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Ana Lúcia dos Santos Faria

DEVELOPMENT AND CLINICAL VALIDATION OF INTERACTIVE TECHNOLOGIES FOR COGNITIVE REHABILITATION OF STROKE PATIENTS

Doctoral thesis in Psychology, speciality in Rehabilitation, supervised by Professor Doctor Sergi Bermúdez i Badia and by Professor Doctor Maria Salomé Estima Pinho and presented to Faculdade de Psicologia e de Ciências da Educação da Universidade de Coimbra.

January of 2020

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Doctoral Thesis

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Aos meus pais Jaime e Jovita
Às minhas irmãs Luísa e Margarida
Ao meu marido Sérgio
Ao meu filho Salvador e à minha filha Laura Benedita

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Abstract

Cognitive impairments after stroke do not always receive sufficient attention, despite the limitations they impose in activities of daily living (ADL's). Cognitive rehabilitation methods mostly consist of paper-and-pencil tasks that target specific cognitive domains. Besides limited ecological validity, most interventions lack personalization, which may result in reduced effectiveness. Virtual Reality (VR) is a promising tool for the development of ecologically valid systems. Numerous tools were developed, but many lack clinical validation with Randomized Controlled Trials (RCT's). Also, similarly to paper-and-pencil approaches, VR lacks a theoretical framework for the selection and personalization of training content.

In this thesis, we present a framework for the design of personalized cognitive rehabilitation tasks based on a participatory design approach. We parameterized 11 paper-and-pencil tasks, which were assessed according to their cognitive demands (attention, memory, language and executive functions) by 20 rehabilitation professionals. Using computational modeling, we operationalized them and developed a web tool that generates personalized paper-and-pencil tasks – the Task Generator (TG). Clinical evaluation of the TG with 20 stroke patients showed that, by enabling the personalization of tasks' cognitive parameters according to patient assessment, this tool provides an adequate cognitive training.

Despite the positive impact of personalization, paper-and-pencil tasks are not fully accessible for most stroke patients whose dominant arm is paretic. As such, we developed a virtual cognitive-motor task, based on traditional cancelation tests (with numbers, letters and symbols) for attention and memory training, to be solved through adapted arm reaching movements: Reh@Task. The system progressively adjusts the difficulty according to patient performance, based on the personalization framework. In a one-month intervention with 24 stroke participants, we investigated the benefits of this integrative VR approach by comparing Reh@Task and conventional rehabilitation through 12 time-matched training sessions. Results showed that both groups improved in motor function, but Reh@Task displayed higher between-group outcomes in the arm assessment. Concerning the cognitive domain, improvements were similar in both groups, suggesting that the mere integration of cognitive and motor training is not enough to promote its efficacy.

We believe that Reh@Task lacks ecological validity to have a more significant impact on cognition and functionality. Hence, we developed Reh@City v1.0, a VR simulation where memory, attention, visuospatial abilities and executive functions tasks are integrated into the performance of several ADL's at the pharmacy, supermarket, bank and post-office. We performed a one-month RCT with 18 stroke participants, comparing Reh@City with conventional rehabilitation within 12 sessions time-matched intervention with pre and post neuropsychological assessment. Reh@City v1.0 group improved in global cognitive functioning, attention, memory, visuospatial abilities, executive functions, emotion and overall recovery, while the control group only improved in self-reported memory and social participation. Between groups, VR was also superior to conventional rehabilitation in global cognitive functioning, attention and executive functions, suggesting that Reh@City v1.0, an ADL's simulation, has more impact in cognitive rehabilitation than conventional methods.

Both Reh@Task and Reh@City v1.0 were compared with non-equivalent interventions, that is, occupational therapy (OT), the conventional treatment offered by the health service. However, these tools should be compared with clinically accepted paper-and-pencil tasks, the gold standard in cognitive rehabilitation. Hence, we developed Reh@City v2.0 with the same task contents and using the same personalization framework as for TG. We performed an RCT with 42 stroke participants comparing time-matched paper-and-pencil training (TG) with content equivalent ADL's simulations tasks at the pharmacy, supermarket, bank, post-office, fashion store, park, magazine kiosk and home (Reh@City); also having a control group of patients undergoing OT. All participants underwent a pre and post neuropsychological assessment; Reh@City and TG groups were also assessed at follow-up. According to results, training with Reh@City v2.0 had a positive impact in general cognitive functioning, attention, visuospatial ability and executive functioning, verbal memory, and processing speed, which generalized to the participants' self-perceived impact of cognitive deficits in ADL's. This generalization did not happen in the TG group that only revealed an impact on orientation, processing speed and verbal memory. TG intervention sustained impact at follow-up, maintaining processing speed and verbal memory gains, with new improvement in language. OT was shown to be an insufficient intervention for cognitive deficits after stroke, with no significant improvements in our outcome measures. Between-groups, Reh@City v2.0 was superior in general cognitive functioning, visuospatial ability and executive functioning. Additionally, we performed an analysis of the participants' performance, both in TG and Reh@City v2.0, during the 12 RCT training sessions and found that both groups performed at the same level and there was not an effect of the training methodology, paper-and-pencil or VR, in overall performance. Still, Reh@City v2.0 offered more intensive training leading to more task repetitions and greater difficulty adaptation progression, which resulted in more cognitive improvements.

KEYWORDS: *cognitive rehabilitation, stroke, virtual reality, paper-and-pencil tests, ecological validity.*

Resumo

Os défices cognitivos pós Acidente Vascular Cerebral (AVC) nem sempre recebem atenção, apesar das limitações no desempenho das atividades de vida diária (AVDs). As metodologias de reabilitação cognitiva consistem principalmente em tarefas de papel-e-lápis para treino de domínios específicos. Além de validade ecológica limitada, a maior parte das intervenções carece de personalização, o que pode limitar a sua eficácia. A Realidade Virtual (RV) é uma ferramenta promissora para o desenvolvimento de sistemas com validade ecológica. Muitos sistemas têm sido desenvolvidos, mas a maioria não tem validação clínica com estudos controlados e randomizados. Além disso, tal como as metodologias papel-e-lápis, a RV necessita de uma estrutura teórica que fundamente a seleção e personalização de tarefas de treino cognitivo.

Nesta tese, apresentamos uma abordagem baseada num *design* participativo para o desenvolvimento de tarefas personalizadas de reabilitação cognitiva. Parametrizamos 11 tarefas papel-e-lápis, avaliadas segundo as suas exigências cognitivas (atenção, memória, linguagem e funções executivas) por 20 profissionais de reabilitação. Através de uma análise estatística baseada em modelos computacionais, desenvolvemos uma ferramenta *Web* capaz de gerar tarefas papel-e-lápis personalizadas - o *Task Generator* (TG). Uma avaliação clínica do TG com 20 pessoas com AVC mostrou que, ao personalizar os parâmetros cognitivos de acordo com a avaliação do paciente, o TG permite um treino adequado.

Apesar do impacto positivo da personalização, as tarefas papel-e-lápis não são acessíveis aos pacientes cujo braço dominante esteja parético. Assim, desenvolvemos um sistema cognitivo-motor em RV, baseado em testes de cancelamento (com números, letras e símbolos) para treino de atenção e memória através de movimentos de braço: a Reh@Task. O sistema ajusta progressivamente a dificuldade de acordo com o desempenho, com base nos parâmetros de personalização. Numa intervenção de um mês com 24 participantes pós-AVC, investigámos os benefícios desta ferramenta de treino integrado, comparando-a com reabilitação convencional ao longo de 12 sessões, de frequência e duração equivalente. Os resultados demonstraram que ambos os grupos melhoraram na função motora, mas o grupo Reh@Task apresentou melhores resultados na avaliação do braço. Relativamente ao domínio cognitivo, as melhorias foram semelhantes nos dois grupos, sugerindo que a simples integração do treino cognitivo e motor é insuficiente para aumentar a eficácia.

A Reh@Task não tem validade ecológica e, como consequência, tem impacto limitado nos domínios cognitivo e funcional. Assim, desenvolvemos a Reh@City v1.0, uma simulação em RV em que tarefas de memória, atenção, capacidades visuoespaciais e funções executivas são integradas em várias AVD's na farmácia, supermercado, banco e correios. Realizámos um estudo controlado e randomizado de um mês com 18 participantes pós-AVC, comparando a Reh@City v1.0 com reabilitação convencional, numa intervenção de 12 sessões, equivalentes na frequência e duração, com avaliação neuropsicológica pré e pós-intervenção. O grupo Reh@City v1.0 melhorou no funcionamento cognitivo global, atenção, memória, capacidades visuoespaciais, funções executivas, emoção e recuperação geral, enquanto o grupo de controlo melhorou apenas na memória auto-reportada e participação social. Entre grupos, a RV foi também superior no funcionamento cognitivo global, atenção e funções executivas, sugerindo que a Reh@City v1.0 tem mais impacto que as metodologias tradicionais.

Ambas Reh@Task e Reh@City v1.0 foram comparadas com intervenções não equivalentes, ou seja, terapia ocupacional (TO), que é o tratamento oferecido pelo serviço de saúde. No entanto, estas ferramentas deveriam ser comparadas com tarefas de papel-e-lápis, que são a referência em reabilitação cognitiva. Neste contexto, desenvolvemos a Reh@City v2.0 com o mesmo conteúdo de tarefas e com a mesma personalização dos parâmetros cognitivos que o TG. Realizámos um estudo controlado e randomizado com 42 pessoas com AVC, comparando uma intervenção, equivalente em frequência e duração, em papel-e-lápis (TG) com tarefas equivalentes em simulação de AVDs na farmácia, no supermercado, no banco, nos correios, na loja de moda, no parque, no quiosque de revistas e em casa (Reh@City v2.0); tendo também um grupo de controlo de pacientes a fazer TO. Todos os participantes realizaram uma avaliação neuropsicológica pré e pós-intervenção, os grupos Reh@City v2.0 e TG também realizaram uma avaliação de seguimento. De acordo com os resultados, o treino com a Reh@City v2.0 teve impacto positivo no funcionamento cognitivo geral, atenção, capacidade visuoespacial e funcionamento executivo, memória verbal e velocidade de processamento, que se generalizou para o impacto auto-percebido dos défices cognitivos nas AVDs. Esta generalização não se verificou no grupo TG que apenas revelou ganhos na orientação, velocidade de processamento e memória verbal. A intervenção através do TG teve maior impacto na avaliação de seguimento, mantendo os ganhos na velocidade de processamento e na memória verbal, com ganho adicional na linguagem. A TO revelou-se uma intervenção insuficiente, sem ganhos significativos em nenhuma das medidas. Entre grupos, a Reh@City v2.0 foi superior no funcionamento cognitivo geral, capacidade visuoespacial e funcionamento executivo. Adicionalmente, analisámos o desempenho, no TG e na Reh@City v2.0, durante as 12 sessões da intervenção e concluímos que ambos os grupos tiveram o mesmo nível de desempenho, não havendo um efeito da metodologia de treino utilizada no desempenho geral. No entanto, a Reh@City v2.0 possibilitou um treino mais intensivo, permitindo mais repetições de tarefas e, consequentemente, maior progressão na dificuldade ao longo da intervenção, resultando em maior impacto cognitivo.

PALAVRAS-CHAVE: reabilitação cognitiva, acidente vascular cerebral, realidade virtual, testes de papel-e-lápis, validade ecológica.

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PART I: Design and Development

PART II: Clinical Validation

Brief presentation of the thesis

This thesis includes a set of scientific papers and communications and is organized in two main parts: Part I refers to the design process of a cognitive rehabilitation framework for the development of cognitive training tools, and Part II includes publications on clinical validation studies of the developed cognitive training tools. All the articles are published with the exception of the one presented in Chapter 5 ("*A comparison of two personalization and adaptive cognitive rehabilitation approaches with treatment as usual: a randomized controlled trial with chronic stroke patients"*), which is submitted. A brief overview of each chapter is presented in the introduction under the title "Cognitive rehabilitation: from paper-and-pencil tasks to information and communication technologies". Given the diversity of the presented studies outcomes, although they are complementary, this thesis includes a brief discussion on results and limitations at its end, with the intent of drawing some conclusions regarding the potentialities and limits of the present research.

Introduction

The problem

Stroke is one of the leading causes of disability in Europe, and projections indicate that if an action plan is not defined and we keep following the same current approaches, the burden of stroke will not diminish (Feigin, Norrving, & Mensah, 2017). Although there are better prevention and treatment healthcare strategies, between 2017 and 2050 there should be an increase of 35% of older people in Europe, which raises the number of people at risk of having a stroke (Norrving et al., 2018). Approximatelly, half of post-stroke survivors stay physically dependent (Campos et al., 2017) with levels of cognitive impairment that are worrying at 6 months post-stroke (Mellon et al., 2015), since they are associated with a poorer quality of life and increased likelihood to develop dementia (Dichgans et al., 2019).

Historically, stroke rehabilitation has been focused on motor rehabilitation with strong evidence concerning improvements after physical rehabilitation (Hatem et al., 2016). However, for a long time, strategies for cognitive impairments have received significantly less consideration resulting on limited data on its effectiveness (Cicerone et al., 2005; Cicerone et al., 2011; Heugten, Gregório, & Wade, 2012; Rogers, Foord, Stolwyk, Wong, & Wilson, 2018). Only in the last few years, attention to cognitive deficits impact started to grow (Andrew et al., 2014) and investigating ways to improve cognition after stroke was considered a research priority at the United Kingdom in 2014 (Pollock, St George, Fenton, & Firkins, 2014). More recently, the International Stroke Recovery and Rehabilitation Alliance 2018 working group has also indentified post-stroke cognitive impairments as a priority area for research (Bernhardt et al., 2019).

In this context, the main goal of our work is to address some limitations of existing cognitive rehabilitation strategies and build on the current knowledge to create a new framework that enables the development of clinically effective and validated cognitive rehabilitation tools.

Cognitive rehabilitation: from paper-and-pencil tasks to information and communication technologies

Paper-and-pencil tasks remain widely used in the context of cognitive rehabilitation because of their clinical validity, reduced cost and ease of use (Parsons, 2016). In the last years, computer-based versions of these traditional tasks are also starting to become clinically accepted (Solana et al., 2015; Tedim Cruz et al., 2014). However, there is an absence of guidelines that inform the health professional which tasks to apply and under what circumstances (Gracey & Wilson, 2013). Consequently, many of the training tasks used by practitioners of cognitive rehabilitation to restore cognitive or functional abilities owe more to a dogmatic belief that the methods work than to any scientific framework which links the training task to a cognitive theory of information processing (Wood & Fussey, 2018). In this endeavor, it would be useful to have a tool that could generate standardized paper-and-pencil tasks, parameterized according to patients' cognitive profile.

Objective 1: Propose a systematic and objective design framework for the development of training tasks capable of addressing multiple domains of cognitive functioning.

In this thesis, an objective and quantitative framework for the creation of personalized cognitive rehabilitation tasks based on a participatory design strategy with health professionals is proposed. Chapter 1, entitled *Capturing expert knowledge for the personalization of cognitive rehabilitation: study combining computational modeling and a participatory design strategy*, describes the framework design process in which a set of 11 paper-and-pencil tasks from standard clinical practice are parameterized with multiple configurations and then assessed according to their cognitive demands (attention, memory, language, and executive functions), and overall difficulty by 20 rehabilitation professionals. Through computational modeling, parameters that significantly affected cognitive functions were identified, and specific models for each task were proposed. Then, the intrinsic parameters of each task were operationalized to develop a Web tool that could generate personalized paper-and-pencil tasks - the Task Generator (TG) (Faria, Pinho, & Bermúdez i Badia, 2018) (Figure 1).

Chapter 2, entitled *Personalizing paper-and-pencil training for cognitive rehabilitation: a feasibility study with a web-based Task Generator*, presents a feasibility study of the TG with 20 stroke patients. The main objective was to validate the adaptation models provided by the framework to personalize the TG cognitive parameters. This was an essential step before performing a longitudinal intervention study with the TG. Indeed, results showed that, by enabling the adaptation of TG cognitive parameters according to patient cognitive screening assessment, this tool provides an optimal cognitive training (Faria & Bermúdez i Badia, 2015; Faria & Bermúdez i Badia, 2018).

The NeuroRehabLab Task Generator is a software that has been developed with the collaboration of over 20 health professionals that uses computational models of cognitive function to deliver a highly personalized training to each individual. The tasks created with the NeuroRehabLab Task Generator are generated procedurally, that is, they are always different every time they are created.

Special thanks to Simone Tieri and Francesco Semprebon for the italian translation.

If you use this software please cite this reference: Faria, A.L., & Bermúdez i Badia, S. (2015). Development and evaluation of a web-based cognitive task generator for personalized cognitive training: a proof of concept study with stroke patients. In REHAB 2015: 3rd Workshop on ICTs for improving Patients Research Techniques Proceedings. Lisbon, Portugal. ACM.

Figure 1: Task Generator web application.

Objective 2. Bridging cognitive paper-and-pencil tasks with virtual tasks according to the established framework guidelines, delivering a highly adapted cognitive and motor intervention.

Although an intervention with the TG can be personalized and adapted, there is still a need to find complementary strategies since rehabilitation based on paper-and-pencil tasks has been shown to have a limited transfer to performance in activities of daily living (ADL) (Parsons, 2016). Over the last years, rehabilitation methodologies based on virtual reality (VR) have been developed as promising solutions to improve cognitive functions (Luca et al., 2018; Maggio et al., 2019). Virtual Rehabilitation has been described as *"a group of all forms of clinical intervention (physical, occupational, cognitive, or psychological) that are based on, or augmented by, the use of VR, augmented reality and computing technology"* (Tieri, Morone, Paolucci, & Iosa, 2018, p. 6). VR-based tools have shown potential and to be ideal environments to incorporate cognitive tasks within the simulation of ADL's (Faria, Andrade, Soares, & Badia, 2016), also allowing the integration of motor training. Recent studies found evidence supporting the interaction between motor and cognitive function in stroke patients undergoing VR (Faria, Vourvopoulos, Cameirão, Fernandes, & Bermúdez i Badia, 2014; Hagovska & Nagyova, 2016; Kizony, Katz, & Weiss, 2004; Subramanian, Chilingaryan, Levin, & Sveistrup, 2015). Yet, there is still an insufficient number of rigorous trials to clinically validate these methods (Aminov et al., 2018), which together with the difficulties in adopting new technologies (WHO, 2011), limits their adoption by health professionals who still prefer paper-and-pencil interventions.

In chapter 3, titled *Combined cognitive-motor rehabilitation in virtual reality improves motor outcomes in chronic stroke - a pilot study*, a randomized controlled trial (RCT) with chronic stroke patients using the Reh@Task for cognitive and motor rehabilitation is presented. The Reh@Task is based on traditional cancelation tests for the training of attention. Targets and distractors incorporate numbers, letters and symbols, colored or black and white. The Reh@Task also involves memory training and progressive difficulty adjustment according to the patient performance. The task consists on finding target elements within a pool of distractors (Figure 2). In the memory variant, the targets need to be memorized and then are hidden during target selection. There are a total of 120 difficulty levels that were defined through the quantitative guidelines extracted from the previously presented framework (Faria, Cameirão, et al., 2018). In this empirical study, we investigated the feasibility of using this virtual cognitive-motor task, which combines adapted arm reaching, attention and memory training, for stroke recovery. Both experimental (*N* = 12) and control (*N* = 12) groups were enrolled in conventional occupational therapy. Additionally, the VR group underwent training with the Reh@Task and the control group performed time-matched conventional occupational therapy. Motor and cognitive abilities were assessed at baseline; end of treatment and at a 1-month follow-up. Results revealed that both groups improved in motor function over time, but the Reh@Task group displayed significantly higher between-group outcomes in the arm assessment, and improvements in cognitive function were significant and similar in both groups. Overall, these results are supportive of the feasibility of VR tools that combine both motor and cognitive training (Faria, Cameirão, et al., 2018). However, training with the Reh@Task is not substantially better than ocuppational therapy, possibly because its tasks lack ecological validity, and consequently less transfer for activities of daily living.

Figure 2: Reh@Task. In the attention variant the patient needs to find target elements within a pool of distractors.

Objective 3: Design and clinically validate a set of virtual reality tasks, related with the ADL's, and targeting the training of memory, attention, executive functions, and language, with increasing levels of difficulty and cognitive demands.

In general, existing ecologically valid VR-based environments are simulations of cities since this context allows the recreation of different locations and tasks requiring the use of multiple cognitive abilities. For instance, Gamito et al. (2017) developed a small town populated with several buildings, a two-room apartment and a mini-market. The authors associated particular everyday life activities simulations to specific cognitive training domains, as for instance: buying several items for working memory training; finding the way to the minimarket as a visuospatial orientation task; finding a virtual character dressed in yellow as a selective attention exercise; recognition of outdoor advertisements as a recognition memory task; and digit retention for calculation purposes. These training tasks are presented through a head mounted display with gradually increasing memory and attention demands from session to session. The authors performed an RCT involving 20 stroke patients, and results evidenced significant improvements in attention and memory only in the VR group (Gamito et al., 2017).

With a focus on executive functioning, Jovanovski et al. (2012) evaluated the convergent validity between the Multitasking in the City Test (MCT) and standardized clinical tests of executive function in a sample of 11 individuals with stroke and two individuals with traumatic brain injury (TBI). The MCT dsimulates several locations as: a post office, a drug store, a stationery store, a coffee shop, a grocery store, an optometrist's office, a doctor's office, a restaurant and a pub, a bank, a dry cleaner, a pet store, and the participant's home. This virtual environment is displayed in a computer monitor to be used with a joystick and participants have to purchase several items, obtain money from the bank, and attend a doctor's appointment within 15 minutes. In comparison with a group of 30 healthy participants, the clinical sample created better plans but accomplished fewer tasks on the MCT. Both patients and healthy participants made similar types of errors, though some of them where more frequent in the clinical sample. This study corroborated the MCT ecological validity finding moderate to high correlations between its' performance and executive and nonexecutive tests. Additionally, authors suggested that patients and healthy individuals could be differentiated through quantitative (i.e., number of errors) aspects of performance (Jovanovski et al., 2012).

Intending to develop a personalized rehabilitation tool for global cognitive functions based on simulated ADL's, Klinger et al. (2013) developed the AGATHE, a virtual city interfaced with a gamepad and a Kinect where participants need to solve topographic tasks, post mail, and do the groceries. A usability study with 15 therapists and 13 individuals with stroke showed positive results regarding both populations: therapists succeeded in customizing the experience to patient functioning and needs, and patients invested themselves in the attractive and rewarding tasks (Klinger et al., 2013).

Finally, Claessen et al. (2016) compared spatial navigation in the real world and a virtual city. A sample of 68 individuals with stroke and 44 healthy subjects participated in a validation study where they were required to navigate within a real and an existing virtual city along a route that contained 11 decision points. According to the authors' results, real-world and virtual performance on route knowledge subtasks was moderately correlated, which suggests that virtual navigation testing could be a valid alternative to real-world navigation testing (Claessen, Visser-Meily, Rooij, Postma, & Ham, 2016).

The need for ecologically valid rehabilitation tools has led to the development of several VR systems. Although with positive results, most studies lack control groups for comparison, and to our best knowledge there is only one RCT demonstrating clinical impact (Gamito et al., 2017). Larger clinical samples and the inclusion of functionality outcome measures are still lacking. Chapter 4, titled *Benefits of virtual reality based cognitive rehabilitation through simulated activities of daily living: a randomized controlled trial with stroke patients*, presents the Reh@City v1.0, a virtual simulation of a city where memory, attention, visuospatial abilities, and executive functions tasks are integrated into the performance of several daily routines: shopping at the supermarket and pharmacy, navigation in the street, going to the post office and to the bank (Figure 3).

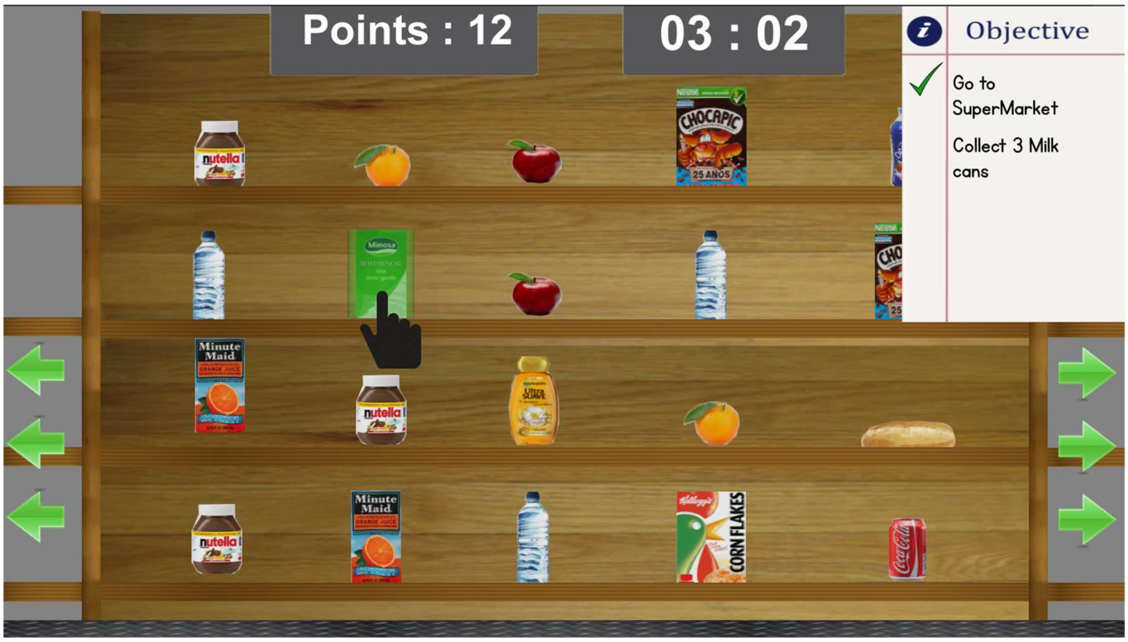

Figure 3: Reh@City v1.0 supermarket task inspired in the cancellation paper-and-pencil task with targets to be selected among distractors.

In this chapter a one-month RCT with 18 stroke in and outpatients from two rehabilitation units: 9 performing a VR-based intervention with the Reh@City and 9 performing conventional rehabilitation is described. The VR intervention had levels of difficulty progression through a method of fading cues (Riley & Heaton, 2000), and patients interacted with the virtual environment through a joystick. There was a pre and post-intervention assessment in both groups and results revealed significant improvements in global cognitive functioning, attention, memory, visuospatial abilities, executive functions, emotion and overall recovery in the VR group. The control group only improved self-reported memory and social participation. Concerning the between groups analysis, the VR group demonstrated significantly higher improvements in global cognitive functioning, attention and executive functions, when compared to conventional therapy. According to this RCT results, cognitive rehabilitation through an ecologically valid VR simulation for the training of ADL's - the Reh@City - had more impact than conventional methods (Faria, Andrade, et al., 2016).

However, results of this study are limited since the control intervention was not equivalent but planned and delivered according to health professionals' clinical experience, which involves a large variety of tasks with uncontrolled difficulty levels and cognitive demands.

Moreover, in this study, cognitive impact after stroke was only assessed through the Memory, Emotion and Communication domains from the Stroke Impact Scale 3.0 (Vellone et al., 2015). Subsequently, we realized the need foroutcome measures to explore the self-perceived impact of cognitive problems in order to measure the effectiveness of our intervention. In the search for such outcome measures, we have identified the Patient Reported Evaluation of Cognitive State (PRECiS) (Patchick, Vail, Wood, & Bowen, 2015) as a potentially useful one. In order to include this instrument in prospective studies, we have asked the authors permission to translate PRECiS from English to European Portuguese using the World Health Organization translation method (WHO, 2010). This work was accomplished, and the PRECiS Portuguese version (Faria, Alegria, Pinho, & Bermúdez i Badia, 2018) is currently freely available at "www.click2go.umip.com/i/coa/precis_pt.html" and is part of the neuropsychological assessment protocol described at Chapter 5.

