the difference between paretic and nonparetic reaching kinematics. We used a 2-tailed Mann-Whitney test for 2-sample between-group comparisons.

To assess the subjective opinion of the patients with respect to the treatment, we computed the average ratings for selected statements, and the between-group effect was assessed with a Kruskal-Wallis test.

For all statistical comparisons, the significance level was set to 5% ($P<0.05$). All statistical analysis was done using MATLAB 2008a (MathWorks Inc, Natick, MA) and SPSS 16.0 (SPSS Inc, Chicago, IL).

Table 1. Baseline Demographic and Clinical Measures

Variable	RGS (n=16)	RGS-E (n=14)	RGS-H (n=14)	*P* Value
Demographics				
Age, y	68.7±10.9	59.4±9.7	59.9±13.0	**0.028 (KW)**
Sex, male/female	9/7	9/5	7/7	0.746 (χ^2)
Days poststroke	1649±300	1598±230	1334±297	0.358 (KW)
Lesion side, left/right	6/10	4/10	6/8	0.729 (χ^2)
Clinical				
Barthel Index (normal=100)	89.4±11.5	90.4±10.4	89.4±6.6	0.743 (KW)
MRC (2/3)	4/12	2/12	4/10	0.642 (χ^2)
Motricity Index (normal=99)	55.8±5.3	53.3±5.9	56.4±6.8	0.339 (KW)
Ashworth (normal=0)	1.4±0.2	1.6±0.1	1.4±0.1	0.548 (KW)
Fugl-Meyer (max=66)	34.9±11.0	32.7±12.1	35.9±12.4	0.767 (A)
Arm (normal=42)	18.8±6.9	17.4±7.1	18.8±8.2	0.836 (KW)
Wrist/hand (normal=24)	12.3±5.1	11.2±5.7	13.3±5.3	0.612 (A)
CAHAI (normal=91)	36.8±20.9	34.5±19.1	35.7±18.2	0.886 (KW)
Nine Hole Peg Test (A/NA)	2/14	2/12	3/11	0.785 (χ^2)
Box and Block Test (A/NA)	7/9	6/8	6/8	0.998 (χ^2)

Bold values indicate significant values, $P<0.05$.

The categorical variables are expressed in terms of the ratio of cases and the quantitative variables are mean±SD. In *P* value, letters between brackets denote the statistical test that was used for the comparison (KW indicates Kruskal-Wallis Test; A, analysis of variance).

RGS indicates Rehabilitation Gaming System; RGS-E, RGS-Exoskeleton; RGS-H, RGS-Haptics; MRC, Medical Research Council; CAHAI, Chedoke Arm and Hand Activity Inventory; Nine Hole Peg Test and the Box and Block Test: A, able to perform and NA, not able to perform.

Results

Outcome Measures

Baseline balance between groups was confirmed for all demographic and clinical measures, except for age, patients in the RGS group being the eldest (Table 1).

First of all, to assess the impact of treatment, we ran a within-subject analysis of the overall impact of treatment over time. This analysis showed that there was a significant effect of treatment from baseline to all measured time points for the Barthel Index, Motricity Index, CAHAI, and the arm and wrist/hand subparts of the Fugl-Meyer Test (Table 2). We found no significant effect for the Modified Ashworth Scale and Box and Block Test.

Table 2. Within-Subject Statistical Comparison (Friedman Test) Between Baseline and Different Time Points

	P Value		
Measure	To End	To Follow-Up 1	To Follow-Up 2
Barthel Index	**0.021**	**0.006**	**0.001**
Motricity Index	**<0.001**	**<0.001**	**<0.001**
Ashworth	0.206	0.274	0.480
Fugl-Meyer Test	**<0.001**	**<0.001**	**<0.001**
Fugl-Meyer Arm	**0.002**	**0.002**	**0.004**
Fugl-Meyer Hand	**<0.001**	**<0.001**	**<0.001**
CAHAI	**<0.001**	**.<0.001**	**<0.001**
Box & Block	0.808	0.662	0.798

Bold values indicate significant values, $P<0.05$.

CAHAI indicates Chedoke Arm and Hand Activity Inventory.

