Impact of combined cognitive and motor rehabilitation in a virtual reality task: an on-going longitudinal study in the chronic phase of stroke

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ABSTRACT

Stroke is one of the most common causes of acquired disability, leaving numerous adults with cognitive and motor impairments, and affecting patients' capability to live independently. Virtual Reality (VR) based methods for stroke rehabilitation have mainly focused on motor rehabilitation but there is increasing interest towards the integration of cognitive training for providing more effective solutions. In this work we present a VR cognitive and motor training task – the Reh@Task – and the preliminary results from an ongoing one-month longitudinal intervention. We show the results from twelve patients divided in two groups: experimental and control. Both groups were enrolled in conventional occupational therapy, which mostly involves motor training. Additionally, the experimental group performed a specific attention and memory training with the Reh@Task and the control group performed time-matched conventional occupational therapy. This VR-based task consists of performing adapted arm reaching movements and has difficulty progression levels implemented with guidelines from a participatory design study. We assessed the impact of both interventions post-treatment (4-5 weeks) and at 4 weeks follow-up through the Montreal Cognitive Assessment, Single Letter Cancellation, Digit Cancellation, Bells Test, Fugl-Meyer, Chedoke Arm and Hand Activity Inventory, Modified Ashworth Scale and Barthel Index. A within groups analysis revealed significant improvements with respect to baseline in the global cognitive functioning in both groups, but only the patients who used the Reh@Task improved significantly in attention and memory. With respect to the motor domain, the control group showed greater improvements. Nevertheless, both groups improved significantly in the functional recovery of the hand and arm scores, revealing that both interventions had an impact in the use of the hand and arm in the activities of daily living. Overall, results are supportive of the viability of tools that combine motor and cognitive training, such as the Reh@Task.

1. INTRODUCTION

1.1 Cognitive and motor impairments after stroke

Stroke is one of the most common causes of adult disability and its prevalence is likely to increase with an aging population (WHO, 2015). It is estimated that 33% to 42% of stroke survivors require assistance for daily living activities 3 to 6 months post stroke and 36% continue to be disabled 5 years later (Teasell et al., 2012). Upper-limb impairments, such as fine and gross motor control, muscle strength, and power loss are the consequences that have a greater impact on functional capacity, what makes its recovery important for minimizing long-term disability and improving quality of life (Saposnik, 2016). In fact, most rehabilitation interventions focus on facilitating recovery through motor learning principles (Kleim & Jones, 2008). However, learning engages also cognitive processes such as attention, memory and executive functioning, all of which may be affected by stroke (Cumming, Marshall, & Lazar, 2013). Still, conventional rehabilitation methodologies are mostly motor focused, although 70% of patients experience some degree of cognitive decline (Gottesman & Hillis, 2010), which also affects their capability to live independently (Langhorne, Bernhardt, & Kwakkel, 2011).

1.2 What is missing in conventional cognitive and motor rehabilitation methodologies?

Although rehabilitation strives to take advantage of neuroplasticity through the intensive repetition of specific learning situations during recovery (Saleh et al., 2011), conventional methodologies have not entirely accomplished this goal (Levin, Weiss, & Keshner, 2014). Currently, paper-and-pencil tasks are widely used in cognitive rehabilitation, and are assumed to be reliable and with adequate construct validity in the assessment and rehabilitation of cognitive functions (Wilson, 2013). However, this methodology is not suited to deliver immediate feedback and reinforcement on progress, which is an important element to increase the motivation and avoid dropouts (Parsons, 2015). Additionally, when the dominant arm is affected by hemiparesis, performing paper-and-pencil tasks may become difficult or impossible. Regarding the motor domain, the persistent repetition of motor actions can be demotivating due to its repetitiveness and, because it is labor and demanding in terms of human resources, it is not as intensive as it should be (Langhorne, Coupar, & Pollock, 2009).