Objective 4: Assess the clinical efficacy of a personalized ecologically valid virtual reality cognitive intervention in comparison to an equivalent paper-and-pencil intervention and a treatment as usual.

In chapter 5, titled *A comparison of two personalization and adaptive cognitive rehabilitation approaches with treatment as usual: a randomized controlled trial with chronic stroke patients*, we address an important limitation in the validation of VR-based cognitive rehabilitation tools: the equivalence of the training content in the intervention impact comparison. The personalization and adaptation framework that was used for the creation of the TG was implemented in an improved version of Reh@City v1.0. Besides its similarity with TG content, Reh@City v2.0 tasks are to be accomplished through paretic arm movements, as in the Reh@Task, providing an integrative cognitive and motor training (Figure 4). In this chapter, we analyse two content equivalent rehabilitation tools developed under the same personalization and adaptation framework: the TG and the Reh@City v2.0, that are compared with the main objective of identifying the specific impact of an ecologically valid VR system over a clinically accepted paper-and-pencil equivalent. In a three-group RCT of 42 participants, 14 were allocated to Reh@City v2.0, 18 to TG and 10 to occupational therapy (OT), the treatment as usual (TAU) offered by the public health service. All participants performed twelve sessions of time-matched training with pre and post-intervention neuropsychological assessment. Additionally, both Reh@City v2.0 and TG groups went through a 2-month follow-up assessment. Results of the one-month longitudinal study have shown a positive impact of a rehabilitation training with the Reh@City v2.0 in general cognitive functioning, visuospatial ability and executive functioning, attention, verbal memory, processing speed, and self-perceived impact of cognitive deficits. The impact was smaller in the paper-and-pencil group that only revealed similar cognitive improvement in the orientation, processing speed and verbal memory domains. The TG intervention sustained impact at follow-up, maintaining processing speed and verbal memory improvements, with a new one in language. TAU was shown to be an insufficient intervention for cognitive deficits after stroke with no significant improvements in none of the outcome measures. Finally, by comparing interventions between themselves, we have found Reh@City v2.0 to be superior in general cognitive functioning, visuospatial ability and executive functioning. Although the intervention with paper-and-pencil allowed cognitive gains to last over time, these need to be considered with caution given the dropout at follow-up. Further, training with the ecologically valid VR ADL simulations had a more far-reaching impact with improvements in cognition and self-perceived cognitive deficits impact in everyday life.

Figure 4: Reh@City v2.0 setting the table task inspired in the action sequencing paper-and-pencil task with the virtual representation of the paretic arm.

Finally, in chapter 6, titled *Comparing adaptive cognitive training in virtual reality and paper-and-pencil tasks in a sample of stroke patients*, both TG and Reh@City v2.0 performance data from the previous intervention are analyzed, in order to understand: if paper-and-pencil and VR training performances are equivalent, if performance is modulated by the difficulty adaptation or the training methodology, and which training method is more intensive. Findings of this analysis support that, despite the differences in task implementations, both groups performed at the same level and there was not an effect of the training methodology in overall performance. Moreover, our results contribute with new evidence about the impact of using adaptation in VR simulations of ADL's in the rehabilitation of cognitive deficits, instead of paper-and-pencil tasks. The Reh@City v2.0 offered more intensive training leading to more task repetitions and higher difficulty adaptation progression, which might be translated in more cognitive improvements (Faria, Paulino, & Bermúdez i Badia, 2019).

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1. Capturing expert knowledge for the personalization of cognitive rehabilitation: study combining computational modeling and a participatory design strategy [1, 2]

Abstract

Background: Cognitive impairments after stroke are not always given sufficient attention despite the critical limitations they impose on activities of daily living (ADLs). Although there is substantial evidence on cognitive rehabilitation benefits, its implementation is limited because of time and human resource's demands. Moreover, many cognitive rehabilitation interventions lack a robust theoretical framework in the selection of paper-and-pencil tasks by the clinicians. In this endeavor, it would be useful to have a tool that could generate standardized paper-and-pencil tasks, parameterized according to patients' needs.

Objective: In this study, we aimed to present a framework for the creation of personalized cognitive rehabilitation tasks based on a participatory design strategy.

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[1] Faria, A. L., Pinho, M. S., & i Badia, S. B. (2018). Capturing expert knowledge for the personalization of cognitive rehabilitation: Study combining computational modeling and a participatory design strategy. *Journal of Medical Internet Research: Rehabilitation and Assistive Technologies*, *5*(2), e10714. doi:10.2196/10714

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Methods: We selected 11 paper-and-pencil tasks from standard clinical practice and parameterized them with multiple configurations. A total of 67 tasks were assessed according to their cognitive demands (attention, memory, language, and executive functions) and overall difficulty by 20 rehabilitation professionals.

Results: After assessing the internal consistency of the data—that is, *alpha* values from .918 to .997—we identified the parameters that significantly affected cognitive functions and proposed specific models for each task. Through computational modeling, we operationalized the tasks into their intrinsic parameters and developed a Web tool that generates personalized paper-and-pencil tasks—the Task Generator (TG).

Conclusions: Our framework proposes an objective and quantitative personalization strategy tailored to each patient in multiple cognitive domains (attention, memory, language, and executive functions) derived from expert knowledge and materialized in the TG app, a cognitive rehabilitation Web tool.

Keywords: stroke rehabilitation; attention; memory; executive function; language; cognition; community-based participatory research; patient-specific modeling.

Introduction

Background

Stroke is one of the most common causes of adult disability, and because of the aging of the population, the number of people having a stroke continues to rise. According to the 2015 Global Burden of Disease study, the total number of stroke events in Europe is predicted to increase by 34% between 2015 and 2035. This increasing number of people living with the effects of stroke results in a growing burden on families, societies, and health care systems. Reducing the long-term disability will help to bring down these costs [1].

Cognitive and Motor Impairments After Stroke

Poststroke impairments impact the individual's ability to safely and independently carry out activities of daily living (ADLs) and to restart prestroke personal, social, and vocational activities. Stroke survivors often express that they feel like a different person, not because of the typical motor sequels but because of changes they suffer in cognitive functions underlying their capacity for language, attention, executive functions, and memory [2].

Currently, rehabilitation following stroke routinely takes a bottom-up approach, with the primary focus placed on motor gait retraining, followed by upper limb rehabilitation and speech and language therapy [3]. Consequently, cognitive impairments are not always systematically assessed and treated. Moreover, current rehabilitation entails a high demand for human resources, making them time consuming and expensive. As a result, there is a high number of patients per therapist that makes it challenging to deliver a rehabilitation program with the appropriate intensity and training, hampering the recovery potential for some patients [4]. It is known that inappropriate cognitive rehabilitation limits patients' capacity of living independently. In fact, it has been shown that the level of cognitive impairment correlates with the length of inpatient stay and the number and frequency of referrals for outpatient and home therapies [5].

In a recent James Lind Alliance study, 799 stroke survivors were interviewed about their unmet needs following a stroke, and they reported problems with concentration (45%), memory (43%), and reading (23%) [6]. A high proportion felt that issues such as memory and concentration had not been addressed appropriately, especially when compared with other issues such as mobility. Similarly, when caregivers and health professionals were consulted, the main conclusion of the study was that investigating ways to improve cognition after stroke should be a research priority [7]. There is, therefore, an avoidable psychosocial and economic cost derived from the currently limited cognitive rehabilitation, which contributes to the patient's increased dependency on relatives, professionals, and health care systems and their premature placement at nursing homes [8].

Cognitive Rehabilitation and What Are We Missing?

Rehabilitation refers to the act of relearning a previously learned behavior that has been disrupted by brain damage. It involves re-establishing connection weights or synapses within the network, diverting the information by building new connection weights or synapses or activating the neurons that were not previously used [9]. Ben-Yishay and Prigatano defined cognitive rehabilitation as “the amelioration of deficits in problem-solving abilities to improve functional competence in everyday situations” [10]. The main point about this definition is the understanding that cognitive rehabilitation should focus on real-life functional problems. In rehabilitation, models and theories are useful to conceptualize processes and think about treatments. Especially, cognitive rehabilitation methodologies urge a comprehensive theoretical framework that incorporates theories and models from different fields. The working memory model [11], the dual route model of reading [12], and the face recognition model [13] are examples of models that helped planning treatment for people with cognitive impairments. Nevertheless, until now, there is no single model or integrative cognitive rehabilitation framework that addresses the multiple aspects of cognitive functions involved in real life [14].

Although paper-and-pencil tasks are reliable tools to assess multiple domains of cognitive functioning (specific task scores can be used to evaluate the capacities of a patient in multiple cognitive domains) [15], there are few solutions to the inverse problem: a set of paper-and-pencil tasks that are specifically adapted to the results of different assessments of cognitive functioning of a patient [16,17]. Cognitive rehabilitation approaches have been relatively successful for focal cortical deficits (eg, neglect and aphasia) but less so for more generalized cognitive impairment (eg, slowed information processing and executive dysfunction) [5]. Additional research is needed to investigate the patient characteristics that influence treatment effectiveness [18]. Consequently, cognitive rehabilitation is still mostly planned and delivered based on the experience of the health professional and based on a subjective selection of paper-and-pencil cognitive tasks or conventional games, which are generally not adjusted to or validated for the specific cognitive needs of the patient [19]. Although we know that stroke-related cognitive problems are weighted more toward attention executive dysfunction than memory dysfunction and that there are marked deficits in abstraction, executive function, and processing speed [20], the cognitive impairment profile of each patient is highly variable and depends on the characteristics of his lesion.

The Impact of Cognitive Rehabilitation on the Improvement of Cognitive Performance in Everyday Life

The American Congress of Rehabilitation Medicine conducted systematic reviews on a total of 370 studies about cognitive rehabilitation for people with traumatic brain injury (TBI) or stroke, published from 1971 through 2008 [21,22,18]. Cognitive rehabilitation was shown to be of greater benefit than conventional rehabilitation in 94.1% of the comparison studies. According to this evidence, there is a clear indication that cognitive rehabilitation is the best available form of treatment for people who exhibit cognitive impairments and functional limitations after TBI or stroke [18]. However, Paiva et al performed a meta-analysis on cognitive rehabilitation in stroke, and the results suggested a lack of sufficient evidence to support or refute the efficacy of cognitive interventions in stroke patients [23]. These divergent results should be interpreted with caution because in this meta-analysis, 504 of 507 studies were excluded because of low quality, and only 3 were considered by the authors. Additional research, using standardized assessment instruments and well-structured training programs, is needed to elucidate the mechanisms of change underlying the efficacy of cognitive rehabilitation.

The primary difficulty in determining the impact of cognitive interventions on the everyday functioning of healthy older adults is that most trials do not include functional outcome measures [24,25]. A review about the impact of cognitive training and mental stimulation on the cognitive and everyday functioning of healthy older adults from Kelly et al's study (2014) found only 2 studies that examined the effects of cognitive training on everyday function [26]. One of them concluded that 6 months of memory training did not significantly improve everyday functioning for older adults at a 2-year follow-up [27], and the other study similarly reported no training effects on everyday functioning after 6 weeks of memory, reasoning, or processing speed training at a 2-year follow-up [28]. Interestingly, the later authors conducted a 5-year follow-up and concluded that successful performance in everyday tasks is critically dependent on executive cognitive function [29], which is supported by prior research that shows that the ability to perform independent living skills is dependent on intact executive function [30].

Information and Communication Technologies

Over the past few years, several computer-based solutions have been proposed to increase the availability and quality of cognitive training, flooding the marketplace with commercial brain exercise programs that claim to improve cognition and have diagnostic abilities [31] such as the CogWeb [16,32,33] and the Guttmann Neuro Personal Trainer [34,35], for instance. There is also an increasing number of research projects focused in using a task modeling approach in poststroke rehabilitation, as the CogWatch, that developed intelligent common objects to help retraining Apraxia or action disorganization syndrome patients on how to carry out ADLs by providing persistent multimodal feedback to them [36]. Preliminary results involving 12 patients interacting with this system validated the ability of the system to assist stroke survivors in tea making. CogWatch was very beneficial to the patients who had difficulties performing the tasks alone, and when patients had access to the output retrieved by the system, their success rate was higher, and they made fewer errors than when they could not interact with the system.

Despite the proliferation of information and communication technologies (ICTs) in cognitive rehabilitation, only 5% to 15% of people with disabilities have access to technological devices that can assist in the rehabilitation process [37]. In addition, many health care providers are unfamiliar or uncomfortable with technology, and only about 27% of these professionals refer to use these computer-assisted technologies in their rehabilitation interventions [38]. Moreover, technological interventions are subject to continuous maintenance and technical support, eventually resulting in delayed interventions or the need to reschedule. Such complications speak to the challenges of implementing interventions dependent on technology within inpatient and outpatient rehabilitation settings. Any delays in these fast-paced settings, requiring the coordination of various professionals, can be disruptive [19].

To maximize the benefits of ICTs and to address the above-stated limitations, we developed a new Web-based tool, the Task Generator (TG). This Web tool capitalizes on the solid aspects of existing computerized training protocols for cognitive rehabilitation [17,32,39] and integrates existing theories and models [15]. The TG addresses multiple domains of cognitive functioning systematically and quantitatively, generating a profile of cognitive demands for each task and enabling the clinician to efficiently deliver a highly adapted training program to each patient's deficits. The TG ultimately generates paper-and-pencil training tasks, making its application low cost and compatible with the current practice and existing limitations of clinical settings, and at the same time, it integrates most of the essential advantages of ICT-based interventions.

Objectives

The objective of this research was to propose a systematic and objective design framework that can guide us on the methodology for the development of training tasks capable of addressing multiple domains of cognitive functioning, yet delivering a highly adaptive training program to each patient's assessed deficits, and showcase its use in a Web-based app for cognitive rehabilitation.

Methods

Development Process

We have based our methodology on a participatory design strategy involving rehabilitation experts interworking with the research and development team through interviews, meetings, and questionnaires. In Figure 1, we describe the process we followed to identify and develop a set of highly personalized cognitive training tasks for a specific clinical group, in this case, stroke patients. It involved 3 main participatory steps: task selection, modeling, and application. However, the process followed is not unique to stroke rehabilitation and generalizes to any application area and target group where personalization of training is of importance.

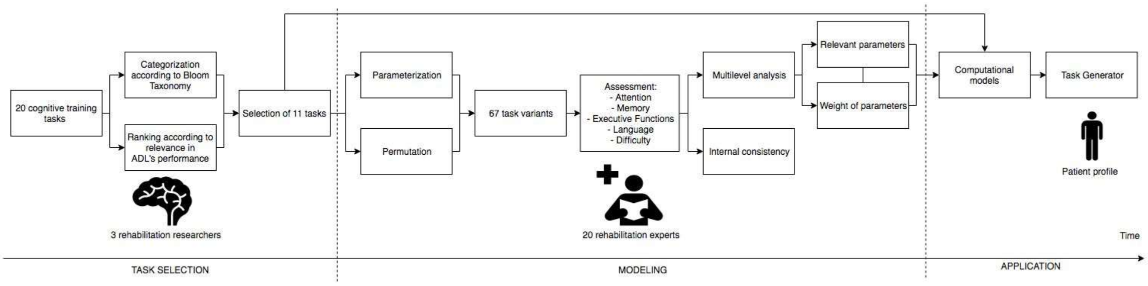


Figure 1. Methodology development process. ADLs: activities of daily living.

Task Selection

As a first step toward the creation of a repertoire of cognitive training tasks, 3 rehabilitation experts (2 neuropsychologists with experience in cognitive assessment and interventions in stroke and dementia and an experienced rehabilitation technology researcher) documented the currently used methodologies in clinical rehabilitation settings (public hospitals, private clinics, and senior houses) and collected the most commonly used training tasks, some of them being available as published training material [40]. Of this search, 20 distinct paper-and-pencil task types were identified and analyzed.

As stated previously, no clear or comprehensive cognitive rehabilitation framework can provide us with general guidelines for cognitive training task selection. In the education field, however, there are multiple frameworks, the Bloom Taxonomy is one of the most relevant ones [41]. Hence, we have chosen and categorized the 20 tasks according to Bloom learning objectives as described below:

- *Knowledge (lower level):* memory of stories; cancellation; questions of general knowledge; find locations; image pairs
- *Comprehension:* differences between similar scenarios; categorization; synonyms and antonyms; association
- *Application*: mazes; problem resolution; tangram; numeric sequences; navigation

- *Analysis*: action sequencing; visual memory; puzzles; word search
- *Evaluation (higher level)*: differentiation between coherent and incoherent situations; comprehension of contexts.

After the identification and organization of the 20 tasks according to their learning objectives, the 3 rehabilitation experts proceeded to a ranking of the 20 available cognitive tasks according to its relevance in the successful performance of ADLs. This *Task Selection* process, according to the learning objective's representativeness and the relevance for ADLs performance, resulted in the selection of the following 11 tasks: word search, problem resolution, numeric sequences, action sequencing, association, cancellation, categorization, comprehension of contexts, image pairs, mazes, and memory of stories.

Modeling

It is necessary to identify the relevant tasks to train a specific cognitive deficit (such as attention and memory) to define a proper rehabilitation program, but that is not sufficient. It is imperative also to consider the learner characteristics to design adapted training capable of providing as best as possible a personalized rehabilitation. In our case, the learners are stroke patients with different deficits that need to be rehabilitated through intensive and continuous training. There is then, no one-fits-all training program. There should be a uniquely adapted rehabilitation program for patients according to their assessment of the multiple domains of cognitive functioning. Currently, this adaptation process is generated through tacit knowledge based on the clinicians' subjective experience—which is essential and results from years of training—but there is no explicit formulation of such knowledge. This implicit knowledge is valid and necessary; however, to generalize, we should be able to transform it in a set of objective guidelines that support the personalization of training to the characteristics of each patient. To obtain such a set of guidelines and an objective way of operationalizing the adaptation in the different cognitive tasks, we followed a participatory design strategy with the main stakeholders.

Task Parameterization

This step had as primary objective to break down each of the 11 previously selected cognitive training tasks and identify their main parameters or variables to quantify their effects regarding demands in different domains of cognitive functioning. For that, we operationalized all tasks into their task parameters (independent variables; IVs) to study their demands in 4 cognitive domains (attention, memory, language, and executive functions) and for their overall difficulty (dependent variables; DVs). The breakdown of the tasks is as follows and is summarized in Table 1:

1. Word search: A predetermined number of words can be found up, down, forward, or diagonally in a pool of randomized letters. Words can overlap so that a letter can be part of 2 or

more words. This task was operationalized according to the *number of words* to find and the *existence of clues* provided to identify words (pictures, words, or none).

2. Problem Resolution: Here, *2 types of problems are presented*, numeric calculations or calculations based on a textual description of daily activities. Problems vary according to the *number of operations* involved and the use of numbers with *ones* or *tens*.

3. Numeric sequences: A numeric sequence is given as a finite sequence of numbers, and the subject must come up with the missing numbers. The task can be operationalized according to the number of *missing numbers* (*1, 2, or 3*) in the sequence, their *position* in the sequence, and the *step size* between numbers.

4. Action sequencing: In this task, a list of randomized steps needed for the execution of several ADLs is presented. The task can be defined by the *number of steps* to be ordered and whether the *goal* of the task is explicitly mentioned or must be guessed.

5. Association: The task comprehends a *number* of randomized pairs of items. These items need to be paired correctly according to a logical relationship between them.

6. Cancellation: The purpose of cancellation tasks is to find predetermined target stimulus in a pool of distractor stimulus. Thus, we operationalized this task according to the *type of stimulus* (letters, black or colored symbols, or numbers), the *pool size*, and their *arrangement* (randomly organized or in a grid structure).

7. Categorization: This task consists of organizing different items into their underlying categories. The names of the categories are not given, it must be guessed from the item's or object's relationships. The task can be defined according to the *number of categories* and the number of *items*.

8. Comprehension of contexts: In this task, some images are given with *some descriptions*, with some being *incorrect descriptions*.

9. Image pairs: In this task, *a number of pairs* of images are presented to be memorized. They are recalled after 30 min.

10. Mazes: The task consists of a labyrinth type of puzzle through which one must find the way out. The task can be operationalized according to the maze *size*.

11. Memory of stories: The task consists of recalling information about a read story or a pictorial scenario by answering questions about it. Stories can be textual or pictorial (*type*) and can have several descriptive elements (*size*) and a variable *number of questions*.

Table 1. List of training tasks, their objectives, and parameters subject to personalization.

Training task	Objective	Parameters
Word search	A number of words can be found up, down, forward, or diagonally in a pool of randomized letters	Words number; clue words; and clue pictures
Problem resolution	Two types of problems are presented, numeric calculations or calculations based on textual descriptions of daily activities.	Type; operations number; ones; and tens
Numeric sequences	A numeric sequence is given, and the subject has to come up with the missing numbers.	Step; ascending; and missing; position
Action sequencing	A list of randomized actions needed for the execution of several activities of daily living is presented.	Actions number and task goal
Association	A number of randomized pairs of items need to be paired correctly.	Pairs number
Cancellation	Find a target stimulus in a pool of distractors.	Distractors; letters; numbers; targets; and arrangement
Categorization	Grouping items into their underlying categories. The categories must be guessed from the items.	Categories number and items number
Comprehension of contexts	Some images are given with some descriptions. Correct descriptions need to be identified.	Descriptions number
Image pairs	A number of pairs of images to be memorized are presented. They must be recalled after 30 min.	Number of pairs
Mazes	Finding the way out of a labyrinth.	Size
Memory of stories	Recalling information about a read story or a picture by answering questions about it.	Type; size; and questions

Task Permutation

After the operationalization of the previously mentioned 11 tasks and the identification of their underlying parameters, multiple variants of each task were created to explore all parameter space. Because it is not feasible to study the complete permutation of all combinations of task parameters for all tasks (a minimum of 134), task parameters were selected and combined according to what was feasible to implement and could be mathematically modeled. Table 1 describes the parameter combinations that were selected. Overall, we created 67 variants of the above 11 tasks.

Assessment

Subsequently, we further involved in this study a total of 20 external rehabilitation experts (3 physiatrists, 5 neuropsychologists, and 12 rehabilitation therapists) from the private and public sectors in the autonomous region of Madeira and mainland Portugal. None of them was involved in the previous steps of the design process. The age range of participants was from 26 to 56 years (mean=40.05, SD=10.26), and the experts' experience range was from 2 to 32 years (mean=16.40, SD=10.54). Participants were 85% (17/20) female.

Each of the 20 study participants rated each of the 67 task variants in a 1 to 10 Likert scale according to their assessment of the tasks' demands on attention, memory, language, executive functions domains, and difficulty. Participants were provided with the questionnaires to be completed within a week and the order in which participants rated the variants, and the amount of time required to complete the 67 of them was not controlled.

Results

Internal Consistency

The internal consistency of each questionnaire was assessed through the *Cronbach alpha*, which reported consistency in the experts' responses for all tasks (Multimedia Appendix 1).

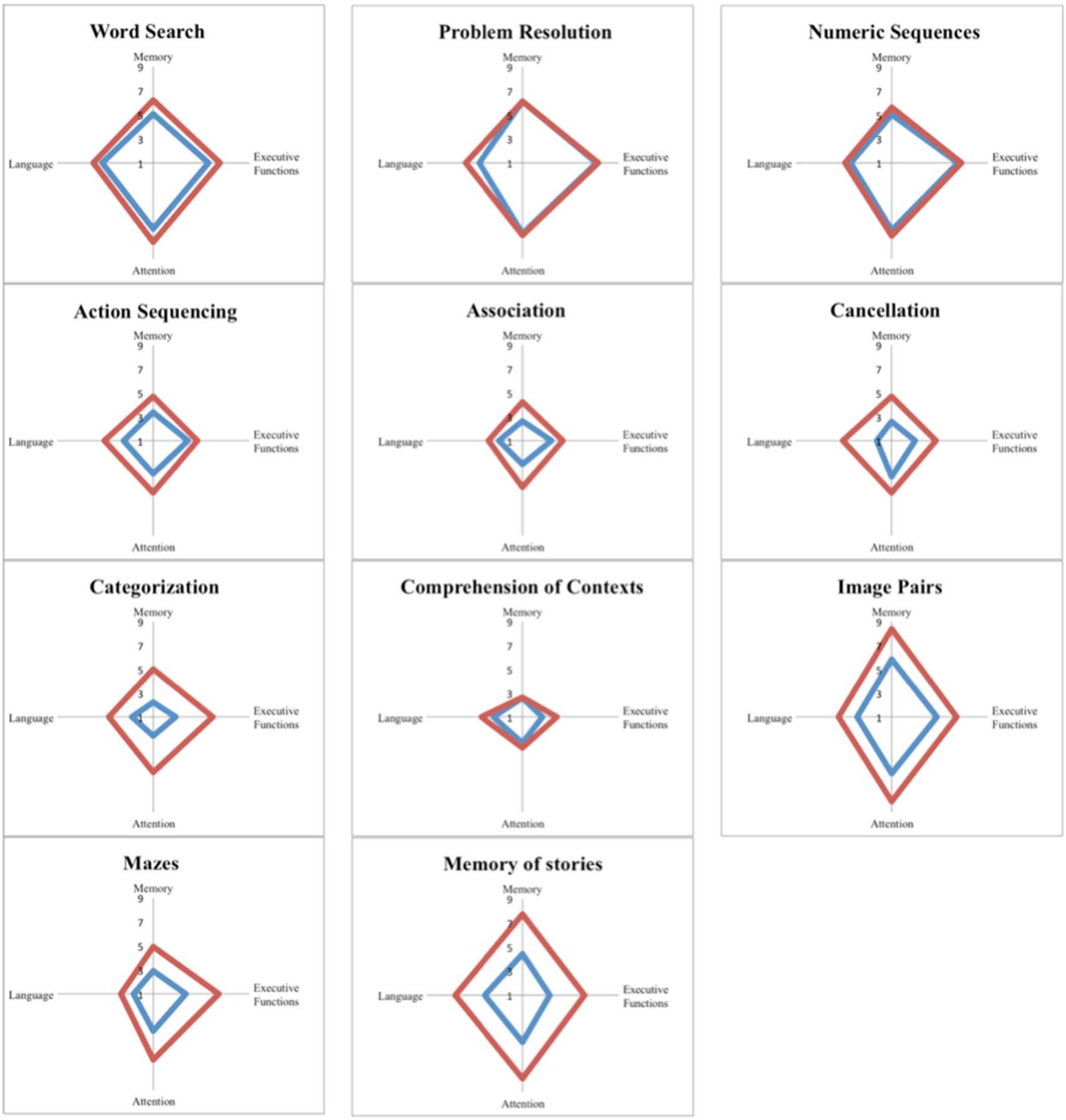
Quantification of the Cognitive Profile of the Tasks

An analysis of the ratings of the 20 rehabilitation experts' answers was performed to proceed to the identification of the relevant task parameters and the quantification of their impact regarding cognitive demands via a computational modeling approach. We have used this computational approach because traditional multiple regression techniques treat the units of analysis as independent observations, which is not the case in our study. The computational modeling was performed with the *R 3.1.1* software (Bell Labs), through the multilevel analysis package, which provides tools to estimate a wide variety of within-group agreement and reliability measures and provides data manipulation functions to facilitate multilevel analyses such as the one presented here [42]. A descriptive analysis per cognitive domain and overall difficulty (Table 2) was performed with the *Statistical Package for the Social Sciences 20* (IBM SPSS Statistics 20).

Table 2. Mean, minimum, and maximum ratings per task variant in each domain and overall difficulty.