Interestingly, a further pairwise analysis of the improvement in the clinical scores from baseline to separate time points for each group revealed condition-specific patterns of gains for the 3 groups (Table 3). The RGS group significantly improved at the end of treatment for all the tested clinical scales with mean improvements of 9% and 13%, respectively, in the arm and wrist parts of the Fugl-Meyer scale as well as a 6.8% increase in the CAHAI scale. Gains were maintained up to follow-up 2 (12 weeks after the end of treatment) for the Motricity Index, total Fugl-Meyer Test, and CAHAI. The exoskeleton group (RGS-E) showed significant gains at the end of treatment for the Motricity Index, total Fugl-Meyer Test (8.9%) and its wrist/hand subpart (15.2%), and CAHAI (9%). However, only the gains for the Motricity Index and CAHAI were preserved up to follow-up 2 (Week 8). The haptics group (RGS-H) showed significant improvements at the end of treatment for all clinical scales except for the Barthel Index, and, as opposed to the other intervention groups, all of these gains were preserved 12 weeks after finishing the treatment. In particular we observed the largest improvements on the functional clinical scales: Fugl-Meyer Test, 11%; Fugl-Meyer arm/hand subpart, 14%/13%; and CAHAI, 14% (Week 16).

Concerning the effect of the specific interface used on the improvement at the different evaluation stages, we found that the group to which a subject was allocated had a significant effect for the Box and Block Test at the end of treatment ($F[2,19]=5.265$, $P=0.020$). A further 2-sample comparisons for this test showed indeed that the RGS-H achieved significantly larger improvements than the RGS and the RGS-E at the end of treatment (Mann-Whitney, $Z=-2.463$, $P=0.014$

Table 3. Change at Time Points Compared With Baseline

Variable	RGS Baseline	RGS Improvement	RGS *P* Value	RGS-E Baseline	RGS-E Improvement	RGS-E *P* Value	RGS-H Baseline	RGS-H Improvement	RGS-H *P* Value
End (Week 4)									
Barthel (normal=100)	89.4±11.5	**1.0±1.7**	**0.043**	90.4±10.4	1.3±3.9	0.144	89.4±6.6	0.4±1.8	0.593
Motricity (normal=99)	55.8±5.3	**2.8±3.6**	**0.018**	53.3±5.9	**3.0±3.6**	**0.017**	56.4±6.8	**2.1±3.4**	**0.043**
Ashworth (normal=0)	1.4±0.2	−0.1±0.3		1.6±0.1	0.0±0.1		1.4±0.1	−0.1±0.3	
Fugl-Meyer (max=66)	34.9±11.0	**3.3±2.9**	**0.002**	32.7±12.1	**2.9±3.4**	**0.013**	35.9±12.4	**3.2±2.5**	**0.002**
Arm (normal=42)	18.8±6.9	**1.7±2.6**	**0.024**	17.4±7.1	1.2±3.1	0.195	18.8±8.2	**2.0±1.9**	**0.005**
Wrist/hand (normal=24)	12.3±5.1	**1.6±1.2**	**0.001**	11.2±5.7	**1.7±1.9**	**0.003**	13.3±5.3	**1.1±1.5**	**0.029**
CAHAI (normal=91)	36.8±20.9	**2.5±4.7**	**0.044**	34.5±19.1	**3.1±5.0**	**0.033**	35.7±18.2	**5.1±5.2**	**0.003**
Box and Block (A/NA)	7/9	−1.7±4.4		6/8	−0.2±1.9		6/8	3.3±2.3	
Follow-up 1 (Week 8)									
Barthel (normal=100)	89.4±11.5	**1.3±2.4**	**0.043**	90.4±10.4	1.0±2.1	0.078	89.4±6.6	0.5±2.1	0.593
Motricity (normal=99)	55.8±5.3	**4.0±3.9**	**0.005**	53.3±5.9	**3.1±4.2**	**0.027**	56.4±6.8	2.4±4.3	0.068
Ashworth (normal=0)	1.4±0.2	−0.1±0.3		1.6±0.1	−0.1±0.3		1.4±0.1	−0.1±0.3	
Fugl-Meyer (max=66)	34.9±11.0	**2.9±2.5**	**0.002**	32.7±12.1	2.3±3.4	0.050	35.9±12.4	**3.1±2.2**	**0.002**
Arm (normal=42)	18.8±6.9	1.0±2.3	0.080	17.4±7.1	0.6±3.0	0.593	18.8±8.2	**2.3±1.6**	**0.003**
Wrist/hand (normal=24)	12.3±5.1	**1.9±1.4**	**0.001**	11.2±5.7	**1.7±2.6**	**0.027**	13.3±5.3	**0.8±1.3**	**0.044**
CAHAI (normal=91)	36.8±20.9	3.6±6.5	0.073	34.5±19.1	**3.1±4.3**	**0.010**	35.7±18.2	**4.3±3.9**	**0.005**
Box and Block (A/NA)	7/9	−2.0±4.9		6/8	0.8±1.2		6/8	3.5±4.9	
Follow-up 2 (Week 16)									
Barthel (normal=100)	89.4±11.5	0.9±1.7	0.068	90.4±10.4	1.5±3.9	0.176	89.4±6.6	**1.7±2.6**	**0.043**
Motricity (normal=99)	55.8±5.3	**3.8±5.7**	**0.029**	53.3±5.9	**3.8±3.5**	**0.011**	56.4±6.8	**2.7±4.3**	**0.043**
Ashworth (normal=0)	1.4±0.2	0.1±0.5		1.6±0.1	−0.1±0.4		1.4±0.1	0.0±0.4	
Fugl-Meyer (max=66)	34.9±11.0	**2.2±3.2**	**0.012**	32.7±12.1	1.5±3.0	0.130	35.9±12.4	**3.7±1.9**	**0.001**
Arm (normal=42)	18.8±6.9	1.2±2.6	0.176	17.4±7.1	0.5±2.7	0.633	18.8±8.2	**2.3±2.2**	**0.006**
Wrist/hand (normal=24)	12.3±5.1	1.1±2.0	0.054	11.2±5.7	1.0±2.3	0.146	13.3±5.3	**1.4±1.3**	**0.005**
CAHAI (normal=91)	36.8±20.9	**3.2±5.7**	**0.044**	34.5±19.1	**2.7±3.6**	**0.028**	35.7±18.2	**4.8±4.8**	**0.003**
Box and Block (A/NA)	7/9	−0.7±3.0		6/8	−1.0±6.6		6/8	5.2±5.8	