In addition, the relationship between cognitive and motor deficits is increasingly being unveiled and cognitive effort appears to contribute to motor recovery (Mullick, Subramanian, & Levin, 2015). For instance, it was found that repeated performance of a movement may not lead to meaningful improvement unless the task is performed within the functional demands of a relevant environment (Levin et al., 2014). In fact, the practice of manipulations that require more cognitive effort were already predicted to be more effective for motor learning compared to those that require less cognitive effort (Hochstenbach, Mulder, Limbeek, Donders, & Schoonderwaldt, 1998). In this endeavor, it is important to investigate the learning potential of patients with post-stroke cognitive and motor impairments by developing new therapeutic strategies that merge cognitive and motor intensive training.

1.3 Virtual Reality as a tool for combined cognitive and motor rehabilitation

Virtual reality (VR) has emerged as a valuable approach in stroke rehabilitation by providing the opportunity to practice cognitive and motor activities in an ecological context, which is not possible within the clinical environment (Klinger, Sánchez, Sharkey, & Merrick, 2014). Such enriched training tasks can be used to provide meaningful motor repetitions in the context of cognitive rehabilitation tasks, together with immediate feedback, thereby maximizing motor learning (Laver, George, Thomas, Deutsch, & Crotty, 2015). These virtual environments have the potential to optimize motor learning by manipulating practice conditions that explicitly engage motivational, cognitive and sensory feedback-based learning mechanisms (Levin et al., 2014).

However, despite the interdependency between cognitive and motor domains, they have mostly been considered separately in the development of VR-based methodologies (Laver et al., 2015). We argue that novel VR tools should focus on integrative cognitive and motor rehabilitation based on tasks that pose both cognitive and motor demands. Assuming the interdependence between the recovery processes, we may provide a more effective rehabilitation tool. Here we present an ongoing longitudinal clinical trial, with the results of the first 12 patients with stroke: six performing a VR-based intervention and six performing conventional rehabilitation. The VR-based intervention, named Reh@Task, consists in the virtual adaptation of paper-and-pencil cognitive tasks to be solved with repetitive arm reaching movements. The Reh@Task automatically adapts the difficulty level according to the patient performance, which increases challenge and the patient's optimal experience (Csikszentmihalyi & Csikszentmihalyi, 1992).

2. METHODS

2.1 Participants

Participants were recruited at the CMM – Centro Médico da Murtosa (Aveiro, Portugal), based on the following inclusion criteria: at least six months after first ischemic stroke; undergoing occupational therapy rehabilitation; no vision problems; no history of premorbid deficits; no neglect; capacity to read and write; no severe depressive symptomology as assessed by the Geriatric Depression Scale (Yesavage et al., 1982); non-aphasic and with sufficient cognitive ability to understand the task instructions as assessed by the clinicians. Patients who scored less than 28 in the elbow flexion and shoulder abduction tests from the Motricity Index (Paternostro-Sluga et al., 2008) were excluded. The sample consisted of twelve patients with stroke randomly distributed in two groups (Table 1). The experimental group comprised six (5 male, 1 female) senior (M=62.17 years old, SD=8.18) patients with stroke (2 right hemisphere, 4 left hemisphere), with an average of 32.17 ± 26.93 months post-stroke, a mean of 5.67 ± 2.07 years of schooling, and 2 out of 4 with self-reported computer literacy. The control group comprised six (4 male, 2 female) senior (*M*=76 years old, *SD*=6.63) patients with stroke (2 right hemisphere, 4 left hemisphere), with an average of 55.33 ± 47.35 months post-stroke, a mean of 3.83 ± .41 years of schooling and no one had self-reported computer literacy. The clinic's board of directors approved the study and all the participants gave previous informed consent.

Pairwise Mann-Whitney tests revealed no differences between groups in the demographic characteristics and in the cognitive assessment tests at baseline. Concerning the motor domain, there were differences between groups at baseline only in the Modified Ashworth Scale.