Training task	Memory	Executive functions	Attention	Language	Difficulty
Word search, mean (range)	5.52 (5.05-6.20)	6.04 (5.60-6.55)	6.93 (6.50-7.60)	5.65 (5.25-6.00)	6.37 (5.70-7.00)
Problem resolution, mean (range)	6.10 (6.10-6.10)	7.23 (7.15-7.30)	6.97 (6.90-7.05)	5.20 (4.65-5.75)	6.19 (5.35-7.20)
Numeric sequences, mean (range)	5.30 (5.00-5.60)	6.65 (6.50-6.80)	6.87 (6.65-7.10)	4.68 (4.45-4.90)	3.06 (1.38-4.50)
Action sequencing	4.72 (3.35-5.65)	4.79 (3.90-5.65)	5.35 (3.80-6.40)	4.83 (3.50-5.75)	4.74 (3.15-6.20)
Association	3.37 (2.65-4.25)	3.92 (3.40-4.35)	3.95 (3.00-4.95)	3.28 (3.00-3.85)	3.78 (3.10-4.90)
Cancellation	3.59 (2.60-4.50)	3.98 (2.95-5.00)	5.09 (4.05-6.15)	2.94 (2.25-3.60)	4.08 (2.85-5.05)
Categorization	3.60 (2.20-5.00)	4.43 (2.85-5.95)	4.18 (2.60-5.65)	3.87 (2.80-4.70)	4.22 (2.35-6.05)
Comprehension of contexts	2.63 (2.60-2.65)	3.25 (2.65-3.85)	3.40 (3.20-3.60)	3.95 (3.45-4.45)	2.93 (2.55-3.30)
Image Pairs	6.97 (5.85-8.40)	5.55 (4.75-6.40)	6.75 (5.75-8.10)	4.62 (3.90-5.45)	6.35 (4.90-7.95)
Mazes	3.87 (2.90-4.90)	5.17 (3.70-6.45)	5.23 (4.10-6.50)	3.28 (2.65-3.70)	4.63 (3.20-6.10)
Memory of stories	6.36 (4.40-7.70)	4.89 (3.25-6.15)	6.67 (4.90-7.90)	5.41 (4.15-6.65)	5.95 (3.85-7.40)

By assessing the minimum and maximum ratings per task variant in each domain, we can create a profile for every task, which is graphically represented in Figure 2, which determines each task's training range. These profiles allow us to quickly judge the demands of each task and their adaptability in each cognitive domain. For instance, in the word search task, the demands range from 5.05 to 6.20 for memory, from 5.60 to 6.55 for the executive functions, from 6.50 to 7.60 for attention, and from 5.25 to 6 for language.



Word Search

Problem Resolution

Numeric Sequences

Action Sequencing

Association

Cancellation

Categorization

Comprehension of Contexts

Image Pairs

Mazes

Memory of stories

Figure 2. Task adaptation profiles represented as radar plots. Each plot has 4 axes—memory, executive functions, attention, and language—and the area between the blue (minimum) and the red line (maximum) represents the range interval in which the task varied depending on the selected task parameters in the study.

Multilevel Analysis and Modeling

The above-reported ranges correspond to the ranges of the tested task variants, which are limited to the parameters described in Table 1. Through computational approaches, it is possible to further generalize these profiles by modeling the effect of untested parameters and combinations. Multilevel analysis was selected to accommodate the specificity of the data collected with partial observations (not all parameter combinations were assessed). The objective of the modeling approach was to quantitatively determine how the IVs (task parameters) impact each of the DVs (memory, executive functions, attention, language, and difficulty). To model this relationship, the parameters of each task (IVs) were used as predictors of the demands in each cognitive domain (DVs). A multilevel model of the following type was computed for each task:

$$DV=intercept+C1*IV1+C2*IV2+...+Ci*IVi$$

where Ci indicates the contribution of each IV to the DV. These models considered a linear relationship with the order that the tasks were analyzed, allowed the slopes of these relationships to randomly vary, and incorporated an autoregressive structure with serial correlations in the error structures.

The basic procedure started by examining the nature of the outcome (task difficulty or cognitive load). First, we estimated the intraclass correlation coefficient and determined whether the outcome or DV (task difficulty or cognitive load) did not randomly vary among rehabilitation professionals. Thereafter, we considered only the significant IVs of the model. Second, we examined the form of the relationship between the order of the rated cognitive tasks and the outcome task difficulty or cognitive load. We wanted to know whether there was an order effect of the task's rating. Third, we attempted to determine whether the relationship between the task order and the outcome or DVs is constant among individuals or whether it varies on an individual-by-individual basis. Fourth, we modeled the error structures such as autocorrelation [42].

The model quality was quantified, after each iteration, through the Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), and *P* values. AIC is an estimate of a constant plus the relative distance between the unknown true likelihood function of the data and the fitted likelihood function of the model so that a lower AIC means a model is considered to be closer to the truth. AIC does not provide a test of a model in the sense of testing a null hypothesis; therefore, it can tell nothing about the quality of the model in an absolute sense. BIC is an estimate of a function of the posterior probability of a model being true, under a specific Bayesian setup, so that a lower BIC means that a model is more likely to be the true model. Both criteria are based on various assumptions and asymptotic approximations. Hence, AIC and BIC provide a means for model selection. Each, despite its heuristic usefulness, has also been criticized as having questionable validity for real-world data. Our modeling process stopped at the step where the best model was generated according to AIC.

Through the computational analysis, we quantified how the manipulation of the IV impacted the DV. In some tasks and for some specific cognitive domains, it was not possible to model the relationship between IV and DV, which means that some parameter manipulations had no significant effects on the DV. In those cases, the mean rating is assumed in that domain. Task parameters that do not have a significant contribution to either of the cognitive domains or overall difficulty are omitted in the guidelines below. In the following, we present the detailed guidelines for the customization of training. Multimedia Appendices 2-10 and Tables 3-6 contain the mathematical models together with the AIC and BIC values, which helped us to determine if we should perform the third *(Order)* and fourth *(AutoCorr)* steps of the modeling process.

Word Search (Impact Memory, Attention, and Executive Functions)

Through raising the number of words, it is possible to increase overall difficulty, memory, attention, and executive functions' demands. In addition, if clues are given in images, it is more difficult and demanding for memory, attention, and executive functions (Multimedia Appendix 2).

Problem Resolution (Impact Language)

The task allows the training of language by presenting the problems through real daily living situations. A higher number of operations and number of digits increase the general difficulty of this task (Tables 3 and 4).

Table 3. Problem resolution task models for language and difficulty.

Problem resolution task	Language			Difficulty		
	Coefficient value	SE	*t* value	Coefficient value	SE	*t* value
Intercept	4.65	0.562	8.281	4.870	0.568	8.573
Type	1.10	0.242	4.548	—[a]	—	—
Operations number	—	—	—	0.542	0.080	6.737
Tens	—	—	—	0.365	0.186	1.964

[a]Not applicable.

Table 4. Problem resolution task models quality for language and difficulty.

Model Quality	Language	Difficulty
Akaike Information Criterion	645.2693	794.0537
Bayesian Information Criterion	668.2871	813.7529
Order	Yes	Yes
Autocorrelation	Yes	Yes

Numeric Sequences (Impact Memory, Attention, Executive Functions, and Language)

The higher the demands for training memory, attention, executive functions, and language, the more the missing numbers, and yet higher if they are omitted at the beginning of the sequence. Concerning overall difficulty, the task is more laborious if the sequence is in descending order and the higher the step size between the sequence numbers is (Multimedia Appendix 3).

Action Sequencing (Impact Memory, Attention, Executive Functions, and Language)

A higher number of steps are needed to increase the cognitive demands. Also, it is possible to make the training more demanding for attention and language if the task goal is not explicitly mentioned (Multimedia Appendix 4).

Association (Impact Memory, Attention, Executive Functions, and Language)

Augmenting the number of pairs will increase the difficulty as well as the training of memory, attention, executive functions, and language (Multimedia Appendix 5).

Cancellation (Impact Memory, Attention, Executive Functions, and Language)

Memory and attention demands can be increased by using symbols and letters instead of numbers and by having more distractors and targets. For training in the language domain, we should use symbols and increase the number of distractors. By increasing both targets and distractors and using symbols, the task gets more difficult and more demanding in executive functions (Multimedia Appendix 6).

Categorization (Impact Memory, Attention, Executive Functions, and Language)

Augmenting the number of categories will increase the difficulty of the task as well as the training of memory, executive functions, and language. Concerning attention, besides augmenting the number of categories, we need to have more items per category (Multimedia Appendix 7).

Comprehension of Contexts (Impact Executive Functions and Language)

The higher the number of descriptions per context, the higher the demands for executive functions, language, and difficulty (Tables 5 and 6).

Table 5. Comprehension of contexts task models for executive functions, language and difficulty.

Comprehension of contexts task	Executive functions			Language			Difficulty		
	Coefficient value	SE	*t* value	Coefficient value	SE	*t* value	Coefficient value	SE	*t* value
Intercept	0.25	1.235	0.202	1.45	1.268	1.144	1.05	0.694	1.513
Descriptions number	1.20	0.457	2.629	1.00	0.453	2.207	0.75	0.228	3.290

Table 6. Comprehension of contexts task models quality for executive functions, language and difficulty.

Model Quality	Language	Difficulty
Akaike Information Criterion	645.2693	794.0537
Bayesian Information Criterion	668.2871	813.7529
Order	Yes	Yes
Autocorrelation	Yes	Yes

Image Pairs (Impact Memory, Attention, Executive Functions, and Language)

Increasing the number of images to pair will increase the difficulty of the task and the training of memory, attention, executive functions, and language (Multimedia Appendix 8).

Mazes (Impact Memory, Attention, Executive Functions, and Language)

They can be used to train memory, attention, executive functions, and language. By augmenting the size of the mazes, the cognitive demands and general difficulty are increased (Multimedia Appendix 9).

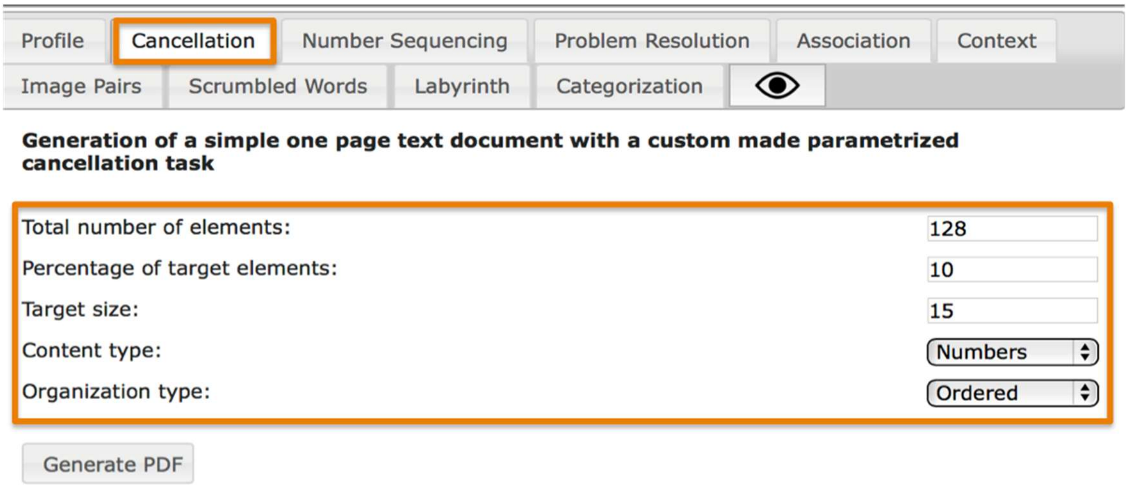
Memory of Stories (Impact Memory, Attention, Executive Functions, and Language)

To increase demands for memory, attention, and general difficulty, we need to increase the length of the story and the number of questions about it. To train executive functions and language, increasing the story length is enough (Multimedia Appendix 10).

App: the Task Generator

Still today, paper-and-pencil tasks are the most widely used means of cognitive rehabilitation [43] because of their acceptance, clinical validity, and reduced cost [44]. However, one of their limitations is that they lack flexibility and personalization. Consequently, it would be advantageous to have a tool that could generate standard, accepted, and validated paper-and-pencil tasks, yet customized according to any patient profile. This approach would mitigate some of the most critical limitations of paper-and-pencil tasks. For this reason, we have created a free and world-accessible Web-based tool, the TG, for the generation of personalized cognitive training tasks. The TG is a Web-based app and does not require to be installed on the computer; the only software required is a PDF reader to open the downloaded files. Through this tool, clinicians can define appropriate parameters of training for memory, attention, executive functions, language, and difficulty, and it automatically generates the requested personalized cognitive training tasks based on the task adaptation profiles represented as radar plots in Figure 2 (the area between the minimum and the maximum line represents the range interval in which each task can vary).

Tasks can be created either individually by directly specifying the values of their parameters (Figure 3) or as a full cognitive training program containing the whole set of 11 personalized training tasks.

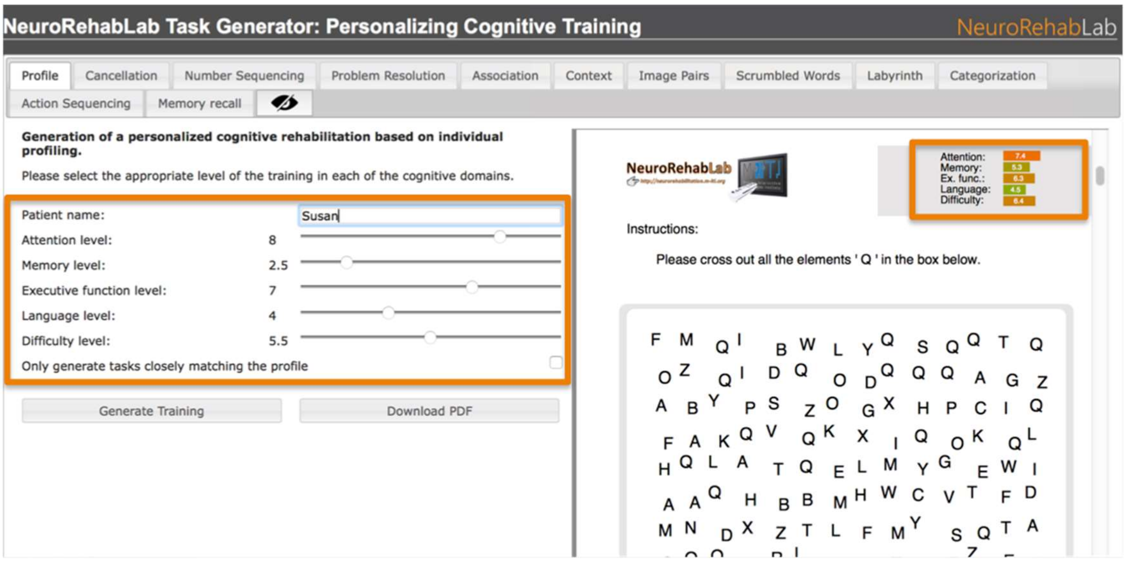


Generation of a simple one page text document with a custom made parametrized cancellation task

Total number of elements: 128
Percentage of target elements: 10
Target size: 15
Content type: Numbers
Organization type: Ordered

Figure 3. Individual tasks can also be generated by specifying the value of their parameters (cancellation task example).

Tasks are created procedurally; 2 training tasks are never the same, allowing for the repeated use of this tool. Besides, the generated tasks have a task profile (Figure 4)—a graphical representation of their demands in each cognitive domain and difficulty—enabling clinicians to efficiently and continuously adapt the training to the patient’s needs (Figure 5).



Generation of a personalized cognitive rehabilitation based on individual profiling.

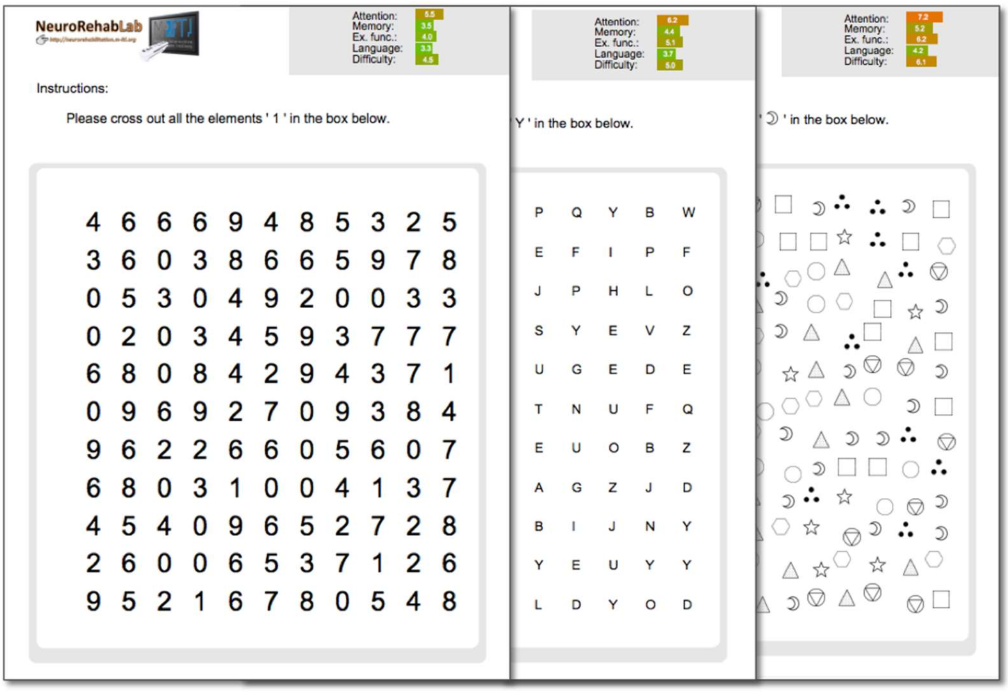
Please select the appropriate level of the training in each of the cognitive domains.

Patient name: Susan
Attention level: 8
Memory level: 2.5
Executive function level: 7
Language level: 4
Difficulty level: 5.5
Only generate tasks closely matching the profile ☐

Instructions:

Please cross out all the elements ' Q ' in the box below.

Figure 4. A cognitive training program can be generated by specifying the intended training intensity in each cognitive domain. Each training task contains a visual task profile, indicating its demands in attention, memory, executive functions, language, and difficulty.



Instructions:

Please cross out all the elements ' 1 ' in the box below.

4	6	6	6	9	4	8	5	3	2	5
3	6	0	3	8	6	6	5	9	7	8
0	5	3	0	4	9	2	0	0	3	3
0	2	0	3	4	5	9	3	7	7	7
6	8	0	8	4	2	9	4	3	7	1
0	9	6	9	2	7	0	9	3	8	4
9	6	2	2	6	6	0	5	6	0	7
6	8	0	3	1	0	0	4	1	3	7
4	5	4	0	9	6	5	2	7	2	8
2	6	0	0	6	5	3	7	1	2	6
9	5	2	1	6	7	8	0	5	4	8

'Y ' in the box below.

P	Q	Y	B	W
E	F	I	P	F
J	P	H	L	O
S	Y	E	V	Z
U	G	E	D	E
T	N	U	F	Q
E	U	O	B	Z
A	G	Z	J	D
B	I	J	N	Y
Y	E	U	Y	Y
L	D	Y	O	D

' ☽ ' in the box below.

Figure 5. Example of different parameterizations of the cancellation task. The graphical profile changes according to the parameters defined by the clinician.

Training Adaptation Over Time

When the patient finishes a set of tasks, the clinician may use one of these 2 procedures:

1. *From training session to training session*: By scoring the TG task's performance using a 0% to 100% scale and computing the mean performance of the whole task's set. If the mean performance is higher than a specific threshold (for instance, assuming an optimal performance from 70% to 100% [45]), the clinician should increase by 0.5 only the difficulty parameter while keeping the ones related to memory, attention, executive functions, and language constant. Alternatively, if performance is from 0% to 50%, the difficulty parameter should be reduced by 0.5.

2. *After a progress evaluation point*: By performing a new assessment of the patient profile. A new set of training tasks is generated with the new assessment following the same procedure stated in the *Cognitive Training Program Generation* section.

Full Cognitive Training Program Generation

Once a patient is assessed, and the patient's deficits and cognitive profile are known, the clinician's challenge is that of adapting the available training tasks to this patient. TG solves that problem by allowing clinicians to quickly generate a complete cognitive training program, containing the whole set of 11 tasks by simply specifying the cognitive profile for a patient in 4 cognitive domains (memory, attention, executive functions, and language), and the overall task difficulty in a 1 to 10 scale. This can be easily done through the characterization of the patient with validated instruments such as the Montreal Cognitive Assessment (MoCA) [46]. The TG *Attention* parameter can be defined from MoCA's attention component score (0-6); the delayed recall and orientation scores (0-11) can be used to parameterize *memory; executive functions* can be parameterized through the sum of the visuospatial, executive, and abstraction MoCA subscores (0-7); MoCA's naming and the language scores (0-6) can be used to parameterize *language;* and the total score (0-30) can be used to parameterize the overall *difficulty.* After the characterization of a patient, through the normalization of these assessment results on a 1 to 0 scale, a full training program is generated by pressing the *Generate Training* button and then can be downloaded as a PDF file by pressing the *Download PDF* button. In addition, there is an optional check box in the patient profile page that when selected only generates tasks closely matching the chosen profile. Tasks that would differ substantially from the selected profile can then be filtered out as they can represent nonoptimal task parameter choices. Nonetheless, the user can disable this feature by unchecking the selection box and the TG will generate the complete set of 11 tasks, with the best possible personalization allowed by their parameters.

Discussion

Principal Findings

We developed a design framework where we borrowed concepts from educational psychology and a participatory design strategy with stakeholders to support the development process. Through this process, we were able to identify a representative group of well-established standard paper-and-pencil tasks currently used for cognitive rehabilitation, and we operationalized them with respect to their parameters. To that end, the expert knowledge of 20 rehabilitation experts was used to model each task for its difficulty and impact on cognitive functions. The task models obtained provide us with valuable guidelines toward the development of personalized cognitive rehabilitation tools. Furthermore, we demonstrated the proposed methodology with an example case: a Web-based tool for the generation of customized paper-and-pencil cognitive training tasks, the TG. We believe that the TG contributes toward the definition of objective procedures for the application of adaptive cognitive rehabilitation through the use of ICTs. The use of TG has virtually zero cost associated, and it is available in English, Portuguese, and Italian.

Comparison With Prior Work

Recent technological advances have allowed improved apps for cognitive rehabilitation, and it has been shown that they can be effective rehabilitation tools for health professionals [33]. However, the lack of a precise design methodology that can guide the development of ICT's applications, applied to rehabilitation, still remains one of the main limitations in this field. Data mining techniques have been applied to predict the outcomes of cognitive rehabilitation in patients with acquired brain injury; however, rehabilitation experts' input should also be included [47]. As an answer to this need, the primary goal of this study was to propose a general framework to guide in the design of future cognitive rehabilitation tools, with objective and expert-based guidelines.

The app here presented guidelines in a Web-based tool as the TG also addresses the accessibility limitations because it can be widely deployed at health care centers and home. This new approach does not interfere with current clinical practices because it produces printable paper-and-pencil tasks. By enabling the adaptation of task parameters and difficulty levels according to patient performance, this tool provides a comprehensive and highly personalized cognitive training.

Limitations

Despite the valuable guidelines obtained, via computational modeling, from our participatory design strategy, some limitations of our study must be considered. First, there is a considerable variety of paper-and-pencil tasks being used in cognitive rehabilitation and stimulation practice, and we have selected a small subset of 11 tasks to be possible to parameterize and present them in a questionnaire; however, we are aware it is a small number. Second, concerning the sample of rehabilitation experts, 20 participants can be considered a small number although we managed to include different professionals: physicians, psychologists, and therapists. Third and last, our participatory design strategy was limited in the sense that we did not include subjective and qualitative feedback from the rehabilitation experts, except for one of the physiatrists who was involved in the task selection phase.

Developments of This Study

Although paper-and-pencil tasks are widely used in cognitive rehabilitation, these tools mostly focus on isolated components of cognitive functioning, which have been reported to disagree with everyday life tasks [44,48]. It has been shown that virtual reality (VR), as a tool, has a significant potential for enhancing the reliability and specificity of cognitive assessment and rehabilitation [19,49]. Due to all the VR advantages, the logical next step is the integration of the computational models obtained through the participatory design study in a cognitive VR rehabilitation environment presented here. In this context, we integrated the findings from our models and transformed the original paper-and-pencil tasks in virtual ADL's tasks within a simulation of a city with streets, sidewalks, realistic buildings, several parks, and moving vehicles—the Reh@City [50]. The activities in the Reh@City are organized in parameterized difficulty levels and target the cognitive domains addressed in the guidelines presented here: memory, attention, executive functions, and language. As an illustrative example, in terms of attention, Reh@City incorporates relevant ADL's, implementation of which helps bridge paper-and-pencil cancellation tasks. More specifically, targets and distractors are embedded in a pharmacy, a supermarket, or a post-office shelf. This kind of implementation allows the operationalization of the training difficulty by changing the number and nature of targets and distractors, their sizes, and their spatial arrangement.

Currently, we are running a 1-month longitudinal randomized controlled trial comparing both TG and Reh@City v2.0 interventions. This study entails a comprehensive neuropsychological assessment not only pre- and post intervention but also at follow-up, with the aim of comparing the impact of a personalized paper-and-pencil program (TG), a personalized and integrative VR-based program (Reh@City v2.0), and conventional therapy. The main objective of this study was to assess the neuropsychological and functional impact of a paper-and-pencil task and a VR intervention, having the same tasks and parameterization guidelines for comparison. In addition, in this study, we are also addressing the usability of the tool through interviews and questionnaires so that we can improve both tools regarding the patients’ perspective.

Future Work

Many health care providers are unfamiliar with ICTs and, as a consequence, a very small percentage of people with disabilities have access to technological devices that can assist them in the rehabilitation process. To mitigate this issue, it would be valuable to improve the usability of both the TG and the Reh@City by interviewing the health care providers after using them as complementary tools for their work.

Moreover, as future work, we are also planning to upgrade the TG app by creating a tablet version that allows remote monitoring by the health care providers and automatic personalization through artificial intelligence and machine learning algorithms.

Authors' Contributions

ALF and SBiB designed the study and performed the data analysis. MSP provided methodology guidelines. ALF performed the data collection. ALF, MSP, and SBiB wrote the paper for publication.

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Multimedia Appendices

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Multimedia Appendix 1

Questionnaire’s internal consistency

Tasks	Word search	Problem resolution	Numeric sequences	Action sequencing	Association	Cancellation	Categorization	Contexts	Image pairs	Mazes	Memory of stories
Alpha	0.981	0.987	0.997	0.973	0.975	0.990	0.953	0.945	0.963	0.975	0.918

Multimedia Appendix 2

Word search task models for memory, attention, executive functions and difficulty.

Word search task	Memory			Attention			Executive functions			Difficulty		
	Coefficient value	Standard error	*t* value	Coefficient value	Standard error	*t* value	Coefficient value	Standard error	*t* value	Coefficient value	Standard error	*t* value
Intercept	4.000	0.752	5.320	6.150	0.617	9.968	5.138	0.715	7.187	5.466	0.688	7.947
Clue words	-1.000	0.346	-2.893	-.700	0.327	-2.142	-0.913	0.229	-3.993	-1.154	0.287	-4.013
Words number	0.269	0.071	3.809	0.144	0.067	2.155	0.171	0.054	3.169	0.176	0.069	2.561

Model quality	Memory	Attention	Executive functions	Difficulty
Akaike Information Criterion	403.9686	384.4461	345.6128	373.7182
Bayesian Information Criterion	416.8422	397.3196	363.6358	391.7411
Order	No	No	Yes	Yes
Autocorrelation	No	No	No	No

Multimedia Appendix 3

Numeric sequences task models for memory, attention, executive functions, language, and difficulty.