The improvements (absolute changes with respect to baseline) are expressed as mean±SD. Bold values indicate significant values, $P<0.05$, Wilcoxon.

RGS indicates Rehabilitation Gaming System; RGS-E, RGS-Exoskeleton; RGS-H, RGS-Haptics; CAHAI, Chedoke Arm and Hand Activity Inventory; Box and Block Test: A, able to perform and NA, not able to perform.

compared with RGS, and $Z=-2.189$, $P=0.026$ compared with RGS-E). Additionally, we observed a significant effect of stroke type (ischemic, hemorrhagic) for the Barthel Index scale at both follow-up stages ($F[1,41]=5.967$, $P=0.020$ at follow-up 1; $F[1,40]=7.408$, $P=0.010$ at follow-up 2), in which patients with hemorrhagic stroke displayed larger improvements. There was no significant interaction effect between stroke type and group allocation ($F[2,41]=1.972$, $P=0.154$ at follow-up 1; $F[2,40]=0.936$, $P=0.402$ at follow-up 2).

Following the previously mentioned results, we observe that the overall treatment with RGS in all its configurations leads to significant improvements over time as assessed by different clinical scales extending up to 12 weeks posttreatment. However, analyzing the groups separately, we observed heterogeneity in the specific pattern of improvement and specifically in the ability to retain the gains as assessed in the follow-up. Thus, although at the end of the treatment the groups were quite balanced in their improvements, it is interesting to note that the RGS and RGS-H groups showed benefits at the level of arm functioning (Fugl-Meyer, arm subpart), whereas the RGS-E group was not significantly better than baseline at the end of treatment on this scale. Moreover, the RGS-H group was significantly better at the Box and Block Test than the other 2 groups. In addition, the RGS-H group systematically shows a higher average improvement in the ability to perform activities of daily living as assessed by the CAHAI at particularly at Week 4: RGS-H: 5.1 (14.3%); RGS: 2.5 (6.8%); and RGS-E: 3.1 (9%). All groups show improvements on this scale, however (overall the difference between these groups was not statistically significant; $P>0.05$). Moreover, the RGS-H group was not only able to retain all of its improvements in the Week 16 follow-up as opposed to the other 2 groups (Table 3); they also show a trend toward further improvements in the absence of RGS training: the difference to baseline in the Fugl-Meyer and its subscales goes from approximately 10%, 11%, and 10% to 11%, 14%, and 13%.

To try to understand what the differences in training were among the 3 RGS conditions that gave rise to this pattern of improvements and retention, we looked at the quantitative data obtained during the training sessions. From the spheroids