Table 1. *Experimental and control group demographics (Mean ± SD).*

	Experimental	**Control**
Age	62.17 ± 8.18	76 ± 6.63
Gender	5 male; 1 female	4 male; 2 female
Schooling	5.67 ± 2.07	3.83 ± .41
Time post-stroke	32.14 ± 26.93	55.33 ± 47.35
Stroke location	2 Right; 4 Left	2 Right; 4 Left

2.2 *Reh@Task for cognitive and motor training*

The Reh@Task was designed as an adaptation in VR of the Toulouse Piéron (TP) task (TP-VR) (Faria, Vourvopoulos, Cameirão, Fernandes, & Bermúdez i Badia, 2014), extended to incorporate numbers, letters and symbols. Reh@Task is a variation of cancellation tests used by conventional rehabilitation methodologies with the objective of training attention. Reh@Task also adds a memory variant by displaying the targets for an amount of seconds at the beginning and then hiding them in the target selection step. Figure 1a shows an illustration of the Reh@Task for attention training, where the targets are always visible. Figure 1b illustrates the memory variant, where the targets are displayed for a number of seconds and then disappear for the selection task. Figure 1c shows the different target elements used in Reh@Task ordered by increasing complexity.

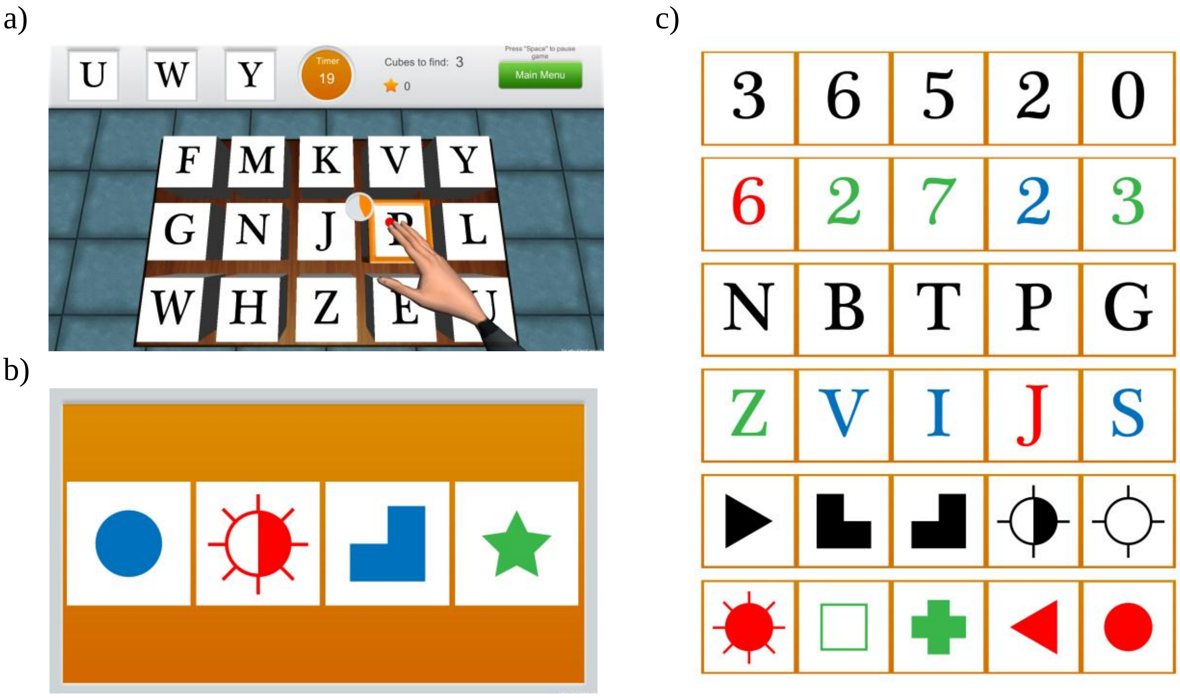

Figure 1. *Reh@Task subsets of stimulus.* ***a)*** *Attention training: cancellation task with black and white letters.* **b)** *Memory training: The target stimuli (symbols) are presented in the center of the screen and then disappear; the participant has to select them by memory.* **c)** *Target stimuli ordered by increasing complexity.*