Numeric sequences task	Memory			Attention			Executive functions			Language			Difficulty		
	Coefficient value	Standard error	*t* value	Coefficient value	Standard error	*t* value	Coefficient value	Standard error	*t* value	Coefficient value	Standard error	*t* value	Coefficient value	Standard error	*t* value
Intercept	5.364	0.700	7.667	6.923	0.528	13.103	6.682	0.570	11.715	4.722	0.630	7.497	1.290	0.515	2.506
Step	___	___	___	___	___	___	___	___	___	___	___	___	1.232	0.126	9.750
Ascending	___	___	___	___	___	___	___	___	___	___	___	___	-0.841	0.154	-5.457
Missing	-0.027	0.009	-3.142	-0.020	0.006	-3.342	-0.014	0.005	-2.818	-0.020	0.007	-3.100	___	___	___
Position	-0.003	0.001	-2.835	-0.003	0.001	-3.017	-0.002	0.001	-2.546	-0.003	0.001	-2.799	___	___	___

Model quality	Memory	Attention	Executive functions	Language	Difficulty
Akaike Information Criterion	177.0194	-97.91632	-272.89619	-34.42772	480.4425
Bayesian Information Criterion	208.8909	-66.04483	-241.02470	-2.55623	504.8925
Order	Yes	Yes	Yes	Yes	Yes
Autocorrelation	Yes	Yes	Yes	Yes	Yes

Multimedia Appendix 4

Action sequencing task models for memory, attention, executive functions, language, and difficulty.

Action sequencing task	Memory			Attention			Executive functions			Language			Difficulty		
	Coefficient value	Standard error	*t* value	Coefficient value	Standard error	*t* value	Coefficient value	Standard error	*t* value	Coefficient value	Standard error	*t* value	Coefficient value	Standard error	*t* value
Intercept	1.507	0.669	2.254	2.90	0.691	4.197	2.838	0.911	3.113	3.325	0.812	4.096	1.950	0.664	2.937
Actions number	0.635	0.153	4.159	0.75	0.125	5.988	0.487	0.202	2.409	0.525	0.146	3.601	0.862	0.124	6.966
Task goal	___	___	___	-1.10	.251	-4.391	___	___	___	-1.200	0.292	-4.115	-1.325	0.248	-5.351

Model quality	Memory	Attention	Executive functions	Language	Difficulty
Akaike Information Criterion	334.9841	307.1238	358.3382	331.2999	302.795
Bayesian Information Criterion	349.1244	318.8428	367.7650	343.0189	314.5140
Order	Yes	No	No	No	No
Autocorrelation	No	No	No	No	No

Multimedia Appendix 5

Association task models for memory, attention, executive functions, language, and difficulty.

Association task	Memory			Attention			Executive functions			Language			Difficulty		
	Coefficient value	Standard error	*t* value	Coefficient value	Standard error	*t* value	Coefficient value	Standard error	*t* value	Coefficient value	Standard error	*t* value	Coefficient value	Standard error	*t* value
Intercept	1.367	0.782	1.747	1.513	0.721	2.099	2.729	0.721	3.788	2.221	0.403	5.511	1.533	0.701	2.186
Pairs number	0.400	0.117	3.426	0.487	0.100	4.892	0.237	0.088	2.701	0.106	0.038	2.816	0.450	0.104	4.323

Model quality	Memory	Attention	Executive functions	Language	Difficulty
Akaike Information Criterion	334.9841	307.1238	358.3382	331.2999	302.795
Bayesian Information Criterion	349.1244	318.8428	367.7650	343.0189	314.5140
Order	Yes	No	No	No	No
Autocorrelation	No	No	No	No	No

Multimedia Appendix 6

Cancellation task models for memory, attention, executive functions, language, and difficulty.

Cancellation task	Memory			Attention			Executive functions			Language			Difficulty		
	Coefficient value	Standard error	*t* value	Coefficient value	Standard error	*t* value	Coefficient value	Standard error	*t* value	Coefficient value	Standard error	*t* value	Coefficient value	Standard error	*t* value
Intercept	3.125	0.505	6.193	4.314	0.532	8.103	3.459	0.504	6.862	2.839	0.497	5.717	3.610	0.514	7.018
Distractors	0.009	0.003	2.959	0.014	0.003	4.327	0.014	0.003	4.087	0.009	0.003	3.383	0.015	0.003	4.601
Letters	___	___	___	___	___	___	-0.814	0.211	-3.853	-0.480	0.178	-2.701	-0.494	0.210	___
Numbers	-0.813	0.214	3.126	-0.697	0.235	-2.969	-0.845	0.236	-3.587	-0.790	0.204	-3.869	-1.054	0.240	-4.385
Targets	0.017	0.005	-3.802	0.021	0.006	3.526	0.012	0.005	2.150	___	___	___	0.012	0.006	2.115
Arrangement	___	___	___	___	___	___	0.724	0.266	2.716	___	___	___	___	___	___

Model quality	Memory	Attention	Executive functions	Language	Difficulty
Akaike Information Criterion	738.4285	773.6644	743.1042	691.5384	749.9689
Bayesian Information Criterion	758.0972	793.3330	772.5149	714.4852	776.1529
Order	No	No	Yes	Yes	Yes
Autocorrelation	No	No	Yes	Yes	Yes

Multimedia Appendix 7

Categorization task models for memory, attention, executive functions, language, and difficulty.

Categorization task	Memory			Attention			Executive functions			Language			Difficulty		
	Coefficient value	Standard error	*t* value	Coefficient value	Standard error	*t* value	Coefficient value	Standard error	*t* value	Coefficient value	Standard error	*t* value	Coefficient value	Standard error	*t* value
Intercept	0.6	0.684	0.877	-3.26	1.981	-1.645	1.136	0.695	1.635	1.914	0.724	2.644	0.234	0.462	0.506
Categories number	0.9	0.156	5.754	3.75	1.262	2.971	0.989	0.148	6.702	0.586	0.151	3.871	1.165	0.145	8.048
Items number	___	___	___	-0.41	0.185	-2.213	___	___	___	___	___	___	___	___	___

Model quality	Memory	Attention	Executive functions	Language	Difficulty
Akaike Information Criterion	260.2888	233.4358	259.6256	263.7335	244.8731
Bayesian Information Criterion	268.5306	243.6511	267.8674	271.9753	257.2357
Order	No	No	No	No	Yes
Autocorrelation	No	No	No	No	No

Multimedia Appendix 8

Image pairs task models for memory, attention, executive functions, language, and difficulty.

Image Pairs task	Memory			Attention			Executive Functions			Language			Difficulty		
	Coefficient value	Standard error	*t* value	Coefficient value	Standard error	*t* value	Coefficient value	Standard error	*t* value	Coefficient value	Standard error	*t* value	Coefficient Value	Standard error	*t* value
Intercept	3.779	0.600	6.293	3.813	0.660	5.774	3.488	0.659	5.290	2.723	0.809	3.367	2.538	0.615	4.124
Number of pairs	0.637	0.081	7.867	0.587	0.096	6.123	0.412	0.081	5.062	0.388	0.114	3.409	0.762	0.092	8.276

Model quality	Memory	Attention	Executive Functions	Language	Difficulty
Akaike Information Criterion	230.5643	244.6216	236.9498	250.4309	237.4246
Bayesian Information Criterion	238.8061	252.8633	245.1916	260.7332	245.6663
Order	No	No	No	Yes	No
Autocorrelation	No	No	No	Yes	No

Multimedia Appendix 9

Mazes task models for memory, attention, executive functions, language, and difficulty.

Mazes task	Memory			Attention			Executive functions			Language			Difficulty		
	Coefficent value	Standard error	*t* value	Coefficent value	Standard error	*t* value	Coefficent value	Standard error	*t* value	Coefficent value	Standard error	*t* value	Coefficent value	Standard error	*t* value
Intercept	1.867	0.475	3.932	2.876	0.612	4.701	2.390	0.678	3.527	2.233	0.416	5.364	1.733	0.628	2.759
Size	1.000	0.221	4.532	1.200	0.186	6.460	1.375	0.217	6.328	0.525	0.198	2.655	1.450	0.188	7.706

Model quality	Memory	Attention	Executive functions	Language	Difficulty
Akaike Information Criterion	245.2409	230.2526	249.9474	232.7764	245.6437
Bayesian Information Criterion	257.6036	238.4944	258.1892	245.1390	253.8855
Order	Yes	No	No	Yes	No
Autocorrelation	No	No	No	No	No

Multimedia Appendix 10

Memory of stories and images task models for memory, attention, executive functions, language and difficulty.

Memory of stories task	Memory			Attention			Executive functions			Language			Difficulty		
	Coefficient value	Standard error	*t* value	Coefficient value	Standard error	*t* value	Coefficient value	Standard error	*t* value	Coefficient value	Standard error	*t* value	Coefficient value	Standard error	*t* value
Intercept	3.60	0.561	6.413	4.2	0.644	6.517	1.90	0.705	2.693	3.083	0.726	4.248	2.800	0.529	5.295
Size	4.20	1.011	4.155	3.9	0.822	4.746	1.45	0.278	5.216	1.250	0.265	4.718	3.950	0.982	4.024
Questions	-0.85	0.331	-2.569	-0.8	0.263	-3.039	___	___	___	___	___	___	-0.725	0.321	-2.257

Model quality	Memory	Attention	Executive functions	Language	Difficulty
Akaike Information Criterion	234.0854	237.5185	270.4890	271.7985	227.5656
Bayesian Information Criterion	244.3007	249.7768	278.7308	280.0402	237.7809
Order	No	No	No	No	No
Autocorrelation	No	No	No	No	No

2. Personalizing paper-and-pencil training for cognitive rehabilitation: a feasibility study with a web-based Task Generator [3, 4]

Abstract

Cognitive impairments impose important limitations in the performance of activities of daily living. Although there is important evidence on cognitive rehabilitation benefits, its implementation is limited due to the demands in terms of time and human resources. Moreover, many cognitive rehabilitation interventions lack a solid theoretical framework in the selection of paper-and-pencil tasks by the clinicians. In this endeavour, it would be useful to have a tool that could generate standardized paper-and-pencil tasks, customized according to patients' needs. Combining the advantages of information and communication technologies (ICT's) with a participatory design approach involving 20 health professionals, a novel web-tool for the generation of cognitive rehabilitation training was developed: the Task Generator (TG). The TG is a web-based tool that systematically addresses multiple cognitive domains, and easily generates highly personalized paper-and-pencil training tasks. A clinical evaluation of the TG with twenty stroke patients showed that, by enabling the adaptation of task parameters and difficulty levels according to patient cognitive assessment, this tool provides a comprehensive cognitive training.

Keywords: Cognitive Rehabilitation; Personalization; Stroke; Technology Barriers.

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[3] A. L. Faria and S. Bermúdez i Badia, "Personalizing paper-and-pencil training for cognitive rehabilitation: a feasibility study with a web-based Task Generator," In Proceedings of the International Conference on Applied Psychology (IKnowD), Funchal, Portugal, 2018.

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Introduction

Cognitive impairments following stroke are common and are present in approximately 70% of patients in the acute stages of recovery [1], causing problems in activities of daily life and social participation. These cognitive impairments commonly include focal disorders, such as aphasia and neglect, as well as more diffuse abnormalities, such as slowed information processing and executive dysfunction [2]. Cognitive rehabilitation is the treatment of choice for these deficits and can be defined as a therapy designed to restore, substitute or compensate for lost cognitive abilities due to injury or illness. Additionally, it targets the improvement of skills by re-establishing or strengthening abilities that were intact prior to the loss [3].

Cognitive training has been proven to be successful in improving cognitive deficits after stroke [4] [5], but its efficacy highly depends on the intensity of treatment over an extended period of time. However, the implementation of cognitive training programs with the appropriate intensity and duration becomes difficult because of important limitations. First, the traditional intervention model requires multidisciplinary teams to manage exercises based on patients' profile and performance [6]. The cost of this process limits the intensity and length of the treatments, compromising its sustainability, accessibility and scalability, resulting in a large economic burden to both health systems and families [7]. Besides, the patient needs to travel to the rehabilitation centre, making the duration of the treatment conditional to the patient's availability. Second, since patients usually need to travel to clinical facilities to receive rehabilitation, interventions are subject to the availability of vacancies and transportation [8]. Third and last, in the neuropsychological rehabilitation field there is an absence of clinical practice guidelines to allow a rational extension of these services. For instance, classic cognitive training mainly involve solving paper-and-pencil tasks under specialized supervision because they are clinically validated and have a reduced cost [9]. Unfortunately, these tasks selection and adjustment to the patient's needs generally lack a solid theoretical framework [10].

The American Congress of Rehabilitation Medicine (ACRM) conducted systematic reviews on a total of 370 studies about cognitive rehabilitation for people with TBI or stroke, published from 1971 through 2008 [11],[4],[5]. Cognitive rehabilitation was shown to be of greater benefit than conventional rehabilitation in 94.1% of the comparisons studies. According to this evidence, there is a clear indication that cognitive rehabilitation is the best available form of treatment for people who exhibit cognitive impairments and functional limitations after TBI or stroke [5]. However, Paiva and colleagues performed a meta-analysis on cognitive rehabilitation in stroke and the results suggested a lack of sufficient evidence to support or refute the efficacy of cognitive interventions in stroke patients [12]. These divergent results should be interpreted with caution since in this meta-analysis 504 of 507 studies were excluded due to its low quality, only 3 were considered by the authors. Additional research, using standardized assessment instruments and well-structured training programs, is needed to elucidate the mechanisms of change underlying the efficacy of cognitive rehabilitation.

An international group of researchers and clinicians (known as INCOG) recommends that cognitive assessment and rehabilitation should be tailored to the patient neuropsychological profile, premorbid cognitive characteristics and goals for life activities and participation [13]. The existing cognitive rehabilitation theories and models have been relatively successful when applied to focal cortical deficits (e.g. neglect and aphasia), but almost inexistent for more generalized cognitive impairment (e.g. slowed information processing and executive dysfunction) [14]. It is more challenging when we are addressing multiple aspects of cognition simultaneously. Hence, it is difficult to provide clear guidelines on how to parameterize cognitive training tasks and how to adapt them to the specific needs of each patient [15]. Currently, cognitive rehabilitation is mostly planned and delivered based on a selection of a limited set of paper-and-pencil cognitive tasks. Consequently, most cognitive training tasks may not be properly adjusted to the specific needs of each patient [9]. Further, task selection is also heavily grounded on the experience of the clinician - a type of knowledge that is difficult to objectively capture - therefore making it difficult to transmit and share [15].

Information and Communication Technologies (ICT's) based solutions such as serious games, Virtual Reality (VR) simulations or other computer mediated approaches, have an enormous potential for enhancing the intensity and personalization of cognitive rehabilitation by supporting the ability to carry out controlled, highly adaptive and ecologically valid tasks [16]. Over the past few years, several computer based solutions have been proposed to increase the availability and quality of cognitive training, flooding the marketplace with commercial brain exercise programs that claim to improve cognition and have diagnostic abilities [17] such as the CogWeb [18] and the Guttmann Neuro Personal Trainer [19], for instance.

VR offers the possibility to simulate daily tasks in a virtual environment, adapting the task parameters according to the patient performance, which increases training specificity and patient's motivation by avoiding boredom and frustration in a more sophisticated and ecologically valid approach [20]. Nevertheless, the clear enthusiasm for the use of technology in rehabilitation must be tempered by an acknowledgement of potential barriers, such its inherent costs, accessibility and usability by patients and healthcare professionals. Most virtual environments used in clinical studies are not commercially available and only a few research laboratories have access to them. Despite the proliferation of ICT's in cognitive rehabilitation, only 5-15% of people with disabilities have access to technological devices that can assist in the rehabilitation process [21]. Additionally, many healthcare providers are unfamiliar with VR technology, only about 27% of these professionals refer to use these computer assisted technologies in their rehabilitation interventions [22]. Also, technological interventions are subject to continuous maintenance and technical support, eventually resulting in delayed interventions or the need to reschedule. Such complications speak to the challenges of implementing interventions dependent upon technology within inpatient and outpatient rehabilitation settings. Any delays in these fast paced settings, requiring the coordination of various professionals, can be disruptive [23].

In order to increase the benefits of ICT's and to address its limitations, a web-based tool - the Task Generator (TG) – was developed through a participatory design approach with 20 rehabilitation professionals [24]. Besides integrating existing theories and models [10], it capitalizes on the solid aspects of existing computerized training protocols for cognitive rehabilitation [8], [18], [25]. The TG addresses multiple domains of cognitive functioning in a systematic and quantitative manner, generating a profile of cognitive demands for each task and enabling the clinician to easily deliver a highly adapted training program to each patient's deficits. Given that the TG ultimately generates paper-and-pencil training tasks, its application is compatible with the current practice and existing limitations of clinical settings.

This paper presents the main characteristics of the developed system and the results of a feasibility study with stroke patients. To evaluate the personalization of the TG tasks, we designed a study with the objective of answering two main questions: 1) Does TG personalization properly adapt to patient's needs? and 2) How accurate is the generated profile of cognitive demands of each task?

Materials and Methods

A. Task Generator

The TG is a free and worldwide accessible tool (neurorehabilitation.m-iti.org/TaskGenerator), able to generate personalized paper-and-pencil cognitive rehabilitation programs in PDF format, composed by a set of 11 tasks (Table 1) gathered from clinical settings and parameterized through rehabilitation experts input.

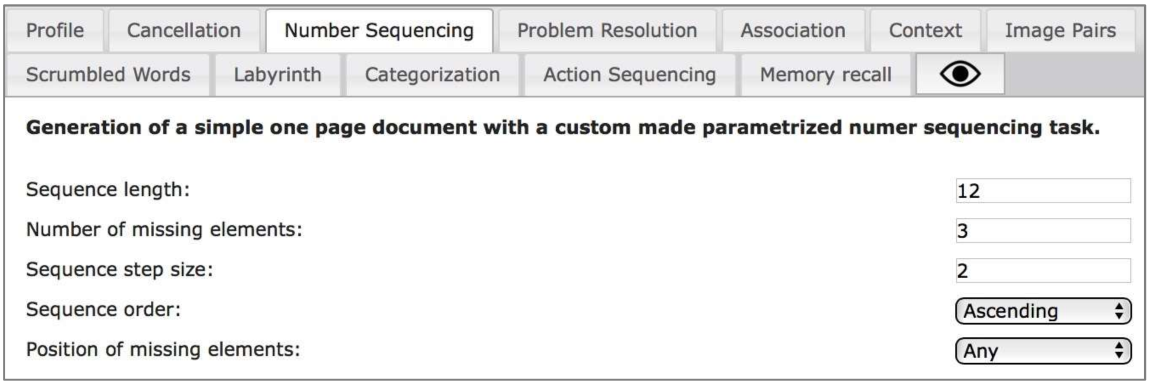
Table 1. List of training tasks and their objectives.

Tasks	***Objectives***
Cancellation	Find a target stimulus in a pool of distractors.
Numeric Sequences	A numeric sequence is given and the subject has to come up with the missing numbers.
Problem Resolution	Two types of problems are presented, numeric calculations or calculations based on textual descriptions of daily activities.
Association	A number of randomized pairs of items need to be paired correctly.
Comprehension of Contexts	Some images are given with a number of descriptions. Correct descriptions need to be identified.
Image Pairs	A number of pairs of images to be memorized is presented and have to be recalled after 30 minutes.
Word Search	A number of words can be found up, down, forward, or diagonally in a pool of randomized letters.
Mazes	Finding the way out of a labyrinth.
Categorization	Grouping items into their underlying categories. The categories have to be guessed from the items.
Action Sequencing	A list of randomized steps needed for the execution of several activities of daily living is presented.
Memory of Stories	Recalling information about a read story or a picture by answering questions about it.

In short, 11 standard tasks have been operationalized according to how their different parameters impact different cognitive domains (Attention, Memory, Executive Functions, Language). This was achieved by means of a participatory design methodology involving 20 rehabilitation experts who rated multiple variations of the task parameters in terms of its cognitive demands [24].

1) Individual Parameterization

The TG is able to procedurally generate each of the 11 tasks individually by directly specifying the values of their parameters (Figure 1). Every time a task is generated by the TG is different, even if sharing the exact same parameters. This allows for the repeated use of the tool, thus avoiding repetitiveness while making sure that the intrinsic parameters of each task are adjusted to the clinicians' specifications.



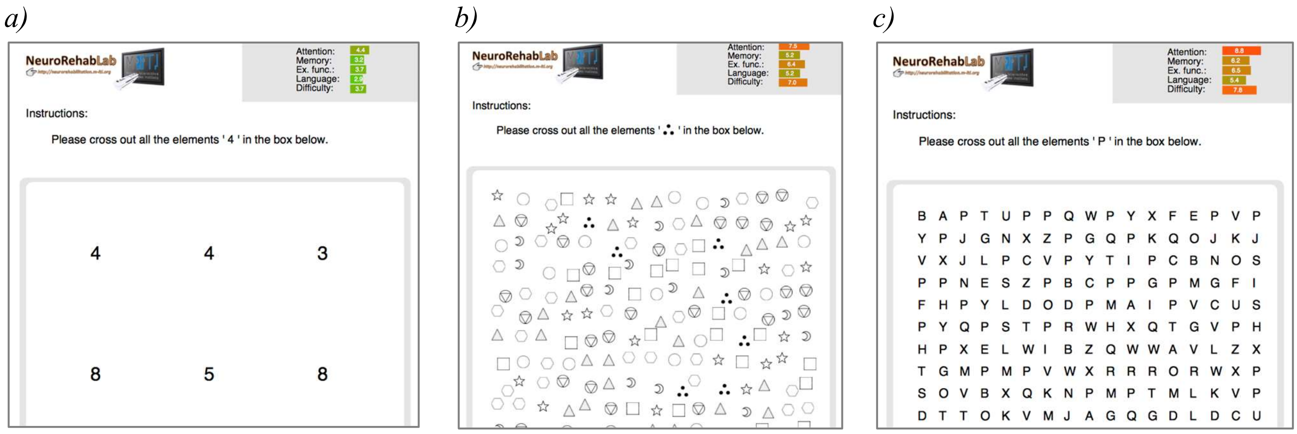
Generation of a simple one page document with a custom made parametrized numer sequencing task.

Sequence length: 12
Number of missing elements: 3
Sequence step size: 2
Sequence order: Ascending
Position of missing elements: Any

Figure 1. Parameterization example of the Number Sequencing task, where task parameters can be manually selected.

2) Task Profile

All the generated tasks have a graphical representation of the profile of their cognitive demands (Memory, Attention, Executive Functions and Language) and overall Difficulty, enabling clinicians to intuitively visualize and interpret the generated training, being thus able to adapt it to each patient's needs (Figure 2).



a) Instructions:

Please cross out all the elements ' 4 ' in the box below.

b) Instructions:

Please cross out all the elements ' ∴ ' in the box below.

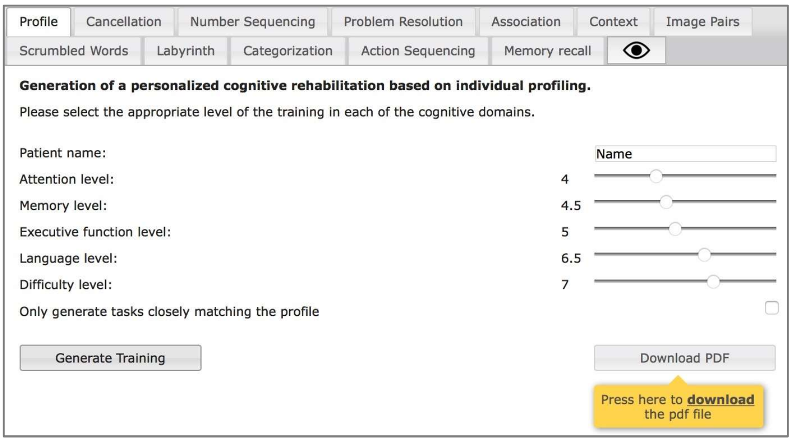
c) Instructions:

Please cross out all the elements ' P ' in the box below.

Figure 2. Example of the Cancellation task with different parameter selection. The graphical profile changes according to the parameters defined by the clinician: a) Attention 2.5, Memory 3, Executive Functions 2.5, Language 3 and Difficulty 3.5; b) Attention 4.5, Memory 6, Executive Functions 7, Language 8 and Difficulty 7.5; c) Attention 9, Memory 6.5, Executive Functions 8.5, Language 5 and Difficulty 8.

3) Full Cognitive Training Program Generation

Once a patient is assessed and the patient's deficits and general cognitive profile is known, the challenge of the clinician is how to select the best set of parameters for each specific patient. TG solves that problem by allowing clinicians to easily generate a complete cognitive training program containing the whole set of the 11 tasks by simply specifying the cognitive profile for a patient in 4 cognitive domains (Memory, Attention, Executive Functions, Language) and the overall task difficulty in a 1 to 10 scale (Figure 3). This can be easily done through the characterization of the patient with validated instruments such as the MoCA [26]. After the characterization of a profile, a full training program is generated by pressing the "Generate Training" button and then downloaded as a pdf file by pressing the "Download PDF" button.



Generation of a personalized cognitive rehabilitation based on individual profiling.

Please select the appropriate level of the training in each of the cognitive domains.

Patient name: Name
Attention level: 4
Memory level: 4.5
Executive function level: 5
Language level: 6.5
Difficulty level: 7
Only generate tasks closely matching the profile ☐

Figure 3. Cognitive training program generation based on a specific patient profile.

4) Training adaptation over time

When the patient finishes a set of 11 tasks, the clinician may use one of these 2 procedures:

- From training session to training session - By scoring the task performance using a 0 – 100% scale, and computing the mean performance of the 11 tasks set. If the mean performance is greater than a specific threshold (for instance assuming an optimal performance above the 70% [27]), the clinician should increase in 0.5 the difficulty parameter, while keeping the ones related to Memory, Attention, Executive Functions and Language constant.
- After a progress evaluation point - Performing a new assessment of the patient profile and generating in a systematic and objective manner a new set of training tasks following the same procedure stated in the *Cognitive Training Program Generation* section.

B. Clinical Evaluation

1) Participants

Participants were recruited at the Nélio Mendonça, João Almada and Santo António Rehabilitation Units (Madeira Health Service, Portugal), based on the following inclusion criteria:

no vision deficits; capacity to be seated; non-aphasic and with sufficient cognitive ability to understand the task instructions (as subjectively assessed by the clinicians). The sample consisted of twenty (10 female, 10 male) middle-aged (*M*= 61.75 years old, *SD*=8.89) stroke patients (9 right hemisphere and 11 left hemisphere lesion), with a mean of 4.05 ± 3.73 months post-stroke, and with a mean schooling of 4.95 ± 4.03 years. The Madeira Health Service Ethical Committee approved the study and all the participants gave previous informed consent.

2) Characterization of patients' cognitive profile and training personalization

The cognitive profile of each participant was assessed with the Montreal Cognitive Assessment (MoCA) [26], a cognitive screening instrument that, besides a high sensitivity to post-stroke deficits [28], includes a reduced version of the Trail Making Test - version B [29], a representative measure of the executive functions domain. The TG *Attention* parameter was defined from MoCA's attention component score (0-6). The delayed recall and orientation scores (0-11) were used to parameterize *Memory*. *Executive Functions* were parameterized through the sum of the visuospatial, executive and abstraction MoCA sub-scores (0-7). Finally, MoCA's naming and the language scores (0-6) were used to parameterize *Language*. The MoCA total score (0-30) was used to parameterize the overall *Difficulty* of the TG training. All TG parameters were normalized on a scale 1-10 and a personalized training was generated for each participant, and printed on paper. Participants completed the generated tasks in two sessions of 30 to 45 minutes with the assistance of a psychologist.