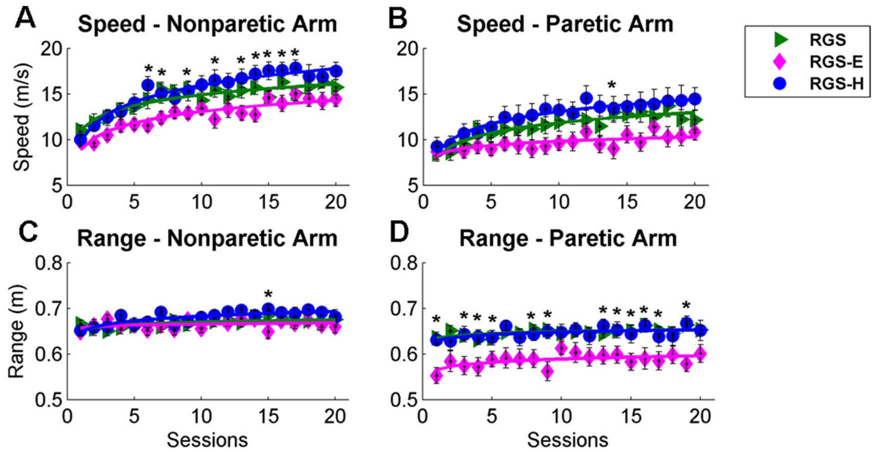

Figure 2. Game parameters over time in the spheroids task for the nonparetic (left) and paretic arms (right). Average speed of the spheres (**A–B**) and range of dispersion (**C–D**) are shown for the individual groups. Error bars indicate the SEM. *Significant effect at the $P=0.05$ level, Kruskal-Wallis.

task we analyzed the maximum difficulty reached during each session, separated for both paretic and nonparetic arms, over the whole treatment period (20 sessions; see the online-only Data Supplement for a graphical representation of the difficulty over time). It is important to note that the difficulty parameter is set by a combination of game parameters (speed of the spheres, range of dispersion, and time interval between spheres) that are adapted online to the individual capabilities of the user (see "Methods"). In all groups, the effect of training over the number of sessions can be analyzed by the learning curves associated with the task. We observed that there was a significant effect of group allocation, over most of the treatment period, for both the paretic and the nonparetic arms (Figure 2). The exoskeleton group in general reached significantly lower levels of performance, that is, difficulty, during the training sessions (see the online-only Data Supplement). Because difficulty is a function of the specific gaming parameters, an additional analysis of the gaming parameters, in particular the speed of the spheres and their range of dispersion (Figure 2A–D), allowed us to assess which features of the task led to this difference in difficulty. In the case of the nonparetic arm, this difference is explained by differences in the speed of the spheres (Figure 2A). We observed that the RGS-E group worked with significantly slower moving spheres than the RGS and RGS-H groups in 45% of the sessions. This indicates that patients allocated to the exoskeleton group were performing slower movements during training and therefore could not catch the faster moving spheres due to the different nature of the interface. However, this does not explain the discrepancy in attained difficulty observed for the paretic arm. The game parameter that had the most determining effect on the level of difficulty for the paretic arm in the case of the RGS-E group was the range of dispersion of the spheres (Figure 2D). This group got a significantly smaller range of sphere dispersion during 60% of the sessions. This means that the patients in the exoskeleton group were not able to perform as wide reaching movements as the patients in the other groups with their paretic arm. However, range was indistinguishable between all the groups in case of the nonparetic arm.

To better understand this interface-specific effect, we need to get access to the movement kinematics. The RGS data obtained in the calibration task allow us to analyze the coordination between shoulders and elbows at the same time as reaching for any of the 4 target positions. If we observe the behavior of the 3 groups at the last week of treatment, we see that indeed the movements displayed by the RGS-E group had a different pattern when compared with the RGS and RGS-H groups (Figure 3A). Looking at the nonparetic arm, patients in the RGS-E group displayed more elbow extension and shoulder adduction when reaching toward a specific position than the other groups (Figure 3A). In addition, several patients in the RGS-E group showed an increased shoulder adduction to compensate the limited elbow extension of their paretic arm (Figure 3B). This effect becomes clearer when we analyze the mismatch between nonparetic and paretic arm movements for shoulder and elbow angles (Figure 3C–D). Indeed, patients in the RGS-E group used significantly more shoulder adduction with their paretic arm (smaller difference with respect to nonparetic arm) when compared with the other 2 groups (Mann-Whitney, $Z=-2.639$, $P=0.008$ compared with RGS, and $Z=-2.877$, $P=0.004$ compared with RGS-H; Figure 3C). Conversely, patients in the RGS-E group did not display as much elbow extension as the RGS and RGS-H groups (Figure 3D). Therefore, they show an increased angular difference with respect to the nonparetic arm that is significantly different in comparison with the RGS and RGS-H groups (Mann-Whitney, $Z=-4.791$, $P<0.001$ compared with RGS, and $Z=-3.8960$, $P<0.001$ compared with RGS-H).