Reh@Task is designed to be performed by repetitive arm reaching movements on a tabletop surface, and implemented by using the representation of the paretic arm for navigating and targeting symbols arranged in a three-dimensional environment. The target selection is made through a timer. The interaction with the computer is made through 2D arm movements with a camera-based Augmented Reality (AR) pattern tracking software (AnTS) (Mathews, Badia, & Verschure, 2007) (Figure 2). The VR environment has a built-in calibration function that is able to compute the active range of motion of the patient, normalizing the motor effort required to the skill set of the patient (Vourvopoulos, Faria, Cameirão, & Bermúdez i Badia, 2013).

Figure 2. *Interaction with the Reh@Task through the AnTS tracking software.*

This gamified VR task has a total of 120 difficulty levels, defined through a participatory design study, where the input of 20 health professionals was operationalized in quantitative guidelines (Faria & Bermúdez i Badia, 2015). The difficulty of the stimulus progression (Equation 1) was obtained through the manipulation of the variables: number of targets, number of distractors, and type of stimulus:

$$Difficulty = 3.610 + N_{targets}*0.12+N_{distractors}*0.15+Stimulus_{type} \qquad (1)$$

where $N_{targets}$ is the number of target elements, $N_{distractors}$ the number of distractors, and $Stimulus_{type}$ can take the following values: −0.494 for *numbers*, −1.054 for *letters*, and 0 for *symbols*, meaning that letters are easier than numbers and numbers easier than abstract symbols. The progression of the number of targets and distractors, the time available to solve the task, the duration of the selection timer and, in the memory variant of the task, the amount of time for memorizing the target was operationalized according to Figure 3. In summary, for higher difficulty levels, more target and distractor elements appear, less time is available for completing the task and memorizing the target images, and action selection is quicker. When a patient does not solve a specific level in the established timing, more time is given for that level. This additional time can be incremented up to three times. If the patient fails three times in a row, he goes back to the previous level. If the patient succeeds, the level must then be successfully performed within the original established time.

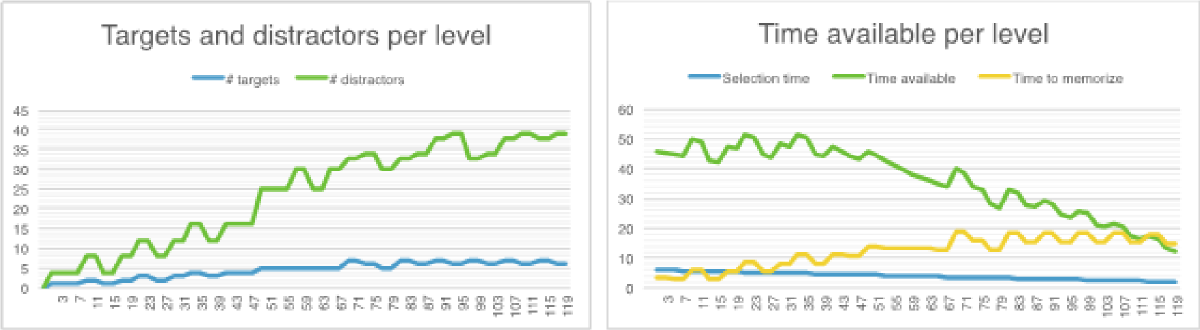

Figure 3. *Progression of the parameters of Reh@Task for the 120 different difficulty levels, including number of target elements, distractor elements as well as time related variables. See text for further information.*

In addition, a rule was defined to select the starting level in each training session as in Equation 2:

$$StartLevel_t = StartLevel_{t-1} + (EndLevel_{t-1} - StartLevel_{t-1})/2 \quad (2)$$

where *StartLevel* and *EndLevel* denote the starting and finishing levels respectively, and t indicates the session number. For instance, if the level achieved by a participant in the first session was 28, the second session would start in level 14 (28/2). If in the second session level 44 would be reached, the third session would start in level 29 (14 + (44-14)/2), and so on for the following levels.