3) Data analysis

The Statistical Package for the Social Sciences v.20 was used for the data analysis. Missing data were replaced through the single regression method. The normality of the distribution was assessed using the Kolmogrov-Smirnov test and, because most distributions deviated from normality, non-parametric correlations (Spearman *rho*) were performed.

In order to analyze task performance in each cognitive domain, we applied the following formula:

$$Domain\ _{i}Performance = \sum_{j=0}^{10} \frac{\left(Task_{j}\_performance * Task_{j}\_Domain_{i}\_demands\right)/10}{11}$$

where *Domain$_i$ Performance* is a metric that measures in percentage the contribution of each cognitive domain (Memory, Attention, Executive Functions, Language) taking into account the cognitive demands of each generated *Task$_j$*. This approach allows us to correct task performance for the amount of challenge posed. That is, 100% task performance on a task that has 5 points (out of 10) Memory demands results on a 50% Memory performance, and so on and so forth.

Results

According to the Kolmogorov-Smirnov (KS) test, data were normally distributed for age (KS=.147, p=.200) but not for gender (KS=.335, p<.001), years of schooling (KS=.293, p<.001), stroke location (KS=.361, p<.001) and time post-stroke (KS=.261, p=.001). Data were normally distributed concerning the cognitive assessment with the MoCA (KS=.149, p=.200) and the performance in the TG (KS=.236, p=.005).

A. Does the TG personalization adapt to the patients' needs?

When comparing the patients' overall performance in MoCA and that in the adapted TG tasks, we observe that patients showed higher performances that those of their cognitive assessment (Z=-3.808, p<.001) (Figure 4). This indicates that patients with lower MoCA scores were presented with easier tasks, thus scoring higher. Consistent with this finding, we found a moderate correlation (r_s=.520, p=.019) between performance in the TG training (Mdn=83.25, IQR=67.88-91.5) and cognitive functioning as assessed by MoCA (Mdn=18, IQR=16-21.75, strongly suggesting that TG task performance is not only determined by the skillset of the patient. Hence, these data are consistent with the notion of a successful adaptation of the TG training parameters based on the cognitive characterization of each patient, increasing the average task performance and dissociating it from the cognitive skillset of the patient.

In addition, our data shows that more difficult tasks were automatically assigned to the participants performing at a higher level. That is, regardless of the task adaptation procedures, a very strong correlation (r_s=.872, p<.001) was found between the average TG task performance (Mdn=83.25, IQR=67.88-91.5) and the difficulty setting assigned to those patients by the TG (Mdn=4.83, IQR=3.24-6.43). This finding suggests that the personalization of the challenge of each task was properly adapted to the capabilities of each patient.

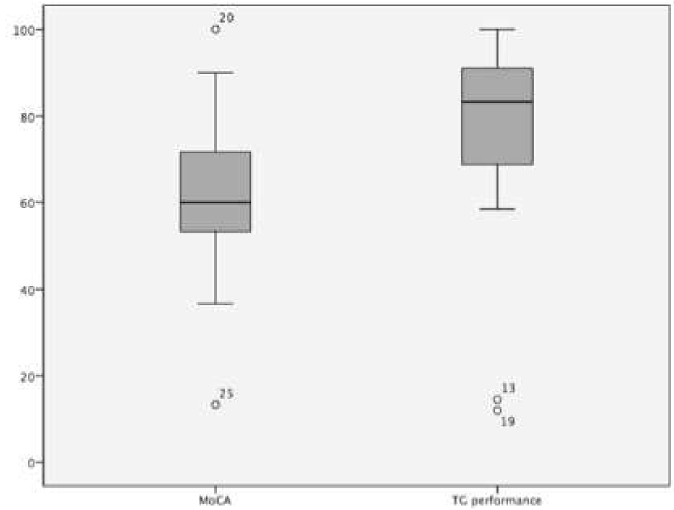


Figure 4. Comparison of MoCA assessment vs. TG performance scores. MoCA scores were converted to a 0-100 scale to allow comparison.

B) How accurate is the generated profile of cognitive demands of each task?

To address this question, we considered the Domain Performance metric - task performance weighed by their demand in each cognitive domain – as described in the Data Analysis section. This allows us to consider both task performance and personalization in a single metric. That is, a 100% performance in a task of difficulty 5 is equivalent to a 50% performance on a task of difficulty 10.

A strong correlation (r_s=.686, p=.001) was found between the performance in attention (Mdn=5.25, IQR=3.55-6.19) and the MoCA attention score (Mdn=3, IQR=3-4.75). Between the performance in memory (Mdn=3.97, IQR=293-5.23) and the MoCA memory score (Mdn=8, IQR=6-8.75) the correlation was also strong (r_s=.730, p<.001). The performance in the executive functions (Mdn=4.91, IQR=3.74-5.8) was also strongly correlated (r_s=.742, p<.001) with the MoCA executive functions score (Mdn=4, IQR=2.25-4.75). Finally, the performance in language (Mdn=3.43, IQR=2.66-4.37) and MoCA language score (Mdn=4, IQR=2-5) was moderately correlated: r_s=.475, p=.034 (Table 2).

Table 2. Spearman correlations between the tg performance (weighed by their demand in each cognitive domain and total score) and the moca subdomains scores.

	MoCA Attention	**MoCA Memory**	**MoCA Executive**	**MoCA Language**
TG Attention	.686**	.662**	.621**	---
TG Memory	.755**	.730**	.773**	---
TG Executive	.723**	.721**	.742**	---
TG Language	.682**	.688**	.719**	.475*
TG Total	.492*	.507*	.460*	---

** Correlation is significant at the 0.01 level. * Correlation is significant at the 0.05 level.

C) Reliability of the training

The internal consistency of the TG training was assessed through the Cronbach's alfa, using the median performance of each task. The TG revealed and acceptable internal consistency (α=.786) which means that, despite the great diversity in the type of training tasks, the consistency in its performance is acceptable. By performing this reliability analysis removing the Image Pairs task, a greater internal consistency level (α=.818, which is good) is obtained.

Discussion

In this paper we presented a feasibility study with the TG, a web-based tool that was developed through the combination of guidelines from a participatory design approach with 20 rehabilitation professionals, ICT's and existing rehabilitation models and theories. The TG enables the parameterization and generation of personalized cognitive paper-and-pencil training tasks. A clinical study with stroke patients has led us to four main conclusions concerning the feasibility of this web-based tool.

First, we can determine that, although moderately correlated, the TG training performance is higher and statistically different from the patients general cognitive functioning, as assessed by the MoCA. This finding leads us to conclude that performance is modulated by the TG adaptation. Second, our results demonstrate that more difficult tasks were assigned to the patients that could perform at higher levels. This finding indicates that our personalization adapts properly to each patient's skillset, providing an adaptive challenge level. Finally, we found moderate and strong correlations between attention, memory, executive functions and language assessment scores with the TG performance in the corresponding domains. These results largely support the existing task profiling, that is, the methodology used to quantify how each task impacts demands on each domain. Consequently, since our *Domain Performance* is correlated with the scores of all MoCA subdomains, this suggests that it may be possible to rely on actual TG task performance to provide an iterative TG training adaptation without requiring repeated clinical assessments.

Finally, the TG was very well received by patients and rehabilitation professionals, who showed interest and motivation to use it in the future.

Conclusions

We believe that the TG contributes towards the definition of objective procedures for the application of adaptive cognitive rehabilitation through the use of ICT's. The use of TG has virtually zero cost associated and can be widely deployed at healthcare centers. This new approach does not interfere with current clinical practices. By enabling the adaptation of task parameters and difficulty levels according to patient performance, this tool provides a comprehensive and highly personalized cognitive training. Given the encouraging results of this study, we are performing a longitudinal clinical trial to measure the impact of intensive cognitive training with the TG. In the meantime, the TG will continue to evolve with the development of more exercises.

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3. Combined cognitive-motor rehabilitation in virtual reality improves motor outcomes in chronic stroke - a pilot study [5, 6]

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 toward the integration of cognitive training for providing more effective solutions.

Here we investigate the feasibility for stroke recovery of a virtual cognitive-motor task, the Reh@Task, which combines adapted arm reaching, and attention and memory training. 24 participants in the chronic stage of stroke, with cognitive and motor deficits, were allocated to one of two groups (VR, Control). Both groups were enrolled in conventional occupational therapy, which mostly involves motor training. Additionally, the VR group underwent training with the Reh@Task and the control group performed time-matched conventional occupational therapy. Motor and cognitive competences were assessed at baseline, end of treatment (1 month) and at a 1-month follow-up through the Montreal Cognitive Assessment, Single Letter Cancelation, Digit Cancelation, Bells Test, Fugl-Meyer Assessment Test, Chedoke Arm and Hand Activity Inventory, Modified Ashworth Scale, and Barthel Index.

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Our results show that both groups improved in motor function over time, but the Reh@Task group displayed significantly higher between-group outcomes in the arm subpart of the Fugl-Meyer Assessment Test. Improvements in cognitive function were significant and similar in both groups.

Overall, these results are supportive of the viability of VR tools that combine motor and cognitive training, such as the Reh@Task.

Keywords: virtual reality, stroke, motor rehabilitation, cognitive rehabilitation, task adaptation.

1. Introduction

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 33–42% of stroke survivors require assistance for daily living activities 3–6 months post-stroke and 36% continue to be disabled 5 years later (Teasell et al., 2012). Loss of motor control and muscle strength of the upper extremity are the most prevalent deficits and are those that have a greater impact on functional capacity (Saposnik, 2016). Hence, its recovery is fundamental for minimizing long-term disability and improving quality of life. In fact, most rehabilitation interventions focus on facilitating recovery through motor learning principles (Kleim and Jones, 2008). However, learning engages also cognitive processes such as attention, memory and executive functioning, all of which may be affected by stroke (Cumming et al., 2013). Still, conventional rehabilitation methodologies are mostly motor focused, although 70% of patients experience some degree of cognitive decline (Gottesman and Hillis, 2010), which also affects their capability to live independently (Langhorne et al., 2011).

1.1 What Is Missing in Conventional Cognitive and Motor Rehabilitation Methodologies?

Although motor and cognitive neurorehabilitation after acquired brain injury is strongly based on intensive training and task-specific learning for promoting neural reorganization and recovery (Alia et al., 2017; Galetto and Sacco, 2017), conventional methodologies still strive to accomplish this goal (Levin et al., 2014). 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 after brain injury (Wilson, 1993). 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 laborious and demanding in terms of human resources, it is not as intensive as it should be (Langhorne et al., 2009). In addition, the relationship between cognitive and motor deficits is increasingly being unveiled and cognitive effort appears to contribute to motor recovery (Pichierri et al., 2011; Mullick et al., 2015; Verstraeten et al., 2016). Studies with stroke survivors have shown differential patterns of motor outcomes depending on the cognitive deficits of patients (Čengić et al., 2011; Påhlman et al., 2011). Moreover, 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 et al., 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.

1.2 Virtual Reality as a Tool for Combined Cognitive and Motor Rehabilitation

Virtual reality (VR) can nowadays be seen as a valuable approach in stroke rehabilitation, particularly in the motor domain where studies showed benefits at the level of upper limb function and ADL (Laver et al., 2018). This is potentially related to the fact that VR allows creating conditions to optimize motor learning by promoting meaningful and iterative practice, together with the delivery of immediate feedback (Levin et al., 2014). Although less explored, VR also provides the opportunity to integrate the practice of cognitive and/or motor activities in more ecologically valid contexts (Rand et al., 2009; Faria et al., 2016a; Adams et al., 2018). In such scenarios, motor training could be combined with the execution of cognitive rehabilitation tasks consisting of activities for improving cognitive domains such as attention, memory, or executive functions. Moreover, limitations in cognitive function have been shown to have an effect on VR performance (Kizony et al., 2004), and thus VR systems should be designed to address different cognitive profiles. Although the evidence is still modest, some studies with VR for simultaneous motor and cognitive rehabilitation have shown the potential of such strategy (Rand et al., 2009; Kim et al., 2011; Lee et al., 2015; Cameirão et al., 2017). Hence, 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 the results of a feasibility study with the Reh@Task, a multi-purpose desktop based virtual scenario that combines arm reaching and cognitive training through virtual adaptations for the training of memory and attention of traditional paper-and-pencil tasks.

1.3 Previous Work With the Reh@Task

The Reh@Task is a multi-purpose VR scenario for upper limb reaching and cognitive training that has been deployed in different configurations and with different rehabilitation paradigms. It allows the customization of stimuli, training task and training progression. In its first version, it originated as an adaptation in VR of the Toulouse Piéron (TP) cancelation task for the training of attention (Faria et al., 2014). The prototype was our first attempt to combine motor and cognitive training. It was primarily an attention only task that consisted on selecting target elements from a pool of distractors through arm reaching. This concept was tested in a 1-month intervention case study with three stroke survivors that presented both motor and cognitive deficits. Results indicated improvements both at motor and cognitive levels, suggesting the feasibility of the proposed approach (Faria et al., 2014). Following those results, the Reh@Task prototype was proposed with stimuli customization – to encompass varying cancelation tests with different stimuli – and the incorporation of a memory variant of the cancelation task for the training of memory, always relying on upper limb reaching movements. Thus, this new prototype enables the simultaneous training of upper limb reaching movements, memory, and attention. One of the advantages of a system such as the Reh@Task is that it can be easily customized to test different research hypotheses on the impact of such technology on stroke survivors with different profiles. In a previous controlled impact study, the Reh@Task was used to evaluate if cognitive tasks supported by personalized stimuli with positively valence could lead to improved motor and/or cognitive outcomes in an understudied population in comparison with conventional rehabilitation. This was done through stimulus selection from emotionally tagged pictures and through content personalization to patients' preferences, including music, in a group of sub-acute stroke survivors with mild cognitive impairment (MCI) (Cameirão et al., 2017). Results showed that the Reh@Task was as effective as conventional rehabilitation, although motor and cognitive improvements were poor in both groups. This suggested that patients with MCI have a poorer recovery prognostic, specifically when presenting simultaneous motor and cognitive deficits. In fact, there is evidence that cognitive deficits interfere with motor recovery (Mullick et al., 2015), and that patients with MCI might have more difficulties in dual-tasking (Schaefer and Schumacher, 2010).

In the present study, the Reh@Task was used with stimuli different to those used in the above mentioned studies, focusing on neutral stimuli that do not have an emotional charge and are traditionally used in standard rehabilitation (symbols, numbers, and letters), with a difficulty progression based on computational models of how stimuli properties affect task difficulty (Faria and Bermúdez i Badia, 2015). Further, in this case our population is chronic. Hence, this study presents a novel cognitive training, task progression, tested on a different patient population, and compares the impact of such approach to time matched conventional rehabilitation activities. We hypothesize that rehabilitation with the Reh@Task will result in improved motor and cognitive outcomes when compared to patients in the conventional rehabilitation condition.

2. Materials and Methods

2.1 Experimental Setup and Reh@Task

The setup consists on a PC (OS: Windows 7, CPU: Intel core 2 duo E8235 at 2.80 GHz, RAM: 4 Gb, Graphics: ATI mobility Radeon HD 2600 XT), a PlayStation Eye camera (Sony Computer Entertainment Inc., Tokyo, Japan) and a customized handle with a tracking pattern. The user works on a tabletop, facing a LCD monitor (24″) and moves the handle on the surface of the table with his/her paretic arm (Figure 1A). 2D upper limb reaching movements are captured through a camera-based Augmented Reality (AR) pattern tracking software (AnTS) (Mathews et al., 2007) (http://neurorehabilitation.m-iti.org/tools/ants). For adapting the task to individual users, the VR scenario has a built-in calibration function that normalizes the motor effort required in the task to the skillset of the user. The movements of the user are then mapped onto the movements of a virtual arm on the VR environment.

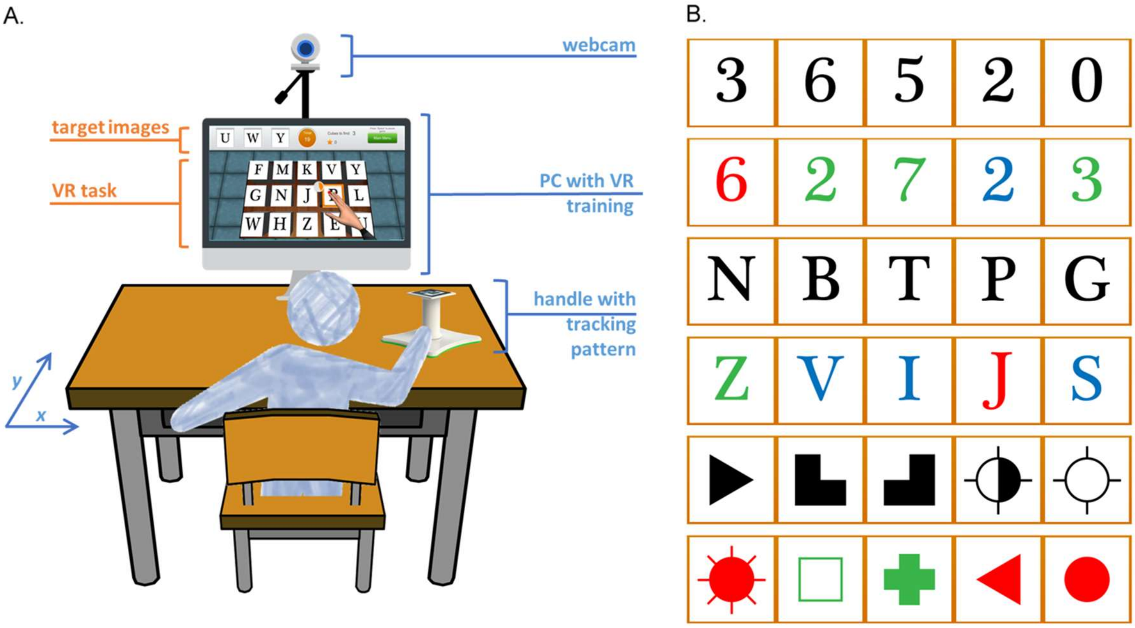

Figure 1. Experimental setup and VR task. **(A)** The user works on a tabletop and arm movements are captured by augmented reality pattern tracking. These movements are mapped onto the movements of a virtual arm on the screen for the execution of the cancelation task. **(B)** The target stimuli can be letters, numbers, and symbols in black or different colors. The target stimuli in this picture are ordered by increasing complexity.

The Reh@Task is based on traditional cancelation tests for the training of attention, and has been extended to incorporate numbers, letters and symbols, and the training of memory, and progressive difficulty adjustment according to the evolution of the patient (Figure 1B). The task consists on finding target elements within a pool of distractors. In the memory variant, the targets need to be memorized first and are hidden during target selection. The VR cancelation task has incremental difficulty and is adjusted to the individual performance of each user. There is a total of 120 difficulty levels that were defined through a participatory design study, where the input of 20 health professionals was operationalized in quantitative guidelines (Faria and Bermúdez i Badia, 2015). The progression of difficulty is made through the manipulation of the number of targets and distractors, the type of stimulus, the time available to solve the task, the time for selection and, in the memory variant of the task, the amount of time for memorizing the target.

These parameters are all operationalized in a way that increases the difficulty of the task incrementally (see Faria et al., 2016b) for further details on the difficulty adjustment algorithm). 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 user fails three times in a row, he/she goes back to the previous level. If the user succeeds, the level must then be successfully performed within the original established time.

Finally, a rule was defined to select the starting level in each training session according to:

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

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.

2.2 Participants

The sample was a convenience sample with a final size of 24 participants recruited at two outpatient rehabilitation units of CMM – Centros Médicos e Reabilitação (Murtosa and Aveiro, Portugal) between June of 2015 and April of 2017. The inclusion criteria were the following: chronic stroke (>6 months); undergoing occupational therapy rehabilitation at CMM; motor impairment of the upper extremity with sufficient observable movement to perform the virtual task, corresponding to a minimum score of 28 in the Motricity Index (MI) (Demeurisse et al., 1980) for elbow flexion and shoulder abduction combined; cognitive deficit but with enough capacity to understand the task and follow instructions, as assessed by the therapists; and able to read and write. Exclusion criteria included: history of premorbid deficits; unilateral spatial neglect assessed through paper-and-pencil cancelation tests; severe depressive symptomatology with a score above 20 points in the Geriatric Depression Scale (GDS) (Yesavage et al., 1983); and vision disorders that could interfere with the execution of the task. Thirty-two stroke survivors were included and randomized for participation in this study. Minor deviations from inclusion/exclusion criteria were permitted for two participants, and did not affect the participants' health, wellbeing, and rights (1 participant was 5 months post-stroke; 1 participant had a GSD score of 22). 25 participants completed the protocol, 1 dropped out, and 6 did not fulfill the experimental protocol. One participant was not included in the analysis because this participant was later confirmed to be in the acute stage of stroke (Figure 2). Hence, 24 participants (12 in VR group, 12 in Control group) were included in the analysis (Table 1). There were no significant differences between groups in demographics, except for age, the control group was significantly older (Mann–Whitney, $U = 31.0$, $p = 0.017$). This study was carried out in accordance with established ethical guidelines and was approved by the board of CMM – Centros Médicos e Reabilitação. All participants gave written informed consent in accordance with the Declaration of Helsinki.

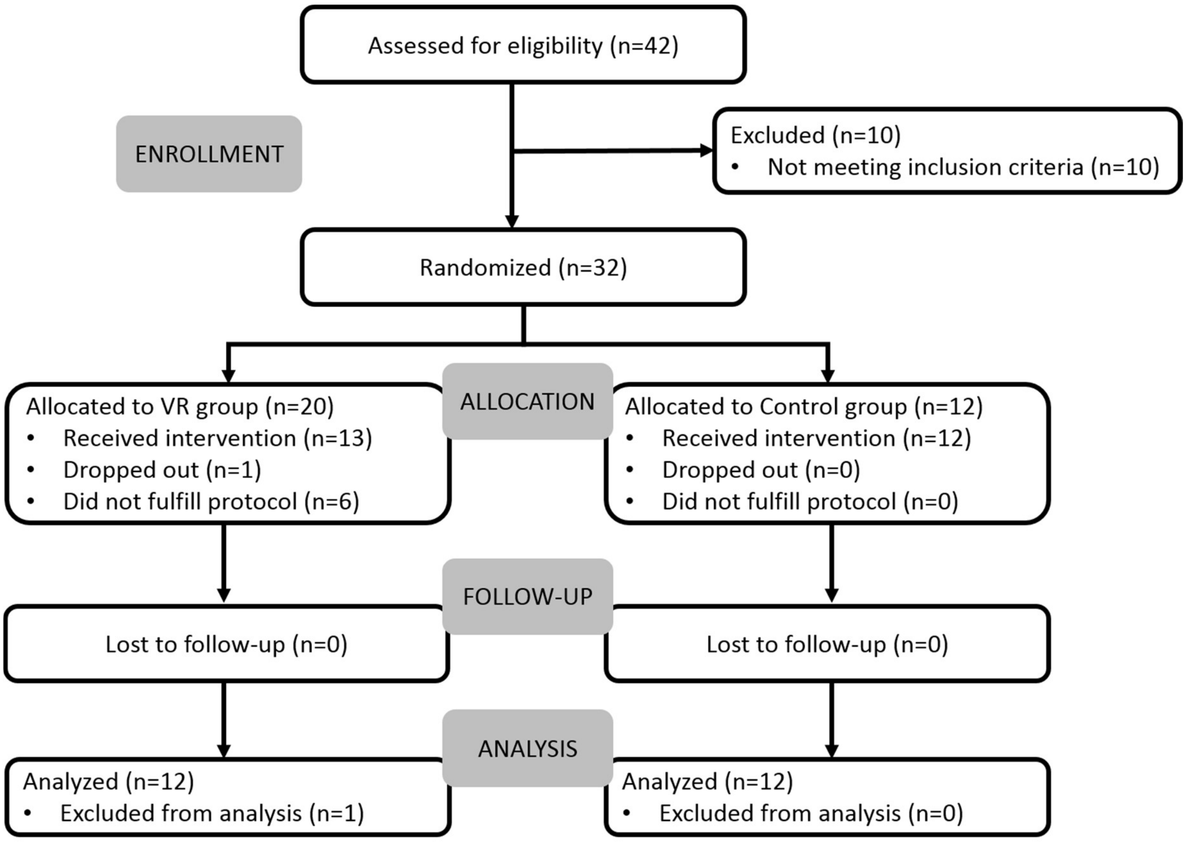

Figure 2. Flow diagram of enrollment, intervention allocation, follow-up, and data analysis.

Table 1. Characteristics of participants.

Group	**Sex**	**Age**	**Schooling**	**Months post-stroke**	**Type of stroke**	**Side of lesion**	**GDS**
VR	F	59	4	55	I	L	11
	M	57	6	40	I	L	8
	M	57	4	70	I	R	6
	F	55	6	16	I	L	8
	M	58	9	7	I	L	12
	M	78	4	6	I	R	14
	M	64	7	15	I	L	16
	F	68	3	14	I	L	22
	M	61	4	13	I	R	3
	M	37	9	23	H	L	4
	F	41	4	10	I	L	18
	M	51	12	30	I	R	3
Control	M	67	3	30	I	R	17
	F	76	4	61	I	L	17
	M	85	4	34	I	L	8
	M	75	4	84	I	L	11
	F	75	3	132	I	R	16
	M	65	4	12	I	L	13
	M	80	4	9	I	R	8
	F	62	3	88	I	R	14
	M	54	4	5	I	R	0
	F	53	11	18	U	L	10
	M	70	17	9	H	L	7
	F	65	7	12	U	L	13
VR	***4/8***	***57.1±11.0***	***6.0±2.8***	***24.9±20.3***	***1/11/0***	***8/4***	***11.2±5.7***
Control	***5/7***	***68.9±9.8***	***5.7±4.2***	***41.1±41.0***	***1/9/2***	***7/5***	***11.2±5.0***

Sex: F = Female, M = Male; Schooling is presented in years; Type of stroke: I = ischemic, H = hemorrhagic, U = Unknown; Side of lesion: L = Left, R = Right.

2.3 Experimental Protocol

This study followed a between-subjects design. After recruitment and baseline assessment, the participants were randomly assigned to one of two groups (VR or Control) by a researcher not involved in data collection, using the Research Randomizer, a free web-based service that offers instant random sampling and random assignment (Research Randomizer, https://www.randomizer.org/). Participants in the VR group underwent 12 sessions of 45 min with the Reh@Task, three times a week, for 1 month. Before the first session, participants went through an average of three short training trials with the Reh@Task 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 control group intervention was time-matched and included twelve sessions of 45 min of standard occupational therapy, spatial and time orientation activities, and writing training. Both interventions were in addition to conventional occupational therapy that typically entails 2–3 weekly sessions of 45–60 min and includes upper limb motricity training, practice of fine motor skills, cognitive-motor training, dexterity training, ADL, normalization of muscle tone, balance training and communication training. Participants underwent motor and cognitive assessment through a number of standardized clinical scales, at baseline, end of treatment and 1-month follow-up.

2.4 Cognitive, Motor, and Functional Assessment

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 assessor was not blind for the type of intervention. The cognitive profiling was made through the Montreal Cognitive Assessment (MoCA) (Freitas et al., 2011), which provides sub-scores for the following domains: Executive Functions, Naming, Memory, Attention, Language, Abstraction, and Orientation. The attention task-related capabilities were assessed with the Single Letter Cancelation (SLC) (Diller et al., 1974), the Digit Cancelation (DC) (Mohs et al., 1997) and the Bells Test (BT) (Gauthier et al., 1989). Motor deficits were assessed through the upper extremities part of the Fugl-Meyer Assessment Test (FM-UE) (Fugl-Meyer et al., 1975) for motor and joint functioning of the paretic upper extremity. Of the total score of 66, we also analyzed separately proximal (shoulder, elbow, forearm, coordination, 42/66) and distal (wrist, hand, 24/66) function. For functionality of the paretic upper extremity, the Chedoke Arm and Hand Activity Inventory (Barreca et al., 2004) (CAHAI) was used. MI was used to assess muscle power of the paretic upper extremity. Spasticity was assessed through the Modified Ashworth Scale (MAS) (Bohannon and Smith, 1987). Finally, the Barthel Index (BI) (Mahoney and Barthel, 1965) was used to assess independence in activities of daily living (ADLs).