Acceptance and Satisfaction

The analysis of the self-report questionnaire showed that the level of satisfaction in relation to the treatment was very high. Patients in all groups reported positively on their participation in the treatment (see the online-only Data Supplement for a graphical representation of the ratings). To the statement "I am happy that I did this treatment," the average rating was 4.7 for RGS, 4.9 for RGS-E, and 5 for RGS-H. Notice that 5="I totally agree." In addition, the treatment was also rated as being very entertaining (4.3 for RGS, 4.6 for RGS-E, and 4.9 for RGS-H). For what concerns the perceived impact of the treatment on the recovery of the paretic limb, here we found some differences in the ratings depending on group allocation. To the statement, "I feel that this treatment improved the movement of my arm," the average rating was 2.8 for RGS,

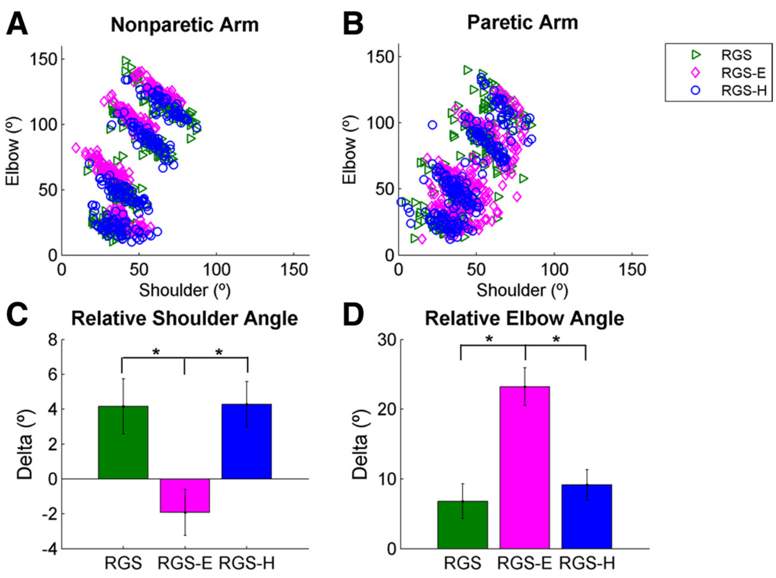

Figure 3. Shoulder elbow coordination. **A–B**, Elbow extension versus shoulder adduction at 4 predefined positions measured in the calibration task during the last week of treatment. Each point indicates the angular relation of one position of the arm for a specific patient. **C–D**, Average (mean±SEM) angle difference between nonparetic and paretic arms for shoulder and elbow angles over the last week of treatment. *$P<0.01$, Mann-Whitney.

2.9 for RGS-E, and 3.7 in RGS-H. This means that on average, the haptics group considered that the mobility of their arms improved as opposed to the RGS and RGS-E that on average did not report such improvements. Interestingly enough, for these 2 groups, the clinical outcomes were opposite to the subjective rating of improvement. There was, however, no statistically significant difference between the ratings (Kruskal-Wallis, $\chi^2[2] \geq 3.563$, $P=0.168$). Another way of assessing the patient's satisfaction with the treatment is by reporting their wish to continue with the treatment after it is finished. Also here, the groups rated this aspect differently. To the statement "I would like to continue this treatment," the average rating was 3.4 for RGS, 4.4 for RGS-E, and 4.4 for RGS-H. Hence, although on average patients in all groups wished to extend their treatment, patients in RGS-E and RGS-H were the ones that were more motivated to do so. However, again this difference did not reach significance (Kruskal-Wallis, $\chi^2[2]=4.736$, $P=0.094$).

Discussion and Conclusions

There are a number of studies with VR systems that suggest that the use of this technology in rehabilitation can have a positive impact on the recovery of motor deficits resulting from stroke.[1,4,6] However, a number of aspects of this technology and its application to stroke rehabilitation are not clearly understood. On the one hand, it is not yet obvious that VR approaches are more effective than other standard approaches[2] and/or whether training effects are clinically and practically relevant. On the other hand, we do not know which characteristics of these systems are the most relevant in neurorehabilitation and how they exactly affect recovery. To address these issues, we evaluated the impact of the RGS on the functional recovery of patients with chronic stroke at the same time as considering 3 different interface configurations. We coupled the RGS with a passive bimanual exoskeleton (RGS-E) to aid movement and control arm kinematics and with a haptic interface (RGS-H) to provide tactile feedback during the interactions with the virtual environment. Thus, the action execution and observation paradigm of RGS that has shown to be an effective treatment in the acute phase of stroke[4] was maintained at the time we added different interfaces. This allowed us to investigate how the specific type of interaction afforded by the interface system could further modulate recovery.

As a general outcome, patients allocated to any of the 3 groups improved significantly from baseline to the end of treatment at most of the standard clinical evaluation scales. All RGS configurations showed particular significant improvements in the performance of activities of daily living with the paretic arm, as measured by the CAHAI. This result is interesting because it implies that benefits obtained in the VR training provided by RGS translate to activities of daily living. Moreover, our results sharply contrast with other studies that report that VR has a poor impact on functional aspects of recovery.[28–30] In a previous study in which the RGS was used by patients with acute stroke, we also observed particular benefits on activities of daily living.[4] We therefore understand that these improvements are mainly due to the characteristics of the RGS paradigm itself.