2.3 Protocol

After recruitment, the twelve participants were assessed by an occupational therapist to obtain baseline measures for motor and cognitive domains. After the assessment, participants were randomly assigned to one of the groups by a researcher not involved in the data collection, using the Research Randomizer, a free web-based service that offers instant random sampling and random assignment (Research Randomizer, 2016). The assessor was not blind for the type of intervention. In addition to conventional occupational therapy, the experimental group went through twelve sessions of 45 minutes with the Reh@Task, three times a week, during one month. The control group intervention was time-matched, including conventional occupational therapy, spatial and time orientation activities and writing training. In the experimental group, before starting the twelve-session intervention, participants went through an average of three training trials with TP abstract stimuli. The training was intended to provide a clear understanding of the VR task, as well as to become used to the natural user interface (AnTS). After assuring that the patient understood the task and interface instructions, the intervention started with the attention variant of the task, then switched to memory, and so on intermittently. The progression of levels in the attention and memory tasks is independent, and a participant may, for instance, reach level 30 in attention and stay at level 25 in memory. At the end of the intervention and at follow up, all participants were assessed with the same assessment measures. The adherence to therapy rate was of 100% for all patients.

2.4 Cognitive, Motor and Functional Assessment

A number of cognitive and motor scales that are widely applied clinically and in research were used to determine impairment severity and to measure cognitive and motor recovery. The cognitive profiling was made through the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2003), which provides sub scores for the following domains: Executive Functions, Naming, Attention, Language, Reasoning, Memory and Orientation. The attention task-related capabilities were assessed with the Single Letter Cancellation (Diller et al., 1974), the Digit Cancellation (Mohs et al., 1997) and the Bells Test (Gauthier, Dehaut, & Joanette, 1989). The upper-extremity deficits were measured through the Fugl-Meyer (Fugl-Meyer, Jääskö, Leyman, Olsson, & Steglind, 1975) Upper-Extremities components (Sullivan et al., 2011) and the Chedoke Arm and Hand Activity Inventory (Barreca et al., 2004). Spasticity was assessed through the Modified Ashworth Scale (Bohannon & Smith, 1987). Finally, to assess independence in the activities of daily living (ADL's), we used the Barthel Index (Mahoney & Barthel, 1965).

2.5 Data analysis

Data were analyzed using the Statistical Package for the Social Sciences 20. Because most distributions deviated from normality, non-parametric statistical tests were used. A Mann-Whitney test was done to assess differences between groups at baseline. Comparisons were performed between baseline, post-intervention and follow-up. For assessing change over time, a Friedman test was used. For within-subjects pairwise comparisons, the Wilcoxon's T matched pairs signed ranks test was used.

3. RESULTS

3.1 How effective is cognitive training with Reh@Task as compared to conventional rehabilitation?

We observed that both experimental and control groups had improvements, from baseline to post-intervention and follow-up, in the cognitive screening assessment score and in the performance of most cancellation tests (Table 2).

Table 2. *Montreal Cognitive Assessment (MoCA), Digit Cancellation (DC), Single Letter Cancellation (SLC) and Bells Test (BT) scores at baseline, post-intervention and follow up.*