2.5 Data Analysis

The normality of distributions was assessed using the Kolmogorov–Smirnov test for normality. Because most distributions deviated from normality, non-parametric statistical tests were used. Hence, central tendency and dispersion measures of the variables are presented as median and interquartile range (IQR), respectively. For improvements in clinical scores, we show the mean and standard deviation (SD) for an easier comparison with the literature. Differences between groups in demographic and clinical data at baseline were assessed using a Mann–Whitney *U* test in interval and ordinal variables, and a Pearson's chi-square (χ^2) test in nominal variables. A per-protocol analysis was used. For within-group changes over time across the three evaluation moments (baseline, end of treatment, and follow-up), a Friedman test for related samples was used and reported as χ^2 (degrees of freedom). The Wilcoxon's T matched pairs signed ranks (one-tailed because we predicted improvement over time in both groups) was used for further related pairwise comparisons with respect to baseline. No correction was applied to account for the number of pairwise comparisons, as non-parametric tests are already considered conservative. To compare groups at the end of treatment and follow-up, for each group we computed the improvement with respect to baseline. We used a one-tailed Mann–Whiney *U* test to test the hypothesis that improvements in the VR group were superior against the control group.

The Reh@Task software logged data on patient task performance (errors, number of targets and distractors, type of stimuli, time to completion) as well as the movement traces of the paretic arm, smoothed using a Gaussian window of 1 second. Performance improvements over time in the VR group were assessed by comparing the performances of each patient at the first and last training sessions. The error rates were computed as a percentage for each type of stimulus during the 12 training sessions. Movement smoothness was computed from the movement traces by counting the number of movement sequences, defined as trajectory segments in-between null acceleration points. To assess improvements in range of movement (ROM) over time, changes in the tracked position of the hand were assumed in the x- and y-axis of the tabletop surface, and the average improvements of the last three sessions were compared against the average of the 3 first sessions. All comparisons were performed using the two-tailed Wilcoxon's T matched pairs signed ranks test.

Effect sizes (r) are reported on the pairwise comparisons and are computed as $Z/\sqrt{N}$ (Rosenthal, 1991). The criteria for interpretation of the effect is 0.1 = small, 0.3 = medium, and 0.5 = large. For all statistical tests, a significance level of 5% ($\alpha = 0.05$) was set. Data were analyzed using Matlab (MathWorks Inc., Natick, MA, United States) and IBM SPSS Statistics for Windows, Version 22.0 (Armonk, NY, United States: IBM Corp).

3. Results

3.1 How Effective Is Cognitive Training With Reh@Task as Compared to Conventional Rehabilitation?

The baseline MoCA total scores were balanced between groups ($U = 60.5, p = 0.503, r = 0.18$), and so were the scores in MoCA subdomains (data not shown). Also balanced were the number of errors in SLC ($U = 64.5, p = 0.659, r = 0.09$), DC ($U = 57.5, p = 0383, r = 0.19$), and BT ($U = 58.5, p = 0.431, r = 0.16$).

The analysis of the scores over time for each group, considering the three evaluation moments (baseline, end of treatment, and follow-up), showed a significant impact on MoCA total score and some of its subdomains in both groups (Table 2). Specifically, the VR group displayed a significant effect in MoCA-Total [$\chi^2(2) = 8.3, p = 0.016$], MoCA-Recall [$\chi^2(2) = 6.2, p = 0.046$], and MoCA-Orientation [$\chi^2(2) = 8.4, p = 0.015$]. The control group showed a significant effect in MoCA-Total [$\chi^2(2) = 9.1, p = 0.010$], MoCA-Language [$\chi^2(2) = 6.1, p = 0.047$], and MoCA-Recall [$\chi^2(2) = 6.1, p = 0.048$]. Further pairwise comparisons with respect to baseline indicated that for the MoCA total score, both groups showed a significant improvement at end of treatment [VR: $T = 12.5, Z = 1.83, p = 0.034, r = 0.37$; Control: $T = 3.0, Z = 2.68, p = 0.003, r = 0.55$], and follow-up [VR: $T = 2.0, Z = 2.62, p = 0.004, r = 0.53$; Control: $T = 2.0, Z = 2.77, p = 0.003, r = 0.56$]. Mean improvements in MoCA total score at end of treatment were 2.6 ± 4.3 in VR against 3.1 ± 2.8 in Control, and for follow-up 3.4 ± 3.5 in VR against 3.0 ± 3.0 in Control. For MoCA subdomains with significant effects over time, improvements were also significant at end of treatment and follow-up for both groups. For the cancelation tests, the VR group showed a significant effect over time for BT [$\chi^2(2) = 6.6, p = 0.037$] only. Pairwise comparisons with respect to baseline revealed that this effect comes from a significant improvement at follow-up ($T = 2.5, Z = 2.40, p = 0.016, r = 0.49$), but not at the end of treatment. The control group showed a significant effect over time for the DC [$\chi^2(2) = 11.3, p = 0.004$] and BT [$\chi^2(2) = 10.5, p = 0.005$], with significant improvements at end of treatment and follow-up. No significant differences were found in the between-groups analysis, when comparing the significant improvements in the VR group with those of the control group at end of treatment and follow-up.

Table 2. Scores in cognitive assessment at baseline, end of treatment and follow-up for VR and control conditions.

Measure	**Virtual Reality (N=12)**				**Control (N=12)**			
	Baseline	***End***	***Follow-up***	***p***	***Baseline***	***End***	***Follow-up***	***p***
MoCA								
Total (max=30)	**22.5 (6)**	**25.0 (4)***	**26.0 (4)****	**0.016**	**21.5 (5)**	**24.0 (5)****	**24.0 (3)****	**0.010**
Executive (max=5)	3.5 (3)	4.0 (2)	4.5 (2)	0.066	2.0 (2)	2.5 (2)	3.0 (2)	0.102
Naming (max=3)	2.5 (1)	3.0 (0)	3.0 (0)	0.062	3.0 (1)	3.0 (2)	3.0 (0)	0.210
Attention (max=6)	5.5 (2)	6.0 (1)	6.0 (2)	0.204	5.0 (2)	5.5 (1)	5.0 (1)	0.131
Language (max=3)	2.0 (1)	2.0 (0)	2.0 (1)	0.527	**2.0 (2)**	**2.0 (1)***	**2.0 (0)***	**0.047**
Abstraction (max=2)	2.0 (1)	2.0 (0)	2.0 (0)	0.247	2.0 (1)	2.0 (0)	2.0 (0)	0.091
Recall (max=5)	**2.0 (3)**	**3.0 (2)****	**3.0 (2)***	**0.046**	**2.0 (3)**	**3.0 (1)***	**3.0 (2)***	**0.048**
Orientation (max=6)	**6.0 (2)**	**6.0 (0)***	**6.0 (0)***	**0.015**	6.0 (1)	6.0 (0)	6.0 (0)	0.368
Cancellation Tests								
SLC - Errors	1.5 (4)	1.0 (3)	1.5 (4)	0.900	3.0 (6)	2.0 (5)	2.5 (6.0)	0.115
DC - Errors	0.5 (3)	0.0 (1)	0.0 (1)	0.531	**2.2 (2)**	**0.0 (2)****	**0.5 (1)****	**0.004**
BT - Errors	**4.0 (5)**	**3.0 (4)**	**2.0 (2)****	**0.037**	**5.0 (4)**	**2.0 (4)****	**3.5 (4)***	**0.005**

Scores are presented as Median (IQR); p = p-value, Friedman test, bold indicates a significant effect ($p<0.05$) over time; Significant one-tailed pairwise comparison with respect to baseline are indicated with * or ** for $p<0.05$ or $p<0.01$, respectively.

3.2 How Effective Is Motor Training With Reh@Task as Compared to Conventional Rehabilitation?

On the scores in motor assessment scales at baseline, the groups were balanced in the CAHAI ($U = 43.0, p = 0.093$), BI ($U = 56.5, p = 0.360$), and MAS ($U = 54.0, p = 0.281$). However, the groups were not balanced in FM-UE ($U = 28.5, p = 0.010$) and MI ($U = 33.0, p = 0.024$), with the control group having significantly higher scores in these two scales.

The analysis of the scores over time for each group, considering the three evaluation moments, showed for both groups a significant impact on FM-UE [VR: $\chi^2(2) = 12.1, p = 0.002$; Control: $\chi^2(2) = 11.1, p = 0.004$], CAHAI [VR: $\chi^2(2) = 7.5, p = 0.023$; Control: $\chi^2(2) = 11.3, p = 0.004$], and MI [VR: $\chi^2(2) = 12.0, p = 0.002$; Control: $\chi^2(2) = 11.3, p = 0.004$] (Table 3). On the FM-UE arm and hand subparts, both groups showed significant improvements over time for the hand domain [VR: $\chi^2(2) = 8.4, p = 0.015$; Control: $\chi^2(2) = 7.7, p = 0.021$], but only the VR group improved significantly in the arm part [VR: $\chi^2(2) = 11.1, p = 0.004$; Control: $\chi^2(2) = 4.7, p = 0.097$]. The control group showed an additional significant effect in MAS [$\chi^2(2) = 7.6, p = 0.022$], indicating a decrease in spasticity. There was no significant effect over time for BI. Further pairwise comparisons with respect to baseline indicated that for the VR group improvements were significant at end of treatment and follow-up in FM-UE [End: $T = 0.0, Z = 2.20, p = 0.014, r = 0.45$; Follow-up: $T = 0.0, Z = 2.37, p = 0.009, r = 0.48$], FM-Arm [End: $T = 0.0, Z = 2.21, p = 0.013, r = 0.45$; Follow-up: $T = 0.0, Z = 2.20, p = 0.014, r = 0.45$], FM-Hand/wrist [End: $T = 0.0, Z = 1.83, p = 0.034, r = 0.37$; Follow-up: $T = 0.0, Z = 2.03, p = 0.021, r = 0.41$], CAHAI

[End: $T = 0.0, Z = 1.86, p = 0.031, r = 0.40$; Follow-up: $T = 0.0, Z = 1.89, p = 0.029, r = 0.39$], and MI [End: $T = 7.5, Z = 1.78, p = 0.037, r = 0.36$; Follow-up: $T = 1.0, Z = 2.85, p = 0.002, r = 0.58$]. For FM-Arm, the improvement compared to the control group was significantly higher ($U = 45.0, p = 0.031, r = 0.38$) at end of treatment and marginally significant at follow-up ($U = 48.0, p = 0.055, r = 0.33$). The control group showed significant improvements at end of treatment and follow-up in FM-UE [End: $T = 0.0, Z = 2.03, p = 0.021, r = 0.41$; Follow-up: $T = 0.0, Z = 2.38, p = 0.008, r = 0.49$], FM-Hand/wrist [End: $T = 1.0, Z = 1.75, p = 0.040, r = 0.36$; Follow-up: $T = 0.0, Z = 2.21, p = 0.013, r = 0.45$], CAHAI [End: $T = 0.0, Z = 2.23, p = 0.013, r = 0.45$; Follow-up: $T = 0.0, Z = 2.21, p = 0.013, r = 0.45$], and MI [End: $T = 0.0, Z = 2.04, p = 0.020, r = 0.42$; Follow-up: $T = 0.0, Z = 2.38$ $p = 0.009, r = 0.48$]. For the MAS, the improvements were only significant at follow-up [End: $T = 0.0, Z = 1.41, p = 0.078, r = 0.29$; Follow-up: $T = 0.0, Z = 2.24, p = 0.012, r = 0.46$], corresponding to a median decrease of one grade in this spasticity scale, specifically from 1+ to 1. Besides the significant difference in FM-Arm at end of treatment, no other significant differences were found in the between-groups analysis at end of treatment and follow-up.

Table 3. Scores in motor assessment at baseline, end of treatment and follow-up for VR and control conditions.

Measure	Virtual Reality (N=12)				Control (N=12)			
	Baseline	*End*	*Follow-up*	*p*	*Baseline*	*End*	*Follow-up*	*p*
FM-UE								
Total (max=66)	**28.0 (27)**	**32.0 (24)***	**33.0 (25)****	**0.002**	**45.5 (21)**	**51.0 (20)***	**51.0 (22)****	**0.004**
Arm (max=42)	**19.0 (15.5)**	**23.5 (13.7)***	**24.0 (13.5)***	**0.004**	31 (11.5)	32.5 (12.0)	32.5 (12.7)	0.097
Wrist/Hand (max=24)	**9.0 (10.7)**	**9.0 (12.2)***	**9.0 (12.2)***	**0.015**	**14.0 (9.5)**	**18.5 (8.7)***	**18.5 (9.5)***	**0.021**
CAHAI (ma=91)	**39.0 (40)**	**39.0 (38)***	**39.0 (38)***	**0.023**	**59.5 (33)**	**63.0 (30)***	**67.0 (27)***	**0.004**
BI (max=100)	90.0 (23)	95.0 (25)	95.0 (25)	0.097	97.5 (44)	97.5 (44)	97.5 (44)	1.000
MI (max=99)	**53.0 (31)**	**53.5 (20)***	**60.5 (25)****	**0.002**	**63.0 (21)**	**69.0 (16)***	**70.0 (15)***	**0.004**
MAS (max=4)	1.5 (1.6)	1.5 (0.9)	1.5 (1.0)	0.504	**1.5 (0.9)**	**1.5 (0.5)**	**1.0 (0.5)***	**0.022**

Scores are presented as Median (IQR); p = p-value, Friedman test, bold indicates a significant effect (p<0.05) over time; Significant one-tailed pairwise comparison with respect to baseline are indicated with * or ** for p<0.05 or p<0.01, respectively.

The mean improvements with respect to baseline at end of treatment and follow-up in the measures where a significant within-group effect over time was observed are presented in Table 4. For the VR and control groups, the observed average improvement in FM-UE was 4.6 ± 6.2 and 2.1 ± 3.6, respectively. This improvement in the VR group mainly comes from the FM-Arm subpart and strongly contrast with what was measured in the control group at end of treatment (3.7 ± 5.1 in VR against 0.8 ± 2.0 in Control, $p = 0.031$) and follow-up (4.0 ± 5.5 in VR against 0.9 ± 2.1 in Control, $p = 0.055$). The average improvements in the FM-Hand/wrist subpart, although being significant with respect to baseline, were modest for both groups at end of treatment (0.8 ± 1.4 in VR against 1.3 ± 2.3 in Control) and follow-up (0.9 ± 1.4 in VR against

1.8 ± 2.1 in Control). Also modest were the improvements in the CAHAI for both groups at end of treatment (0.8 ± 1.5 in VR against 2.7 ± 3.1 in Control) and follow-up (1.1 ± 1.8 in VR against 4.3 ± 4.9 in Control). These values are considerably below of what is considered a Minimal Detectable Change (MDC), which should be above 6.3 (Barreca et al., 2005). For the MI, the average improvements were higher in VR when compared to control at end of treatment (4.8 ± 8.3 in VR against 3.9 ± 5.4 in Control) and follow-up (9.1 ± 8.7 in VR against 5.3 ± 5.4 in Control), although not being significantly different.

Table 4. Mean improvement at end of treatment and follow-up.

Measure	**End**		**Follow-up**	
	VR	***Control***	***VR***	***Control***
FM-UE	4.6 ± 6.2	2.1 ± 3.6	4.9 ± 6.3	2.7 ± 3.6
FM-Arm	3.7 ± 5.1	0.8 ± 2.0	4.0 ± 5.5	0.9 ± 2.1
FM-Wrist/Hand	0.8 ± 1.4	1.3 ± 2.3	0.9 ± 1.4	1.8 ± 2.1
CAHAI	0.8 ± 1.5	2.7 ± 3.1	1.1 ± 1.8	4.3 ± 4.9
MI	4.8 ± 8.3	3.9 ± 5.4	9.1 ± 8.7	5.3 ± 5.4

Improvements are presented as Mean ± SD.

3.3 Outcomes in Reh@Task Measures

3.3.1 Task Performance Measures

The Reh@task data allowed us to quantify the evolution of patients in the VR group over time in between assessment points. Several variables are considered for this analysis: difficulty level achieved during each training session, type of task (memory/attention), and type of stimulus.

When looking at changes over time, we observe that patients improve over time in both task types but display a deceleration as levels of higher difficulty are achieved (Figure 3). Patients achieve in average higher difficulty levels in the attention task, display a steeper slope, and exhibit a constant variability over time. In contrast, improvements in the memory task are slower, reaching lower difficulty levels and with increasing variability over time, indicating an uneven increased difficulty of this task in patients when compared to attention. Data show significant improvements in task performance between the first and last sessions [Attention: $Z = 2.99, p = 0.003, r = 0.61$; Memory: $Z = 3.07, p = 0.002, r = 0.63$] (Figure 4). There were comparable performances in the first session for both attention ($M = 35.5 \pm 11.3$) and memory tasks ($M = 30.3 \pm 8.2$), but the difference is statistically significant in the last training session [Attention: 51.3 ± 8.0, Memory: 43.5 ± 11.9, $Z = 2.64, p = 0.008, r = 0.54$].

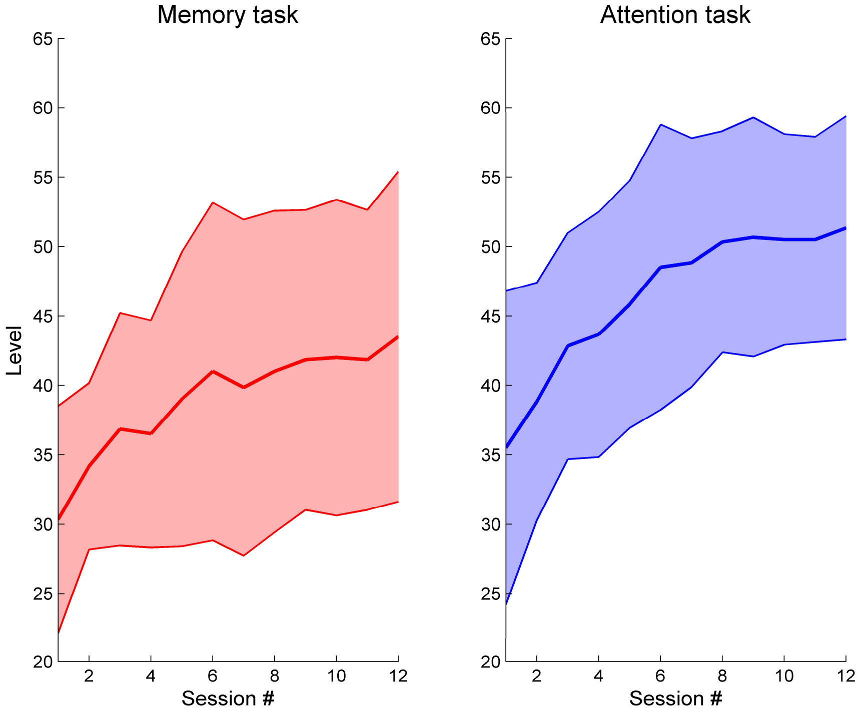

Figure 3. Task performance evolution over time in the Reh@Task. Data show the maximum difficulty level achieved per training session for the memory and attention tasks.

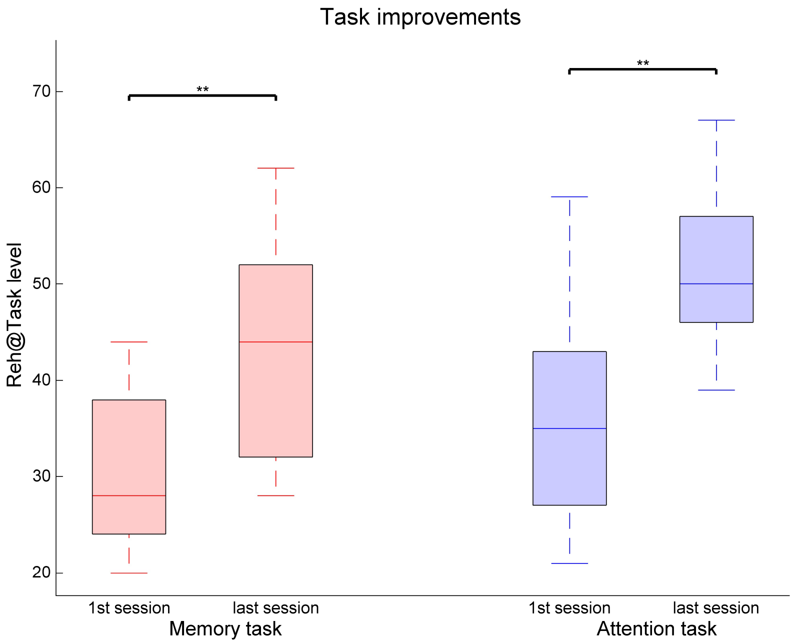

Figure 4. Task performance changes between the first and last training sessions for the memory and attention tasks in the Reh@Task. The whiskers indicate the most extreme data points that are not considered outliers. ** indicates $p < 0.01$.

If task performance is analyzed by type of stimulus, distinct performances can be seen (Figure 5). An increasing average number of errors is observed for Numbers (6.5%), Letters (10.4%), and Symbols (17.5%), and the difference is significant when comparing symbols and numbers ($Z = 2.12$, $p = 0.034$, $r = 0.43$), showing a continuum of difficulty that is consistent with the level of abstraction of each category. In addition, all categories show a significantly increased error rate when comparing the black stimuli with their colored counterpart [Numbers: $Z = 3.06$, $p = 0.002$, $r = 0.62$; Letters: $Z = 2.98$, $p = 0.003$, $r = 0.61$; Symbols: $Z = 2.43$, $p = 0.015$, $r = 0.50$]. Interestingly, error rates are similar for colored numbers (25.50%) and for colored symbols (25.48%) despite numbers being easier than symbols when uncoupled with colors. Surprisingly, error rates are significantly lower for colored letters than for colored numbers [Colored Letters: 17.81%, Colored Numbers: 25.50%, $Z = 2.12$, $p = 0.034$, $r = 0.43$].

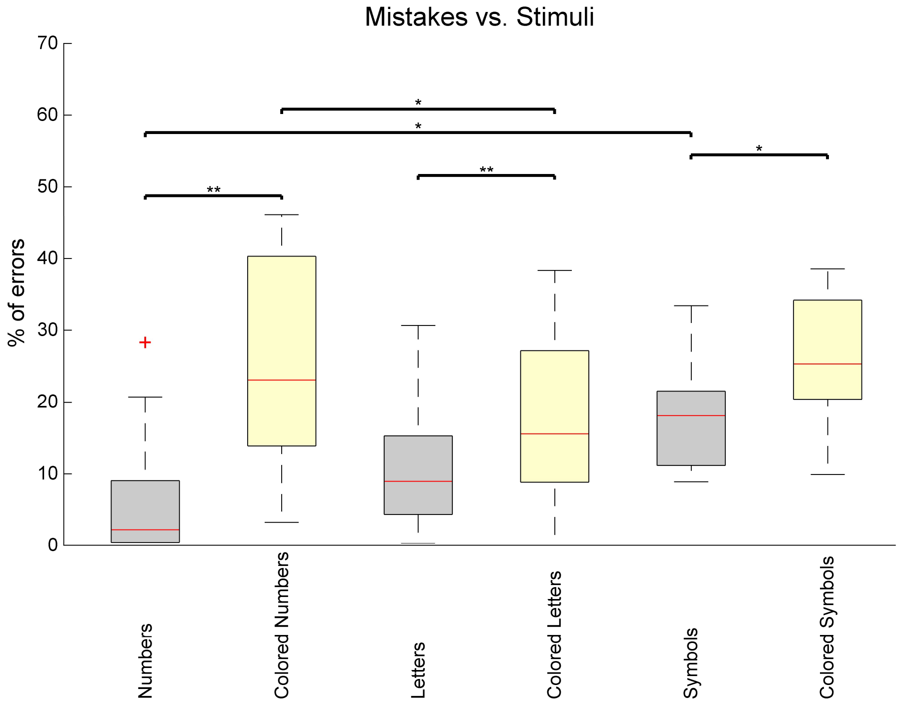

Figure 5. Percentage of task mistakes depending on the category of stimulus being presented in the Reh@Task. The whiskers indicate the most extreme data points that are not considered outliers. Outliers are represented as +. * or ** indicates $p < 0.05$ or $p < 0.01$, respectively.

3.3.2 Motor Performance Measures

The analysis arm movement trajectories provide information on both ROM and movement smoothness. The movement smoothness metric assumes that the movement trajectories that are built of less movement segments, that is, with less accelerations and decelerations, are indicative of a more controlled and smooth movement. A comparison of movement smoothness between the first and the last training sessions revealed a very significant decrease in the number of movement segments, indicating longer and smoother trajectories ($Z = 2.93$, $p = 0.003$, $r = 0.60$) (Figure 6). Finally, an analysis of the changes in ROM as assessed by the system's calibration at the beginning of each session revealed significant improvements in the *x* (30.1% of improvement, $Z = 2.67$, $p = 0.008$, $r = 0.54$) component of the movement, but not on the *y* (Figure **7**).

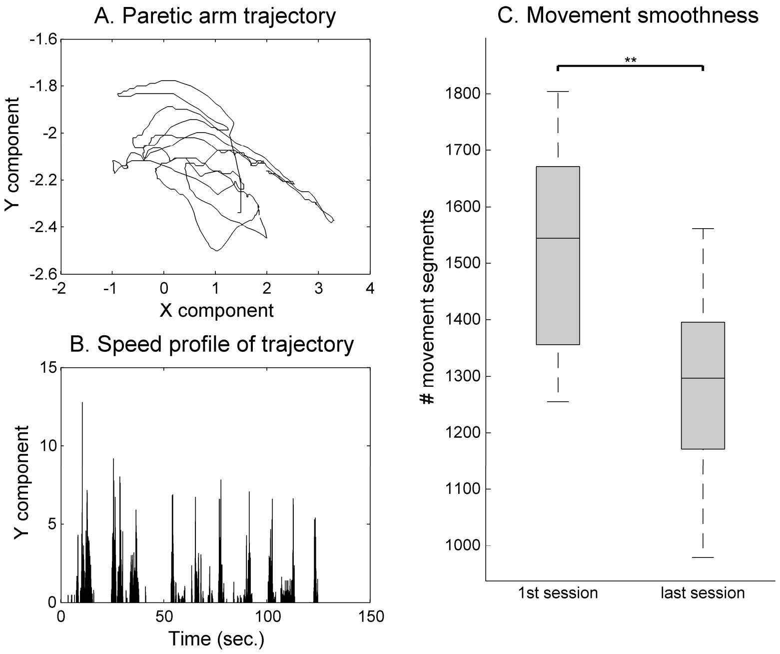

Figure 6. Movement smoothness analysis for the VR group. **(A)** Example 2-min sample of movement trajectory of one patient. **(B)** Computed speed profile of the sample in **(A)**. Movement sequence segments are identified in-between null acceleration points. **(C)** Movement smoothness changes between the first and last training sessions. The whiskers indicate the most extreme data points that are not considered outliers. ** indicates $p < 0.01$.