All groups showed improvements and we did practically not observe statistically significant differences between improvements in the different intervention groups (only the Box and Block Test rendered significant differences). However, we observed much differentiated patterns of improvement for the 3 groups, specifically for what concerns the ability to retain the achieved gains. For example, the exoskeleton group did not retain most of the gains observed at the end of treatment over the 12-period as opposed to the other 2 groups. Interestingly enough, an analysis of the data collected from the spheroids training showed that patients allocated to the exoskeleton group reached lower levels of difficulty in the task, mainly due to shorter arm extension in the paretic arm (Figure 3). We believe that this pattern of results relates to the specific properties of the interface devices used. In essence, the bimanual exoskeleton supports but also constrains the kinematics of the movements and does not facilitate the use of compensatory movement strategies. Moreover, the kinematics of the exoskeleton are not fully anthropomorphic because, for instance, pronosupination of the shoulder is not supported. Our results indicate that this constraint reduces their ability to recover to the same extent as patients allocated to the other groups, who were able to perform unrestrained movements in 2 dimensions. This raises the fundamental question whether to achieve gravitational support for the upper extremities, new constraints are introduced that compromise rehabilitation. Further testing should be performed to investigate this observation, because our results contradict the general assumption that compensatory movements should be prevented in stroke rehabilitation.[9,10]

Regarding the preservation of gains at follow-up stages, the haptics group was the only condition in which all gains were retained at least up to 12 weeks after the end of the treatment. This suggests that adding haptic feedback that coincided with the moments that the subject saw the virtual hands touch the spheres increases the efficacy of the RGS. We believe that there are 2 main hypotheses that can account for this result. First, the inclusion of feedback increases the patient's involvement in the exercise, and this may lead to better retention. For example, it has been observed that the inclusion of auditory feedback improves the clinical outcomes after rehabilitation with robotic therapy systems.[31] Second, and more closely related to the core hypotheses behind RGS, in the configuration that uses haptic feedback, RGS exploits multimodal aspects of the observation of goal-oriented movements and the feedback on one's actions. By increasing the statistical evidence supporting the actions of the user, the recovering brain receives more information on task performance and thus, in the context of the action observation and execution hypothesis underlying RGS, this should enhance the drive onto the mirror neuron system and the action execution system facilitating recovery. Indeed, there is evidence that mirror neurons are not exclusively activated by vision, but also by other sensory modalities that contribute to the understanding and performance of the task.[32] Interestingly enough in some cases, our data also showed further improvements in the absence of treatment. This might be due to a synergistic effect with the improvement in activities of daily living and subsequent increased use of the paretic arm.

Finally, the subjective self-reports of the patients led to a number of interesting observations and corroboration of results found in the clinical assessment. Patients in general were very happy with the RGS treatment in all its configurations. Indeed, other studies reported that VR systems were preferred over standard rehabilitation methods.[12] Of particular interest is that the level of satisfaction was influenced by the interface to the virtual scenario. Here there seems to be a preference toward more sophisticated systems such as the exoskeleton and the haptic interface in our case that may give the impression of a more advanced training. In terms of perceived improvement, the group of patients that gave a higher rating of improvement was the one that indeed scored higher in the clinical assessment, that is, the patients allocated to the RGS-H group (average rating of 3.7 against 2.8 for RGS and 2.9 for RGS-E).

This study does not address the general question whether RGS-based training is beneficial for patients with chronic stroke as compared with patients receiving standard treatment such as occupational therapy. Rather we focus on the specific role of the interfaces deployed. This latter question has to be addressed for at least 2 reasons. By comparing the interface conditions, haptic and exoskeleton, we can distinguish between the impact of multimodal stimulation, which the RGS paradigm would predict is a relevant factor to drive reorganization, and antigravity support and movement constraining whose specific role is unknown in the context of VR-based rehabilitation provided by RGS. Answering this question thus allows us both to advance the principles of neurorehabilitation and identify optimal and effective interface technologies. An issue that may have biased the outcomes is that the level of effort in the manipulation of the interfaces varied between the different RGS configurations because of the particular characteristics of each system. However, we observe that the RGS combined with an exoskeleton that has been proposed as minimizing effort, the T-WREX[8]-based Armeo, shows the least impact on recovery. Finally, one could argue that also depression needs to be assessed because it can affect the impact of training through a modulation of motivation and performance.[33] We have not included such an evaluation because if depression would play such a role, it would bias the outcome of our results toward the null hypothesis.