		Experimental			**Control**		
		Baseline	Post-intervention	Follow-up	Baseline	Post-intervention	Follow-up
MoCA		22.50 (18-23.75)	26 (23.5-27.25)*	26 (21.5-28.5)*	21.5 (16-23.25)	24 (22.75-25.75)*	24.5 (24-25.25)*
DC	Time	5 (4-6.25)	4 (3-4)*	4 (4-5.25)	6 (5-6.5)	5.5 (4.75-7.25)	5.5 (4-7)
	Errors	1 (0-3)	.50 (0-1)	0 (0-1.5)	2 (1.75-2.25)	0 (0-.75)	1 (0-1)
SLC	Time	6 (4-13)	6.50 (4.75-7.75)	7 (4.75-12)	7.5 (6-8.5)	8 (6.5-9.75)	8.5 (7-11.25)
	Errors	2 (0-3.25)	1.50 (1-7.75)	3 (.75-5.25)	3.5 (3-10.25)	2.5 (2-9)	3.5 (2-4.75)
BT	Time	8.50 (5-10.75)	6 (4.75)	6.5 (5-9.5)	11 (9.75-12)	9.5 (8.75-11.75)	10 (10-11.25)
	Errors	4.50 (2.75-8.75)	3 (1.75-3.5)*	1.5 (1-3.25)	4.50 (4-5.25)	2 (2-4)	4 (2.75-5)

Values are presented as medians (quartile 1 – quartile 3).

* Wilcoxon's T matched pairs signed ranks test significance p <.05.

Changes over time in the MoCA scores, assessed with the Friedman's test, are significant in both experimental ($\chi^2(2)=9.478$, p=.009) and control ($\chi^2(2)=9.238$, p=.010) groups. A comparison showed higher average improvements in the group that used the Reh@Task, although not statistically different from control. The Wilcoxon's test revealed significant differences between baseline and post-intervention (Experimental: $W_{(6)}=21.000$, Z=-2.207, p=.027; Control: $W_{(6)}=15.000$, Z=-2.032, p=.042), and baseline and follow-up (Experimental: $W_{(6)}=21.000$, Z=-2.220, p=.026; Control: $W_{(6)}=21.000$, Z=-2.207, p=.027). In the analysis of MoCA subdomains, we found significant improvements for memory only in the experimental group ($\chi^2(2)=6.778$, p=.034), being that these changes are only significant from baseline to post-intervention ($W_{(6)}=15.000$, Z=-2.032, p=.042). Only the experimental group obtained significant improvements over time in the attention domain, as assessed with a reduction of time in the Digit Cancellation test ($\chi^2(2)=9.333$, p=.009) and a reduction of errors in the Bells test ($\chi^2(2)=7.182$, p=.028). However, according to the Wilcoxon's test, these differences are again only significant from baseline to post-intervention in both Digit Cancellation ($W_{(6)}=.000$, Z=-2.060, p=.039) and Bells ($W_{(6)}=.000$, Z=-2.032, p=.042) tests.

3.2 How effective is motor training with Reh@Task as compared to conventional rehabilitation?

Both groups improved quantitatively from baseline to post-intervention and follow-up in all the motor and functional assessment instruments (Table 3).

Table 3. *Fugl-Meyer (FM), Motricity Index (MI), Modified Ashworth Scale (AS), Barthel Index (BI) and Chedoke Arm and Hand Activity Inventory (CAHAI) scores at baseline, post-intervention and follow up.*

	Experimental			**Control**		
	Baseline	Post-intervention	Follow-up	Baseline	Post-intervention	Follow-up
FM	23 (17.50-52.25)	30.5 (22.25-52.25)	30.5 (22.25-53)	45.5 (43-50.5)	49.5 (44.5-52.75)	49.5 (45-63.75)*
MI	35 (30-77)	48 (36.5-77)	54.5 (39-79)	61 (56-69.75)	67 (59.75-78.75)	70 (65.5-78.75)*
AS	2.5 (1.88-3)	2 (1.38-3)	2 (1-3)	1.5 (1.38-2)	1.5 (1.38-1.5)	1 (1-1.5)*
BI	90 (63.75-96.25)	92.50 (63.75-100)	92.5 (65-100)	92.5 (51.25-100)	92.5 (51.25-100)	92.5 (51.25-100)
CAHAI	37 (30.25-74.5)	37 (34.25-75.25)	37 (34.25-75.25)	54.50 (42.75-61.25)	58.5 (48.25-66.25)*	62.5 (53.25-68.5)*

Values are presented as medians (quartile 1 – quartile 3).