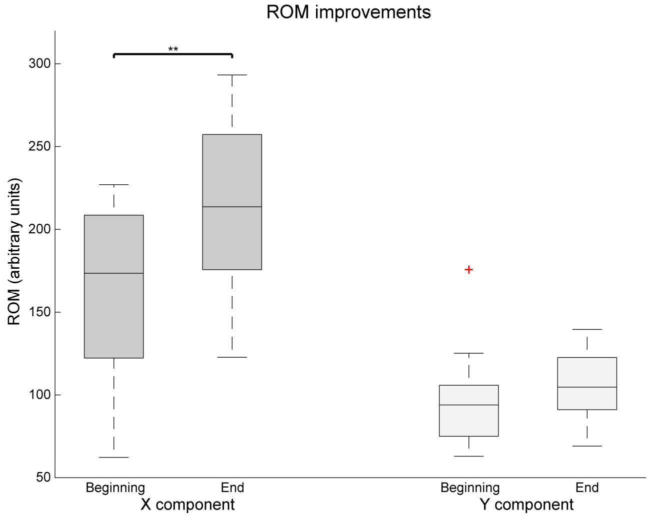

Figure 7. Changes over time of the *x* and *y* component of the Range of movement as assessed by the Reh@Task calibration. The whiskers indicate the most extreme data points that are not considered outliers. Outliers are represented as +. ** indicates $p < 0.01$.

4. Discussion

We presented a randomized controlled study with a VR cognitive and motor training task, the Reh@Task, consisting on a 1-month intervention with 24 chronic stroke survivors. We compared time-matched training with Reh@Task to standard occupational rehabilitation. During the intervention, all patients underwent conventional occupational therapy; only the VR group had specific training with the Reh@Task. The goal of this study was to investigate the benefits for stroke recovery of an integrative VR approach that combines cognitive and motor training. The main hypothesis behind this approach is that when approaching both motor and cognitive components, the context and situatedness of training impact its ecological validity. For this reason, both motor and cognitive challenges are personalized to each patient and presented as a single motor-cognitive VR task.

Our data show that both groups improved significantly in the motor domain in the FM-UE, CAHAI, and MI. However, in the total FM-UE the improvements in the VR group (4.6–4.9) were on average twice of those for the control group (2.1–2.7). This improvement in VR is superior to the ones observed in previous studies with similar VR paradigms in a chronic population (Cameirão et al., 2012; Maier et al., 2017). A more intensive (20 sessions in 1 month) motor-only intervention resulted on FM-UE improvements of about three points (Cameirão et al., 2012). A combined cognitive-motor approach, where the cognitive domain did not follow an automated adjustment approach but was more intensive (5 weekly sessions of 30 min during 6 weeks), led only to average improvements of less than 2 points in FM-UE (Maier et al., 2017). An analysis of our results in the FM components indicates that the improvement in the FM-Arm is significantly higher in comparison to control. Although both groups address proximal movements, this could be attributed to the nature of the VR task, which focuses on reaching movements. This is in line with other cognitive-motor studies with chronic stroke survivors where the training of hand motor competences in VR resulted in gains on manual abilities (Broeren et al., 2008). Nevertheless, our VR task does not address distal movements and comparable FM-Hand/Wrist improvements with the control group are achieved. These improvements in clinical scales are consistent with the Reh@Task data, that showed significant gains in ROM and movement smoothness. Concerning spasticity as measured by the MAS, we observed a significant reduction of one grade (from 1+ to 1) for the control but not the VR group. This is most likely related to the fact that the control group underwent more time of conventional occupational therapy, which includes normalization of muscle tone. Nevertheless, it has been argued that the 1+ and 1 grades do not have enough granularity do discriminate changes in spasticity (Pandyan et al., 1999).

Motor improvements did not generalize into clinically meaningful improvements in ADLs as measured by the BI and CAHAI. Considering that our sample is chronic and presents a very high BI and a low CAHAI at baseline, this indicates that these patients have high levels of independence despite their deficits. This suggests that effective strategies have been learned prior to the study that do not involve the paretic arm, leading to learned non-use, commonly observed in chronic populations (Wolf et al., 1989). If this is the case, an effective VR training should also incorporate strategies to address learned non-use (Ballester et al., 2016). This hypothesis is supported by previous results of an intervention with a modified version of the Reh@Task in a subacute population, in which improvements in CAHAI were larger, reaching meaningful values (Cameirão et al., 2017). This is also consistent with data from another integrative cognitive-motor VR study with patients in the 1st month post-stroke, where a mean improvement in BI of ~20 points was registered (Kim et al., 2011), what strongly contrasts with the average 5 points improvement that we measured in our study with a chronic population.

The impact of both VR and control interventions in cognitive function was significant (3/30 in MoCA) but not different between groups. Still, our results strongly contrast with those obtained using a similar motor and cognitive training paradigm with chronic stroke where improvements in cognitive function where not significant after 6 weeks of training (Maier et al., 2017), despite being a more intensive training with five sessions a week. Both groups in our study showed improvements in total MoCA and recall, which suggests that both interventions had an impact in terms of general cognitive functioning and memory. VR showed an additional improvement in orientation, and the control group in language. The lack of improvements in other sub-domains could be explained by the fact that although MoCA has high sensitivity to detect post-stroke cognitive impairment (Godefroy et al., 2011), it is a screening tool and might have not fully detected the specific cognitive impact of this intervention. Both groups improved in attention as assessed by the cancelation tests. Hence, the VR group had improvements consistent with the dimensions trained in the Reh@Task, and consistent with the Reh@Task performance data. The performance data during VR training show significant improvements over time in both memory and attention training. The lower performance in the memory tasks is also consistent with the lower recall scores of MoCA at baseline. The analysis of task performance depending on the stimulus used supports the importance of the modeling effort of our personalization algorithm, which automatically adjusts the task configuration (including stimulus type, number of targets, and distractors) to provide an appropriate challenge to the patient.

A prototype version of the Reh@Task, combining attention and arm reaching only, was previously tested with three chronic stroke survivors in a less intensive intervention (Faria et al., 2014). In that pilot study, two patients showed improvements in motor and cognitive function, and in ADLs, indicating the potential of an approach that integrates motor and cognitive training. Later, a different customization of the Reh@Task was used in a controlled study with subacute stroke survivors (Cameirão et al., 2017). The intervention was time-matched to the one being presented here and contrasting results were obtained. In that case, the Reh@Task was configured to also train attention, memory and arm reaching, but pictures of positive valence were used instead. In terms of mean improvements, in the here presented study we observed higher improvements in total FM-UE (4.6–4.9 against 0.3–3.0) and MoCA (2.6–3.4 against -0.9–1.7), and lower improvements in CAHAI (0.8–1.1 against 6.6–11.1). These results are interesting because it would be expected to observe a higher impact of training in the subacute population, but this was not the case. The subacute population improved poorly in both motor and cognitive domains. A factor that could contribute to this result is the fact that the subacute population had higher cognitive deficits at baseline (median 20.0 against 22.5), and it has been suggested that cognitive functioning is associated with upper limb motor recovery (Mullick et al., 2015). Additionally, the subacute population had on average higher depressive symptomology (15.1 against 11.2) and less years of schooling (4.6 against 6.0). Both these factors have been associated with poorer cognitive performance (Zahodne et al., 2015; MacIntosh et al., 2017). However, the subacute population did better in the performance of ADLs as measured by the CAHAI. As previously mentioned these differences could be related to learned non-use that is often observed in chronic stroke patients, that limits the impact of actual rehabilitation gains (Wolf et al., 1989). This highlights the importance of an early use of rehabilitation strategies that prevent learned non-use.

We believe that the presented results are supportive of the viability of low-cost rehabilitation solutions that combine motor and cognitive training, such as the Reh@Task. These solutions show potential to be effective tools to address cognitive training in an integrative manner and can be easily deployed at home or at the clinic. Our data supports a larger impact in motor function than in cognitive function when compared to control. One possible reason could be the limited range of cognitive tasks implemented in Reh@Task that do not encompass all domains needed to be addressed in a comprehensive rehabilitation program. A second reason could be the limited ecological validity of the training tasks. Despite being integrative motor-cognitive tasks, these are still far from actual motor-cognitive tasks performed in ADLs. Previous work using VR cognitive training of ADLs in simulated environments like a virtual mall or a virtual city showed translation of competences to real world ADLs (Rand et al., 2009) and improved outcomes when compared to conventional cognitive rehabilitation (Faria et al., 2016a). The relevance of such approaches can also be seen in a recent study with chronic stroke survivors that used a VR scenario for motor training based on the execution of virtual ADLs (Adams et al., 2018). After 8 weeks of treatment, a group of 15 patients showed a mean improvement of ~6 points in FM-UE, which is superior to what we have observed in our study.

Although further research in this area is essential, this work presents a valuable step toward designing more effective rehabilitation technologies that combine motor and cognitive training relying on VR. In fact, the recent Cochrane review on the effect of VR in stroke rehabilitation reports that there are not enough studies to assess the impact of VR in cognitive function (Laver et al., 2018). Hence, we believe that our contribution is relevant to the field. Nevertheless, this study has some limitations that should be considered. First, due to sequential admittance into the study, we used a completely randomized design, resulting in a heterogeneity of groups in age and FM baseline measures. The fact that groups differ in FM may also imply different recovery profiles. Second, although the use of standard of care as control is necessary, this control did not train the exact same competences as the Reh@Task. Third, the use of screening instruments for the assessment of the improvements in cognitive function in this context may lack the sensitivity to capture small improvements in the different domains addressed.

5. Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

6. Author Contributions

AF, MC, and SB defined and designed the research study, analyzed the data, and interpreted the results. JC, JA, and GC ran the intervention and collected the data. All authors revised and approved the current version of the manuscript.

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4. Benefits of virtual reality based cognitive rehabilitation through simulated activities of daily living: a randomized controlled trial with stroke patients [7, 8]

Abstract

Background

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. There is substancial evidence on post-stroke cognitive rehabilitation benefits, but its implementation is generally limited by the use of paper-and-pencil methods, insufficient personalization, and suboptimal intensity. Virtual reality tools have shown potential for improving cognitive rehabilitation by supporting carefully personalized, ecologically valid tasks through accessible technologies. Notwithstanding important progress in VR-based cognitive rehabilitation systems, especially with Activities of Daily Living (ADL's) simulations, there is still a need of more clinical trials for its validation. In this work we present a one-month randomized controlled trial with 18 stroke in and outpatients from two rehabilitation units: 9 performing a VR-based intervention and 9 performing conventional rehabilitation.

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[7] Faria, A. L., Andrade, A., Soares, L., & i Badia, S. B. (2016). Benefits of virtual reality based cognitive rehabilitation through simulated activities of daily living: a randomized controlled trial with stroke patients. *Journal of Neuroengineering and Rehabilitation*, *13*(1), 96. doi: 10.1186/s12984-016-0204-z

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Methods

The VR-based intervention involved a virtual simulation of a city – Reh@City – where memory, attention, visuo-spatial abilities and executive functions tasks are integrated in the performance of several daily routines. The intervention had levels of difficulty progression through a method of fading cues. There was a pre and post-intervention assessment in both groups with the Addenbrooke Cognitive Examination (primary outcome) and the Trail Making Test A and B, Picture Arrangement from WAIS III and Stroke Impact Scale 3.0 (secondary outcomes).

Results

A within groups analysis revealed significant improvements in global cognitive functioning, attention, memory, visuo-spatial abilities, executive functions, emotion and overall recovery in the VR group. The control group only improved in self-reported memory and social participation. A between groups analysis, showed significantly greater improvements in global cognitive functioning, attention and executive functions when comparing VR to conventional therapy.

Conclusions

Our results suggest that cognitive rehabilitation through the Reh@City, an ecologically valid VR system for the training of ADL's, has more impact than conventional methods.

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.

Keywords: cognitive rehabilitation; virtual reality; ecological validity; stroke.

Background

In most countries, stroke is among most common causes of death and one of the main causes of acquired adult disability [1]. Because most patients with stroke survive the initial illness, the greatest impact is usually caused by the long-term consequences for patients and their families [2]. It is estimated that 33 to 42 % of stroke survivors require assistance for daily living activities three to six months post stroke, and of these, 36 % continue to be disabled five years later [3, 4]. Although remarkable developments have been made in the medical treatment of stroke, it continues to heavily rely on rehabilitation interventions. In addition to motor disabilities, more than 40 % of stroke survivors are left with cognitive impairment after the event and almost two thirds are affected by mild cognitive impairment, and therefore are at risk of developing dementia [5]. Besides having a direct influence on the quality of life of patients and their caregivers, cognitive impairment after stroke is also associated with higher mortality [6] and greater rates of institutionalization [7]. Cognition is important for overall recovery since its impairment reduces a person's ability to plan and initiate self-directed activities, to solve problems, to sustain and divide attention, to memorize information and to understand task instructions. It has been shown that recovery of cognitive function of stroke patients in inpatient rehabilitation is directly related to their level of participation in rehabilitation activities [8]. Thus, reducing the impact of post stroke cognitive impairment through appropriate rehabilitation programs is an essential goal.

Current cognitive rehabilitation practice tends to be directed towards isolated cognitive domains including attention (focusing, shifting, dividing or sustaining), executive functions (planning, inhibition, control), visuo-spatial ability (visual search, drawing, construction), memory (recall and recognition of visual and verbal information) and language (expressive and receptive) [9]. Although there is evidence on the efficacy of current methods [10], an important concern is how effectively the improvements of these abilities that are trained separately generalize, leading to sustained improvement in everyday functioning [11, 12]. When we consider the cognitive domains required for activities of daily living (ADL's) such as a successful meal preparation – the patient must define a menu, identify the needed ingredients, write a shopping list, organize the time for shopping and preparing the meal – we acknowledge that multiple dimensions of cognition are engaged and, thereby, suggesting that need to be rehabilitated as a whole as opposed to independently [13]. Unfortunately, there is insufficient evidence to determine if and how the ecological validity of current cognitive rehabilitation methods impacts recovery [14, 15].

Current cognitive rehabilitation methodologies suffer other limitations besides the generalization of improvements to functional activities, social participation and life satisfaction. For instance, it is known that an intensive and individualized training is preferable [16]. Personalized rehabilitation involves an assessment of each patient's impairments, a definition of attainable goals for improvement, an intervention to assist in the achievement of goals and, finally, a reassessment to measure improvements [2]. However, in-depth patient assessment is expensive and time consuming, and currently impracticable due to the scarcity of professionals and resources, resulting in a suboptimal intensity, personalization and duration of rehabilitation interventions [17]. Further, although there is growing evidence that patients may achieve improvements on functional tasks even many months after having a stroke [18], most rehabilitation therapies are only guaranteed within three to 6 months post stroke [19]. Additionally, a James Lind Alliance study [20] interviewed 799 chronic stroke patients who reported that cognitive problems had not been addressed appropriately, especially when compared with mobility, confirming that it is essential to find adaptable and accessible tools that can be used frequently and intensively by patients at the clinic or at home after discharge, in order to maximize rehabilitation outcomes. Caregivers and health professionals were also interviewed and indicated that investigating ways to improve cognition after stroke should be a research priority [21].

Virtual Reality (VR) and interactive technologies have emerged as a valuable approach in stroke rehabilitation by providing the opportunity to practice cognitive and motor activities that are not or cannot be usually practiced within the clinical environment, such as training attention abilities in street crossing situations [22], executive functions by visiting a supermarket [23], or performing simulations of real-life scenarios and activities in urban virtual environments [24, 25]. Yet, the advantages of VR to address stroke impairments go beyond ecological validity of training, with a growing body of evidence especially in the motor rehabilitation domain [26]. Virtual environments are designed to be more enjoyable than conventional rehabilitation methods. The introduction of gaming elements and immediate feedback on performance enhance motivation, thereby encouraging higher numbers of repetitions [27]. Additionally, it enables the systematic presentation of stimulus and challenges in a hierarchical fashion, which can be varied from simple to complex upon success [28], making it progressively challenging according to patients abilities. Further, when stroke survivors suffer of hemiparesis in their dominant arm, this interferes with their ability to perform paper-and-pencil tasks, which in turn may impede cognitive training. Thus, another central advantage of VR is the possibility to be integrated with accessible interfaces such as adapted joysticks, natural user interfaces or robotic systems [29].

Despite important scientific and engineering activity in VR based systems for cognitive and motor rehabilitation, the majority of studies to date have evaluated interventions that were designed to address motor impairments. According to the most recent Cochrane review [26], there are only few randomized controlled studies that include cognitive rehabilitation and/or cognition assessment. Kim and colleagues [30] performed a study with USN patients, where 12 experimental group patients received computer-based cognitive rehabilitation, including IREX system® (Vivid group, Toronto, Canada), and 12 control group patients received only computer-based cognitive rehabilitation with ComCog® (Maxmedica Inc., Seoul, Korea). Their results suggested that VR training might be a beneficial therapeutic technique on USN in stroke patients. Kim and colleagues [31] also investigated the effect of VR on the recovery of cognitive impairment in 28 stroke patients by comparing VR training with the IREX system® to computer-based cognitive rehabilitation with ComCog®. Results showed significant improvements in both groups, with the VR group having greater improvements in the attention domain. A study from

Chirivella and colleagues [32] had 12 stroke patients in a stroke rehabilitation program using Neuro@Home, a cognitive and motor software-based rehabilitation platform. After an intervention of 8 weeks with 60 min sessions focused in attention, working memory, executive functions and visual perception training, patients showed significant improvements in attention, memory or executive functions. More recently and, in a more ADL's simulation perspective, Gamito and colleagues [33] tested the effectiveness of a VR application for neuropsychological rehabilitation in a group of 20 stroke patients. Results showed significant improvements in attention and memory functions in the intervention group, but not in the control group, not subject to any intervention. Also in an ADL's perspective, a pilot study from Rand and colleagues [34] explored the potential of a virtual supermarket (V-Mall) with 4 stroke patients. The intervention entailed ten 60-min sessions and was focused on improving multitasking while the participant was engaged in a virtual shopping task. Their main results support V-Mall potential as an effective tool for the rehabilitation of post stroke multitasking deficits during the performance of daily tasks. Most of these VR-based interventions do not address cognitive deficits in an integrative manner [30, 32, 33], or are not ecologically valid [30, 31]. The ADL's simulation systems may represent a better real-world transfer rehabilitation, however, these systems lack difficulty customization [33, 34]. The AGATHE project developed a tool to suppress this demand, offering patients customized rehabilitation sessions through simulated ADL's [25], however there are no efficacy clinical trials with this tool. Overall, we can conclude that results are encouraging but further research is needed, especially to clarify if VR, and more concretely training through the simulation of activities of daily living, is equivalent or more effective than conventional cognitive training [26].

In this paper we present a one-month clinical randomized controlled trial with 18 stroke patients: nine performing a VR-based intervention and nine performing a conventional intervention. The VR-based intervention involves a virtual simulation of a city – the Reh@City – where several activities of daily living are trained. Reh@City enables an integrative and personalized cognitive rehabilitation process, targeting several cognitive domains such as memory, attention, executive functions and visuo-spatial abilities in a more ecologically valid approach. Additionally, Reh@City makes the interaction with the virtual world accesible through its interface, and the complexity of the scenarios is adapted to the patients' profile.

Methods

Participants

The selection of participants took place at the Nélio Mendonça and João Almada Hospitals (Madeira Health Service, Portugal). In total, we selected 18 out and inpatients, based on the following inclusion criteria: no hemi-spatial neglect as assessed by the clinicians with the Line Bisection test [35]; capacity to be seated; ability to read and write; minimum cognitive function as assessed by the Mini-Mental State Examination (MMSE) ≥ 15 [36]; and motivation to participate in the study. The Token Test [37] was used to identify and exclude patients with moderate or severe language comprehension deficits. The study was approved by the Madeira Health Service Ethical Committee (reference number: 47/2013) and all the patients gave informed consent previous to participation.

Protocol

The 18 patients were randomly assigned to two different conditions: nine to the experimental group and nine to the control group (Figure 1), by a researcher not involved in the collection of the data, using the Research Randomizer, a free web-based service that offers instant random sampling and random assignment [38]. Both groups underwent a twelve-session intervention, of 20 min each session, distributed from 4 to 6 weeks. Patients assigned to the experimental group used, during the training sessions under the supervision of a psychologist, a VR-based simulation of ADL's, the Reh@City. The control group intervention involved time-matched cognitive training. Ideally, these participants should have performed the same simulated ADL's in the real-world environment, as previously done in similar studies [39]. However, in addition to the logistics that could not be supported in this study (insurance and transportation outside the clinical environment), in this clinical population motor impairments would interfere with the tasks accomplishments and unsuccessful actions could be a result of motor instead of cognitive deficits. For this reason, and consistent with the current cognitive rehabilitation exercises at the study hospitals, patients performed puzzles, calculus, problem resolution and shape sorting involving the training of executive functions, visuo-spatial abilities, attention and memory, under the supervision of their occupational therapist.

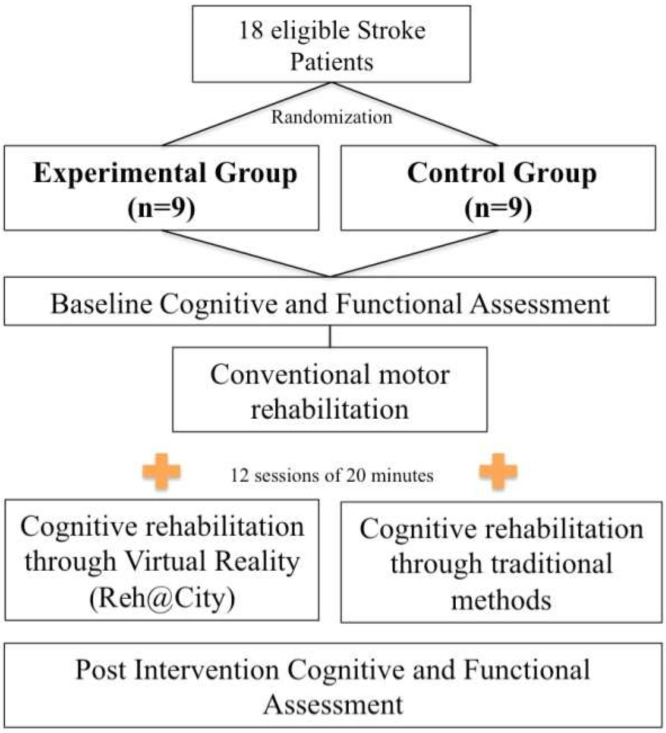

Figure 1: Protocol of the intervention.

Simulation of ADL's with the Reh@City

Paper and pencil tasks allow a very specific intervention in one or several cognitive domains but they lack ecological validity. In an attempt to address this limitation, our VR-based cognitive intervention consisted of a simulation of a city – Reh@City: a three-dimensional environment with streets, sidewalks, commercial buildings, parks and moving cars [40]. Because we are dealing with patients of generally older age and low computer literacy, the city was designed to have only square or rectangular building blocks and regular street intersections. This arrangement helps in memorizing the number of turns to get to a destination, and allows a more precise control of task difficulty.

Reh@City provides an integrative cognitive training experience where patients are required to accomplish some common ADL's in four frequently visited places: a supermarket, a post office, a bank, and a pharmacy. To help the patient relate the VR tasks to the real world, these places display billboards and products of real spaces and trademarks commonly found in Portugal. When a task is given, the goal's optimal path is displayed on a general map highlighted in green. The Reh@City can be configured to provide a mini-map in the lower half of the screen and/or a guidance arrow (Figure 2), which allows increasing, or decreasing the visuo-spatial orientation demands involved in the navigation task. If needed, the patient can press a help button to recall the task instructions and have access again to the task map. Visual feedback elements, such as time and point counters, are used to give feedback on the accomplishment of the task objectives as well as to reward successful actions (Figure 2). Points are accumulated at each objective completion (+20) and at each intermediate task (+1), and points are subtracted (−1) whenever a mistake is performed or a help button is used.

Figure 2: Three-dimensional street view of Reh@City. In a first-person navigation, users are given goal instructions supported with a mini-map indicating the optimal path (*green line and arrow*). Time and point counters are used to provide feedback on performance.

Attention training tasks bridge traditional paper and pencil cancellation tasks (where patients need to cross out target elements among distractors) and real tasks (where target and distractors are embedded in a real 3D environment). The implementation of the supermarket, the pharmacy and the post-office enables full control over the elements that determine the difficulty of training (number of targets, number of distractors and spatial arrangement of the grid). The list of tasks located in the up-right screen corner supports the patient by displaying the current objective and recently completed objectives. By removing the list we require the patient to memorize the sequence of tasks to perform. Further, the Reh@City targets executive functions by defining objectives that the patient needs to accomplish by using problem resolution, planning and reasoning skills (Table 1).

Table 1: Description of the levels of progression and cognitive domains involved

Levels of progression		**Cognitive domains**
1	Simple instructions (e.g. “Go to the supermarket and buy two bottles of water”) with mini-map, arrow and list of tasks cues	Visuo-spatial orientation and attention

2	Simple instructions (e.g. “Go to the Pharmacy and buy one cream”) without cues	Visuo-spatial orientation, attention and memory
3	Complex instructions (e.g. “Go to the Post-office buy two stamps and pick up three packages”) with mini-map, arrow and list of tasks cues	Visuo-spatial orientation, attention and executive functions (reasoning and planning)
4	Complex instructions (e.g. “Go to the supermarket and buy one orange juice, two boxes of cereals and four breads”) without cues	Visuo-spatial orientation, attention, memory and executive functions (reasoning and planning)
5	Problem resolution instructions (e.g. “Pay the electricity bill”) with mini-map, arrow and list of tasks cues	Visuo-spatial orientation, attention and executive functions (problem resolution, reasoning and planning)
6	Problem resolution instructions (e.g. “Get some food for breakfast”) without cues	Visuo-spatial orientation, attention, memory and executive functions (problem resolution, reasoning and planning)

Accessibility

The navigation in the city is three-dimensional but the arrangement in the different locations, such as shelves and cash machine (Figure 3a and b) are two dimensional to facilitate the selection of targets and to avoid motor difficulties in the interaction with hyper-realistic scenarios. Since most stroke patients have motor impairments, the navigation within the virtual environment was made through a joystick handle with only one button for “selection” and one for “help”. This simplified interface facilitates the learning process for those who never used a computer. A pilot study of the Reh@City prototype for a single session with 10 stroke patients [40] revealed a good level of usability (M = 77 %) as assessed through the System Usability Scale [41].

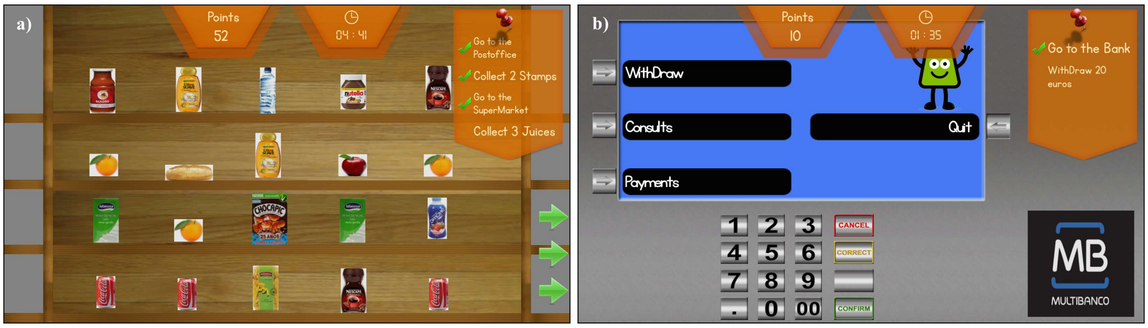

Figure 3: Examples of Reh@City ADL’s simulations. Representation in two dimensions of **a**supermarket shelves, and **b** a cash-machine.

Difficulty gradation and task personalization

Besides defining incrementally objectives with increased complexity (for instance “Go to the Supermarket and buy what is needed for breakfast”) (Table 1), we employed a method of fading cues: the Decreasing Assistance (DA) [42]. Following this methodology, in the first sessions the patient is immediately given all the cues available: mini-map; direction arrow and objectives list. The training continues with all the cues until correct performance is achieved on three consecutive sessions. On the following trial the cues supporting the well-succeeded actions are removed: if the patient easily navigates in the city, the direction arrow is removed; if the patient rapidly locates the places, the mini-map is removed; and if the patient correctly performs the objectives, the list is removed. If at any time the patient fails to produce the correct response, the cues are re-introduced until the performance is successful again.