To summarize, because the 3 RGS configurations led to significant improvements at the end of the treatment, we conclude that all 3 setups are valid for stroke rehabilitation. Taking into account that the common feature shared by the systems is the action execution/observation-based RGS spheroids task, we believe that this is the main attribute leading to these results. Therefore, the lower cost solution, consisting of a computer plus a webcam, is already a valuable tool for rehabilitation that can be easily deployed at large scale in rehabilitation hospitals and for at-home training. However, there is an obvious added benefit of using haptic feedback during the training and the use (or not) of compensatory movement strategies should be further investigated and exploited in VR-based neurorehabilitation systems such as RGS.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

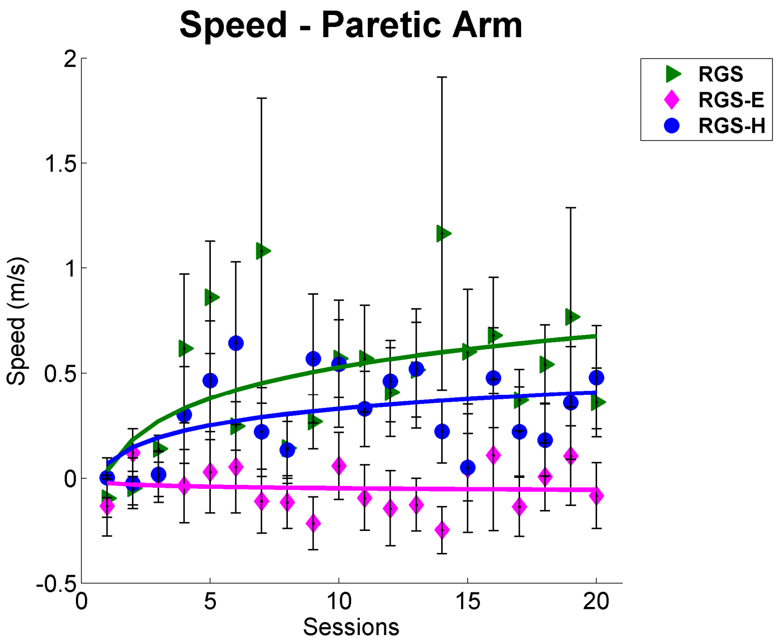
S.1. Description of the patients within each group

Supp_Table 1. Demographic information

Group	ID	Age	Sex	Days after stroke at baseline	Type of Stroke	Infarct Classification	Side of Lesion
RGS	1	75	F	1976	H	-	L
	2	64	M	758	U	TACI	R
	3	34	M	963	A	PACI	R
	4	68	M	494	SVO	TACI	R
	5	80	F	456	C	TACI	R
	6	65	M	4261	A	PACI	R
	7	80	M	526	A	PACI	R
	8	69	M	2182	A	LACI	R
	9	64	F	1863	U	PACI	R
	10	74	F	370	U	LACI	L
	11	64	M	1877	A	LACI	R
	12	65	M	1211	A	LACI	L
	13	79	F	513	A	TACI	L
	14	74	F	3422	U	LACI	R
	15	74	F	2358	U	LACI	L
	16	70	M	3150	A	TACI	L
RGS Haptics	17	69	M	376	A	TACI	R
	18	67	F	479	C	LACI	L
	19	43	M	389	A	TACI	R
	20	53	M	1684	A	TACI	R
	21	50	F	1971	A	TACI	L
	22	70	F	431	C	LACI	R
	23	59	F	3626	H	-	R
	24	32	F	3596	H	-	R
	25	69	F	1355	A	POCI	R
	26	55	M	515	H	-	L
	27	77	F	1727	A	LACI	R
	28	76	M	1086	U	LACI	L
	29	67	M	425	U	LACI	L
	30	52	M	1018	A	LACI	L
RGS Exoskeleton	31	42	M	540	H	-	R
	32	52	M	1617	H	-	L
	33	67	F	2480	H	-	L
	34	65	F	495	A	TACI	R
	35	65	F	2555	H	-	R
	36	52	M	1985	A	TACI	R
	37	60	M	3054	A	TACI	R
	38	72	M	2343	A	LACI	L
	39	74	M	1787	A	LACI	L
	40	66	M	691	A	POCI	R
	41	57	M	482	U	PACI	R
	42	60	M	1803	C	LACI	R
	43	56	F	1731	A	TACI	R
	44	43	F	807	H	-	R

Sex: M=male and F=female; Infarct classification (Bamford et al., 1991): TACI=total anterior circulation infarct, PACI=partial anterior circulation infarct, POCI=posterior circulation infarct and LACI=lacunar infarct; Side of Lesion: L=left and R=right; Type of stroke (Adams et al., 1993): H=hemorrhagic, A=Atherosclerotic, C=Cardioembolic, SVO=small-vessel occlusion and U=undetermined.