* Wilcoxon's T matched pairs signed ranks test significance p <.05.

Considering the CAHAI functional assessment of the recovery of the arm and hand after stroke, we observe significant improvements over time in both experimental ($\chi^2(2)=6.000$, p=.050) and control ($\chi^2(2)=11.273$, p=.004) groups. Wilcoxon's pairwise comparison reveals that these differences are significant from baseline to post-intervention ($W_{(6)}=21.000$, Z=-2.226, p=.026) and to follow-up ($W_{(6)}=21.000$, Z=-2.207, p=.027) for the control group, but not for the experimental group. Only the control group had significant over time changes in upper-limb impairments, as assessed with the Fugl-Meyer ($\chi^2(2)=8.375$, p=.015), the Motricity Index ($\chi^2(2)=8.000$, p=.018) and the Modified Ashworth Scale ($\chi^2(2)=7.600$, p=.022). Pairwise comparisons were only significant from baseline to follow-up (FM: $W_{(6)}=15.000$, Z=-2.060, p=.039; MI: $W_{(6)}=15.000$, Z=-2.032, p=.042; AS: $W_{(6)}=21.000$, Z=-2.207, p=.027). In the case of independence in ADL's, there were no significant changes in the Barthel score for any of the groups.

4. CONCLUSIONS

Here we presented a VR cognitive and motor training task and the preliminary results of twelve patients from an ongoing one-month longitudinal intervention. During the experiment, all 12 patients underwent conventional occupational therapy rehabilitation, which mostly involves motor training and disregards cognitive aspects, but only the experimental group had specific attention and memory training with the Reh@Task. Experimental and conventional rehabilitation groups revealed improvements in the MoCA scores, although our data reveals that only Reh@Task participants improved significantly in the domains specifically trained by the VR task: attention and memory. The control group, despite improving in overall MoCA scores, did not present any specific improvements in any subdomain.

With respect to the motor component, both groups improved significantly in the functional recovery of the hand and arm scores assessed by the CAHAI, revealing that both the Reh@Task and conventional methodologies had an impact in the use of the hand and arm in the ADL's. Nevertheless, overall, the control group showed higher improvements. Improvements measured in Fugl-Meyer and CAHAI did not translate to an increased independence in ADL's, as assessed by the Barthel Index. This result may be explained by the fact that the Barthel Index is known to suffer ceiling effects (Quinn, Langhorne, & Stott, 2011). Improvements in the Fugl-Meyer, the Motricity Index and the Modified Ashworth Scale scores were only measurable in the control group. This might be due to the fact that the control intervention targeted a more generalized motor rehabilitation (occupational therapy based), whereas the Reh@Task system only targeted reaching movements of the hemi paretic arm.

To summarize, this work is part of an ongoing study that intends to include 40 participants, 20 per group. Despite the small sample size so far, our data suggests that both interventions have a positive impact in both motor and cognitive domains. In the cognitive domain, Reh@Task may have more impact in cognition, namely in the domains it directly addressed, memory and attention. In the motor domain, greater improvements are seen in the control condition. As a consequence of the reduced size of the sample, we have heterogeneous groups, with some differences between them concerning age, number of months post-stroke, as well as the Fugl-Meyer and Motricity Index scores at baseline. Although these differences are important and may have an impact in the results, they are not statistically significant. The increase of the sample size is expected to diminish these differences between groups and its impact in the final results.

These preliminary results are supportive of the viability of low-cost rehabilitation solutions that combine motor and cognitive training, such as the Reh@Task, that can be effective tools to address cognitive training in an integrative manner and can be easily deployed at home or at the clinic. Evidence that treatment effectiveness may improve by integrating cognitive and motor rehabilitation is increasing but more research is needed to identify how severity of deficits, chronicity and intervention delivery impact this association. Further research in this area is essential in order to provide more targeted interventions.

Trial registration: This trial was not registered because it is a small sample study that evaluates the clinical validity of a prototype virtual reality system.

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