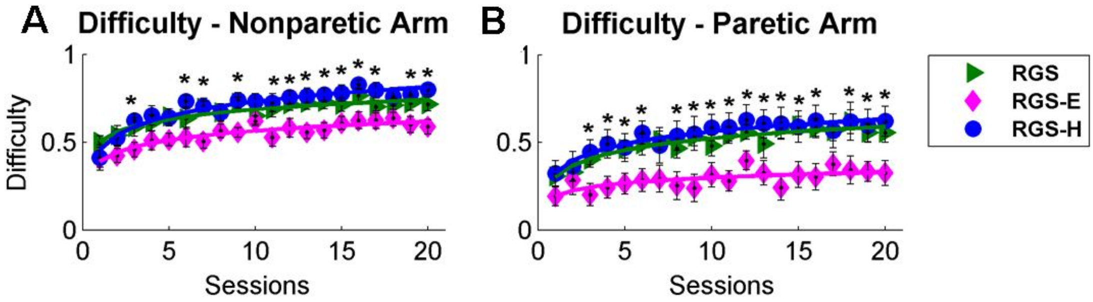
S.2. Speed in the Calibration Task



Supp_Figure 1. Calibration speed over time. The average baseline-normalized speed is shown for the individual groups. The data was fitted with a logarithmic function. Error bars indicate the standard error of the mean.

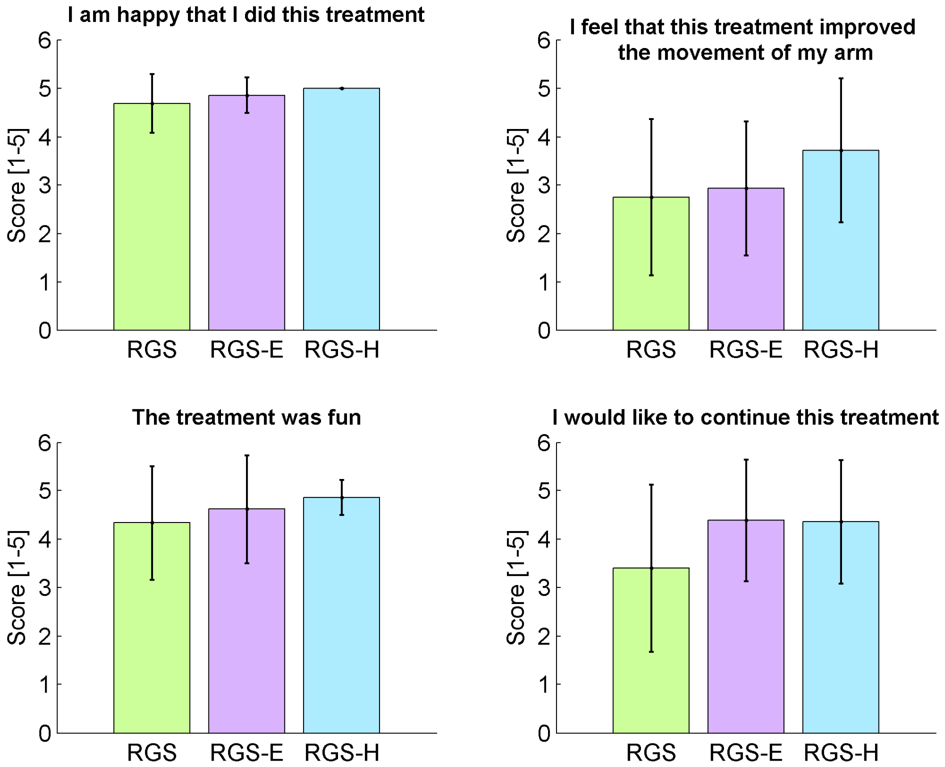
Concerning the baseline-normalized speed time series over the 4 weeks period, we observed that it followed a logarithmic pattern. Hence, by fitting a logarithmic function (y=a+b*log(x)) to the data, we obtained a slope of 0.2134, -0.0107, and 0.1131 m.sessions/s for the RGS, RGS-E, and RGS-H, respectively. This means that at the end of the treatment the RGS group displayed the fastest speed improvement over time, followed by the RGS-H group, while the exoskeleton group displayed no speed improvement. These results have to be interpreted with caution as these measures of speed may be influenced by the interface that is being used. For instance, the patients that worked with the exoskeleton had to move the arm together with the orthosis while measuring the speed; in the case of standard RGS, the arm moves freely.

S.3. Difficulty in the Spheroids Task



Supp_Figure 2. Difficulty over time in the Spheroids task for the nonparetic (left) and paretic arms (right). Average difficulty is shown for the individual groups. Error bars indicate the standard error of the mean. * indicates a significant effect at the p=.05 level, Kruskall-Wallis.

S.4. Acceptance and Satisfaction



Supp_Fig 3. Subjective assessment in the self-report questionnaire. Average ratings (mean ± standard deviation) for selected statements.

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