Reh@City implementation and setup

Reh@City was implemented using the Unity 3D game engine (Unity Technologies, San Francisco, USA). The experimental setup consisted of a desktop computer running Windows 7 (CPU: Intel core 2 duo, RAM: 4Gb) with a 24” LCD monitor. For the study an arcade type of joystick was used (Topway’s Digiusb Joystick Tp-usb670, China) with 2 customized colored buttons corresponding to the in-game actions “selection” and “help”.

Neuropsychological assessment instruments

The same psychologist who supervised the experimental intervention assessed all participants for the trained cognitive domains before and after the interventions with a battery consisting of four neuropsychological instruments, with normative information available to indicate domain-specific deficits.

The primary outcome measure was the global cognitive functioning as assessed through the Addenbrooke Cognitive Examination (ACE) [43], which has good sensitivity (83 %) and specificity (73 %) for MCI after transient ischemic attack and stroke [44]. The ACE is built around the shell of the Mini-Mental State Examination (MMSE) [45] but assesses a wider range of cognitive functions. The application of the instrument takes 20 to 30 min and assesses attention and orientation, memory, verbal fluency, language and visuo-spatial abilities. Additionally, it provides the MMSE score, which was used as exclusion criteria for patients with severe cognitive deficits.

As secondary outcome measures, we had detailed attention and executive functioning assessments. To assess attention we used the Trail Making Test A and B (TMT A and B) [46], a very popular neuropsychological test that provides information on visual search, visual scanning, selective and divided attention, processing speed, mental flexibility, and also executive functioning. In part A, circles numbered from 1 to 25 needs to be connected in numerical order. In part B, numbers from 1 to 13 and letters from A to L need to be connected alternating numbers and letters in ascending order. To specifically assess **executive functions** we used the Picture

Arrangement test from the Wechsler Adult Intelligence Scale III (WAIS III) [47]. This task consists of 11 sets of picture cards, presented in a standard mixed-up order, and the participant has to rearrange these to create a logical story within the specified time limit. It requires perceptual organization, sequencing, verbal comprehension and planning skills, as well as social knowledge.

Also, as a secondary outcome measure we had the subjective general health status, as assessed by the Stroke Impact Scale 3.0 (SIS 3.0), a self-reported questionnaire that functionally assesses 8 domains: motor strength, hand function, ADL's, mobility (which are aggregated in the physical domain), communication, emotion, memory, and social participation [48]. The SIS 3.0 also includes patient's subjective assessment on the perception of recovery since their stroke on a visual analog scale of 0 to 100, with 0 meaning no recovery and 100 meaning full recovery. Internal consistency and test-retest reliability of the SIS 3.0 domains ranges between 0.79 and 0.98 [49].

Both pre and post assessment moments had an approximate duration of 60 min. At the end of the VR-based intervention we additionally used the System Usability Scale (SUS) [41], to assess satisfaction and usability with the Reh@City system. Final scores for the SUS can range from 0 to 100, where higher scores indicate better usability: 90s is exceptional, 80s is good and 70s is acceptable [50]. The questionnaire is technology agnostic, making it flexible enough to assess a wide range of interface technologies.

Data analysis

All statistical analyses were performed using SPSS software (version 20, SPSS Inc., Chicago IL, USA). As criterion for significance we used a α of 0.05. Normality of data was assessed with the Kolmogorov-Smirnov (KS) test. As some data were not normally distributed, nonparametric tests were used to evaluate the inter-group and intra-group differences. The Wilcoxon signed-rank test (W) was used to analyze the within group changes over time, while the two-tailed Mann-Whitney (MW) test was used to compare the between-group differences from baseline to the end of the study. No corrections for multiple comparisons were performed.

Results

According to the Kolmogorov-Smirnov (KS) test, data were normally distributed in both groups for age ($KS_{Experimental} = .156, p = .200$; $KS_{Control} = .196, p = .200$) and in the control group for years of schooling ($KS_{Experimental} = .394, p = .001$; $KS_{Control} = .267, p = .063$). Data were not normally distributed for gender, lesion location and months post-stroke. No differences between groups were found with the Mann-Withney test (Table 2).

Table 2: Demographic characteristics (presented as Medians and IQR) of both groups and differences between groups (MW).

	Experimental (n=9)	**Control (n=9)**	*MW*	*p*
Age	58 (48-71)	53 (50.5-65.5)	35.000	.666
Gender	Female=55.6%; Male=44.4%	Female=55.6%; Male=44.4%	40.500	.100
Schooling	4 (4-10.5)	9 (4-9)	46.500	.605
Lesion location	Right=55.6%; Left=44.4%	Right=55.6%; Left=44.4%	36.000	.730
Months post-stroke	7 (4-49)	4 (3-11.5)	23.000	.136

Concerning the neuropsychological assessment measures at baseline, data were normally distributed in both groups for ACE ($KS_{Experimental} = .218, p = .200$; $KS_{Control} = .185, p = .200$) and only in the control group for the TMT A time ($KS_{Experimental} = .390, p < .001$; $KS_{Control} = .169, p = .200$) and the Picture Arrangement test ($KS_{Experimental} = .371, p = .001$; $KS_{Control} = .240, p = .143$). Data were also normally distributed in both groups for the subjective general health status for the memory ($KS_{Experimental} = .227, p = .200$; $KS_{Control} = .122, p = .200$), emotion ($KS_{Experimental} = .254, p = .096$; $KS_{Control} = .147, p = .200$), communication ($KS_{Experimental} = .151, p = .200$; $KS_{Control} = .175, p = .200$), ADL's ($KS_{Experimental} = .159, p = .200$; $KS_{Control} = .204, p = .200$) an overall recovery ($KS_{Experimental} = .269, p = .059$; $KS_{Control} = .264, p = .071$) SIS dimensions. Social participation had a normal distribution only in the control group ($KS_{Experimental} = .299, p = .020$; $KS_{Control} = .149, p = .200$).

Global cognitive functioning

Table 3 describes the global cognitive functioning, as assessed by the ACE, of both groups in the pre and post intervention assessments. A Wilcoxon test for within-groups differences revealed that only the experimental group presented significant statistical improvements between pre and post assessment moments in both ACE ($W_{(9)} = 44.000$, $Z = -2.549, p = .011, r = .85$) and MMSE ($W_{(9)} = 34.000$, $Z = -2.246, p = .025, r = .75$). Additionally, we also have found significant improvements in attention ($W_{(9)} = 28.000$, $Z = -2.375, p = .018, r = .79$), memory ($W_{(9)} = 28.000$, $Z = -2.384, p = .017, r = .79$) and visuo-spacial ability ($W_{(9)} = 28.000$, $Z = -2.388$, $= .017, r = .80$)

domains only in the experimental group. Concerning the control group, the only significant change was a decline in verbal fluency ($W_{(9)} = 2.500$, $Z = -2.209, p = .027, r = .74$).

Table 3: ACE and MMSE scores (presented as Medians and IQR) pre and post intervention with within-groups (W p-values) comparisons and pre to post-intervention difference (Dif.) scores with between-groups (MW p-values) comparisons.

	Experimental (n=9)				**Control (n=9)**					
	Pre	Post	*W*	*p*	Pre	Post	*W*	*p*	*MW*	*p*
ACE-Total	72 (61-75.5)	81 (68-86.5)	44.000	**.011**	66 (54.5-81)	69 (58-78)	24.000	.398	13.500	**.014**
MMSE	23 (20.5-26)	29 (25-29)	34.000	**.025**	23 (20.5-26)	26 (21-26.5)	28.500	.136	18.000	**.050**
ACE-Attention	15 (14-16.5)	18 (16.5-18)	28.000	**.018**	14 (12-16.5)	16 (12.5-17)	13.500	.518	17.500	**.040**
ACE-Memory	15 (13-18)	18 (15-21.5)	28.000	**.017**	18 (11-19.5)	18 (12.5-21)	11.000	.336	23.000	.136
ACE-Fluency	5 (2.5-6)	6 (4-7.5)	27.000	.196	6 (4-8)	5 (2.5-5.5)	2.500	**.027**	13.000	**.014**
ACE-Language	22 (21.5-23)	24 (21-26)	33.500	.191	19 (16-22)	21 (17-24.5)	22.000	.168	32.500	.489
ACE-Visuo-spatial	12 (7.5-14.5)	14 (13-15)	28.000	**.017**	12 (7.5-13.5)	14 (7 – 15.5)	16.000	.246	26.500	.222

p <.05 is indicated in bold

A Mann-Whitney test indicated that the experimental group improved, significantly more than the control group, in terms of general cognitive functioning, as assessed by ACE ($U = 13.500$, $Z = -2.388, p = .014, r = .56$) and MMSE ($U = 18.000$, $Z = -1.996, p = .050, r = .47$). The experimental group presented also significantly higher scores in the attention domain ($U = 17.000$, $Z = -2.066, p = .040, r = .49$). We also found significant differences between groups in the fluency task ($U = 13.000$, $Z = -2.487, p = .014, r = .59$) with improvements in the experimental group and decline in the control group. There were no differences between groups for memory ($U = 23.000$, $Z = -1.578, p = 136, r = .37$), language ($U = 32.500$, $Z = -.713, p = 489, r = .17$) and visuo-spatial ($U = 26.500$, $Z = -1.263, p = .222, r = .30$) domains.

Attention

Table 4 describes the TMT A and TMT B performance for both groups, in terms of errors and completion time, pre and post intervention. No within group differences were identified by comparing the time to completion of the TMT A test in the experimental ($W_{(9)} = 16.500$, $Z = -.711, p = .477, r = .24$) and control ($W_{(9)} = 17.500$, $Z = -1.153, p = .249, r = .38$) groups, nor were there differences for the number of errors in the experimental ($W_{(9)} = 1.000$, $Z = -1.089, p = .276, r = .36$) and control ($W_{(9)} = 5.000, p = -1.190, p = .234, r = .40$) groups. Consistently for the TMT B, there were no differences for the time to completion in the experimental ($W_{(9)} = 5.000$, $Z = -1.153, p = .249, r = .38$) and the control ($W_{(9)} = 3.000$,

$Z = -1.572, p = .116, r = .52$) groups, as well as differences in the number of errors in the experimental group ($W_{(9)} = .000, Z = -1.890, p = .059, r = .63$). However, we found differences in the control group ($W_{(9)} = .000, Z = -2.060, p = .039, r = .69$).

Table 4: TMT A, TMT B and Picture Arrangement scores (presented as Medians and IQR) pre and post intervention with within-groups (W p-values) comparisons and pre to post-intervention difference (Dif.) scores with between-groups (MW p-values) comparisons.

	Experimental				**Control**				
	Pre	Post	Dif.	*W*	Pre	Post	Dif.	*W*	*MW*
A Time	74 (53-160.5)	67 (60-110)	-7	.477	120 (71.5-166)	97 (80.5-150)	-1	.553	.931
A Errors	0 (0-3)	1 (0-1)	0	.276	1 (0-3)	1 (0-2)	0	.234	1
B Time	360 (224-360)	240 (190-360)	-27	.249	360 (334-360)	296 (226.5-360)	-12	.116	.796
B Errors	4 (1.50-4)	3 (0-4)	0	.059	4 (3-4)	3 (1.50-3.50)	**-1**	**.039**	.666
Picture Arrangement	2 (0-2)	4 (1.50-6.50)	2	**.026**	2 (1-3.50)	2 (1-4)	0	.655	.063

p <.05 is indicated in bold

For the TMT A, both groups took less time to complete the post intervention test but with no significant differences between groups ($U = 39.000, Z = -.132, p = .931, r = .03$). For the TMT B, the experimental group took less time to completion when comparing to the control group, although this difference was not significant. There were no significant between group differences for the number of errors for both TMT A ($U = 40.000, Z = .047, p = 1, r = .01$) and TMT B ($U = 35.500, Z = -.482, p = .666, r = .11$).

Executive functions

Table 4 describes the Picture Arrangement test performance for both groups pre and post intervention. In this executive functioning test, we have found significant differences within the experimental ($W_{(9)} = 21.000, Z = -2.232, p = .026, r = .74$) but not within the control ($W_{(9)} = 2.000, Z = -.447, p = .655, r = .15$) group. There was a tendency to significance for the experimental group to have better performance, when compared to the control, at the end of the intervention ($U = 19.500, Z = -2.042, p = .063, r = .24$).

Subjective general health status

Table 5 describes the answers of both groups pre and post intervention to the SIS questionnaire. The SIS indicated that both groups perceived themselves as being better after the intervention. Improvements within the experimental group were significant for the physical domain ($W_{(9)} = 43.000, Z = -2.431, p = .015, r = .81$), namely strength ($W_{(9)} = 28.000, Z = -2.388, p = .017, r = .80$) and mobility ($W_{(9)} = 36.000, Z = -2.527, p = .012, r = .84$), memory ($W_{(9)} = 40.000, Z = -2.081, p = .037, r = .69$), emotion ($W_{(9)} = 40.500, Z = -2.136, p = .033, r = .71$), social participation ($W_{(9)} = 34.000, Z = -2.240, p = .025, r = .75$) and overall recovery ($W_{(9)} = 28.000, Z = -2.401, p = .016, r = .80$); but not for communication

($W_{(9)} = 21.500$, $Z = -1.279, p = .201, r = .43$), ADL's ($W_{(9)} = 38.000$, $Z = -1.840, p = .066, r = .61$) and hand function ($W_{(9)} = 23.500$, $Z = -1.614, p = .106, r = .54$). The differences within the control group were significant for the physical dimension ($W_{(9)} = 41.000$, $Z = -2.192, p = .028, r = .73$), namely for the mobility ($W_{(9)} = 26.000$, $Z = -2.028, p = .043, r = .68$), memory ($W_{(9)} = 36.000$, $Z = -2.524, p = .012, r = .84$) and social participation ($W_{(9)} = 36.000$, $Z = -2.521, p = .012, r = .84$); but not for strength ($W_{(9)} = 25.000$, $Z = -1.859$, $\mathrm{p} = .063, r = .62$), emotion ($W_{(9)} = 30.000$, $Z = -1.682, p = .092, r = .56$), communication ($W_{(9)} = 20.000$, $Z = -1.014, p = .310, r = .34$), ADL's ($W_{(9)} = 38.000$, $Z = -1.838, p = .066, r = .61$), hand function ($W_{(9)} = 18.000$, $Z = -1.594, p = .111, r = .53$) and overall recovery ($W_{(9)} = 30.500$, $Z = -1.763, p = .078, r = .59$). There were no significant differences between groups in the strenght, mobility, hand function, ADL's, memory, emotion, communication, social participation, and overall recovery dimensions of the SIS.

Table 5: SIS scores (presented as Medians and IQR) pre and post intervention with within-groups (W p-values) comparisons and pre to post-intervention difference (Dif.) scores with between-groups (MW p-values) comparisons.

	Experimental				**Control**				
	Pre	Post	Dif.	*W*	Pre	Post	Dif.	*W*	*MW*
Physical	42.6 (35.5-56.9)	51.6 (37.7-71.7)	9	**.015**	39.4 (12.4-46.9)	38.1 (24.2-58.3)	-1.3	**.028**	.863
Strength	50 (30-59.4)	62.5 (36.3-71.9)	12.5	**.017**	37.5 (12.5-53.1)	43.8 (25-62.5)	12.5	.063	.964
Memory	62.5 (45.3-82.8)	71.9 (53.1-86.6)	9.4	**.037**	56.3 (32.8-70.3)	62.5 (46.9-79.7)	6.3	**.012**	.387
Emotion	75 (55.5-84.7)	83.3 (75-87.4)	8.3	**.033**	58.3 (45.8-73.6)	66.67 ± 27.78	13.9	.092	.387
Communication	75 (60.7-91.1)	85.7 (62.5-94.6)	3.6	.200	67.9 (42.9-80.4)	67.9 (44.6-83.9)	3.6	.310	.863
Mobility	67.5 (42.5-74.9)	75 (51.3-86.3)	5	**.012**	40 (22.5-53.8)	52.5 (31.3-58.8)	7.5	**.043**	.790
Hand Function	15 (0-40)	40 (5-55)	10	.106	25 (0-30)	25 (0-45)	0	.111	.752
ADL's	50 (37.5-80.2)	56.3 (49-86.5)	10.4	.066	43.8 (14.6-53.1)	45.8 (30.2-63.6)	8.3	.066	.863
Social	63.9 (29.2-72.3)	66.7 (53.5-83.3)	6.6	**.025**	36.1 (29.2-51.4)	50 (41.7-58.3)	8.3	**.012**	1
Recovery	50 (40-55)	70 (55-80)	20	**.016**	40 (40-55)	60 (45-75)	20	.078	.436

$p < .05$ is indicated in bold

Usability

Although only 3 out of 9 participants from the experimental group had previous computer experience, there was a good acceptance of the system with no reported problems in the execution of the VR task. Observational information and subjective statements from the participants were consistent with the SUS scores, which reported good levels of usability and satisfaction for the Reh@City (Mdn = 80/100, IQR = 75–87.5).

Discussion

In the past several VR systems have been developed for brain injury rehabilitation, some of which were developed but not field tested [24, 25] or have only gone through studies with a small number of participants and/or without control groups [23, 32, 51]. Most of the existing randomized controlled trials with VR-based cognitive rehabilitation, focus in specific cognitive domains, as memory [52, 53] and attention [33], or specific deficits, as USN [22, 30]. Instead, Reh@City was developed to target the rehabilitation of multiple cognitive domains simultaneously requiring the execution of daily routines in progressive levels of cognitive complexity. Our study, besides its limitations, is the first randomized controlled trial that shows evidence that VR-based cognitive rehabilitation in an ecologically valid context could be more effective than conventional training.

Comparing VR and control interventions, in terms of global cognitive functioning, as assessed with the ACE and the MMSE, only the experimental group improved significantly from pre to post-intervention. These significant improvements were also verified in the between-groups analysis. We have found significant improvements in attention, memory and visuo-spatial abilities for the experimental group. Attention and memory improvements are consistent with a study from Gamito and colleagues [33], which compared a VR-based intervention (ADL's simulations targeting attention and memory) with conventional rehabilitation. The visuo-spatial improvements are consistent with Kim and colleagues [30] study, which compared a VR-based intervention with a computer-based intervention in USN. Considering executive functions, our control group had a significant decline in verbal fluency from pre to post intervention. The Picture Arrangement Test specifically assessed problem resolution and processing speed and its results revealed a pre to post intervention improvement only in the experimental group, which we consider a very promising result for further research.

The assessment of processing speed and attention with the TMT A and B revealed only a significant difference in the reduction of the number of errors, from pre to post intervention in the performance of the TMT B, in the control group. This result is not consistent with the other assessments and with previous studies, which found significant attention improvements, only in the experimental group [31]. The fact that this test is highly influenced by schooling [54] and that our sample had few years of education might explain the persistence of low performance in this test from pre to post assessment.

Besides cognition, we assessed the intervention's impact in the multiple domains of health and life with the SIS 3.0. Self-reported data revealed that the experimental group improved significantly in the physical domain, namely strength and mobility, memory, emotion, social participation and overall recovery. Instead, the control group decreased in the physical domain and only improved in memory, mobility and social participation. Nevertheless, no differences between groups were identified. There are CID's cut-offs for SIS 3.0 motor dimensions (strength = 9.2; ADL's = 5.9; mobility = 4.5; hand function = 17.8) [55] and both groups' improvements were clinically important for strength, ADL's and mobility. These findings are especially relevant because our VR intervention targeted cognitive aspects but also improved the physical domain, more specifically motor strength, and the emotional condition of patients, as well as their own perception of overall recovery after stroke. Finally, the interaction with the our system was reported as very positive, with high levels of engagement and motivation, which is important to enhance adherence to treatment. The good usability and satisfaction scores obtained with the SUS confirmed these observations.

Despite the positive impact, some limitations of our study must be considered when interpreting the results. Concerning the sample, eighteen participants can be considered a small number, though it is comparable with previous similar interventions [31, 33]. In addition, there was heterogeneity between groups, especially related to time post-stroke. Although the experimental group was more chronic than the control, this difference was not statistically significant. The dosing of 4 h was of low intensity, and therefore might have not been sufficient to achieve greater or measurable improvements in both groups. Intervention duration of similar previous studies range from 6 to 18 h distributed in sessions of 30 to 60 min, 3 to 5 times a week [30, 31, 32, 33, 34]. Furthermore, the intervention was not blind since the same person performed the assessment and the intervention. Regarding the cognitive assessment, there might have been learning effects of the tools since none of them have parallel versions for multiple assessments. Yet, even if a learning effect existed, this would apply to both intervention and control groups and the comparison would still be valid. Nevertheless there are not established clinically important differences (CID's) for the cognitive assessment tools, through the improvement scores from pre to post-intervention we can conclude that Reh@City, being it designed to address attention, memory, visuo-spatial abilities and executive functions, revealed to be more effective for cognitive rehabilitation than our control intervention. Although it would be relevant to have complementary information with a real-world assessment in a supermarket, pharmacy, post-office and bank, unfortunately this required logistics that could not be implemented for this study. In addition, the main objective was to clinically assess the impact of the Reh@City as a cognitive rehabilitation tool and not necessarily to assess the extent of transfer from VR to actual ADLs.

Conclusions

This study examined the effectiveness of Reh@City in comparison to conventional methods. Overall, the results of this one-month longitudinal study have revealed that, cognitive rehabilitation through an ecologically valid VR system can have a larger impact than conventional methods. Reh@City showed similar functional impact as the conventional methods and larger improvements in general cognitive functioning. Our results contribute with new evidence and provide further understanding on the impact of using simulations of ADL's in the rehabilitation of cognitive deficits. Nevertheless there is still a need of further research considering other clinical populations, larger sample sizes and more comparative studies. Hence, a comparison of an improved version of this VR system with a comprehensive paper-and-pencil cognitive training, using a greater number of patients is taking place.

Authors' contributions

ALF, SBB and LS designed the study and performed the data analysis. AA performed the data collection and contributed to the data analysis. ALF and SBB wrote the manuscript for publication. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Madeira Health Service - SESARAM Ethical Committee (approval number 47/2013) and all the participants gave their informed consent.

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5. A comparison of two personalization and adaptive cognitive rehabilitation approaches with treatment as usual: a randomized controlled trial with chronic stroke patients [9, 10]

Abstract

Background: Paper-and-pencil tasks are still widely used for cognitive rehabilitation despite the proliferation of new computer-based methods, like VR-based simulations of ADL's. Studies have established construct validity of VR assessment tools with their paper-and-pencil version by demonstrating significant associations with their traditional construct-driven measures. However, VR rehabilitation intervention tools are mostly developed to include mechanisms such as personalization and adaptation, elements that are disregarded in their paper-and-pencil counterparts, which is a strong limitation of comparison studies. Here we compare the clinical impact of a personalized and adapted paper-and-pencil training and a content equivalent and more ecologically valid VR-based ADL's simulation.

Methods: We have performed a trial with 36 stroke patients comparing Reh@City v2.0 (adaptive cognitive training through everyday tasks VR simulations) with Task Generator (TG: content equivalent and adaptive paper-and-pencil training) and treatment as usual (TAU), which was occupational therapy. The intervention comprised 12 sessions, with a neuropsychological

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assessment pre, post-intervention and follow-up, having as primary outcome the screening cognition measure of the Montreal Cognitive Assessment (MoCA).

Results: A within-group analysis revealed that the Reh@City v2.0 improved general cognitive functioning, attention, visuospatial ability and executive functions. These improvements generalized to verbal memory, processing speed and self-perceived cognitive deficits specific assessments. TG only improved in orientation domain on the MoCA, and specific processing speed and verbal memory outcomes. However, at follow-up, processing speed and verbal memory improvements were maintained and it was revealed a new one in language. TAU did not have a significant impact at any of our outcome measures. A between groups analysis revealed Reh@City v2.0 superiority in general cognitive functioning, visuospatial ability, and executive functions on the MoCA.

Conclusions: The Reh@City v2.0 intervention with higher ecological validity revealed higher efficacy with improvements in different cognitive domains and self-perceived cognitive deficits in everyday life, and the TG intervention retained fewer cognitive gains for longer.

Trial Registration: The trial is registered at ClinicalTrials.gov, number NCT02857803.
Registered 5 August 2016,
https://clinicaltrials.gov/ct2/show/NCT02857803?cond=Stroke&cntry=PT&rank=1.

Keywords: cognitive rehabilitation; virtual reality; stroke; ecological validity.

1. Introduction

1.1 Cognitive rehabilitation after stroke

Stroke is a leading cause of long-term acquired disability in adults (1), predisposing patients toward institutionalization and poorer quality of life (2). Over the coming decades, the incidence of post-stroke disability is expected to increase by 35% due to the rising prevalence of cerebrovascular risk and advances in medicine which are reducing post-stroke mortality rates (3). Historically, stroke rehabilitation has been focused on motor rehabilitation (4,5). However, post-stroke cognitive deficits are pervasive causing disability with major impacts on quality of life and independence on everyday life activities (6,7). In the last years, attention to the impact of cognitive deficits has been growing (8) and finding new ways to improve cognition after stroke is considered a priority by stroke survivors, caregivers and health professionals in 2014 (9). Also, more recently, the International Stroke Recovery and Rehabilitation Alliance (ISRRA) 2018 working group has identified post-stroke cognitive impairments as a research priority (10).

Despite advances in new pharmaceutical solutions, brain stimulation, stem cell (11) and brain-computer interface systems (12), cognitive rehabilitation remains the most common approach to improve specific cognitive processes. Regardless of the many new developments in cognitive rehabilitation programs and applications, limited data on the effectiveness of cognitive rehabilitation is available because of the heterogeneity of participants, interventions, and outcome measures (13). Results from recent reviews corroborate that cognitive rehabilitation has a positive impact on post-stroke cognitive outcomes (14,15), although of small magnitude (Hedges' g = 0.48) (14). This result is in line with the quantitative (16) and qualitative (17–19) findings of previous reviews that have analyzed the effect of cognitive rehabilitation across multiple cognitive domains.

1.2 Is cognitive rehabilitation’s impact small or are we missing better cognitive rehabilitation methodologies?

Paper-and-pencil tasks are still the most widely used methods for cognitive rehabilitation because of their accessibility, ease of use, clinical validity and reduced cost (20). In the last years, computer-based versions of these traditional tasks are also starting to become clinically accepted (21,22). However, there is an absence of specific methodologies that inform health professionals which tasks to apply and under what clinical conditions (23). Consequently, rehabilitation professionals perform a selection of tasks based on their clinical experience, missing scientific foundations (24). Faria and colleagues (2018) proposed an objective and quantitative framework for the creation of personalized cognitive rehabilitation tasks based on a participatory design strategy with health professionals (25). In this work, through computational modeling, the authors operationalized 11 paper-and-pencil tasks and developed an Information and Communication Technologies based tool - the Task Generator (TG) - to tailor each of those 11 paper-and-pencil tasks to each patient in the domains of attention, memory, language and executive functions. A clinical evaluation of the TG with twenty stroke patients showed that the TG is able to adapt task parameters and difficulty levels according to patient's cognitive assessment, and provide a comprehensive cognitive training (26). However, although it has been shown that rehabilitation strategies based on paper-and-pencil tasks can be personalized and adapted (26,27), this approach presents a limited transfer to performance in activities of daily living (ADL) (20).

Over the last years, rehabilitation methodologies based on virtual reality (VR) have been developed as promising solutions to improve cognitive functions (28,29). VR-based tools have shown potential and to be ideal environments to incorporate cognitive tasks within the simulation of ADL's (30). A recent trial with a VR-based simulation of everyday life activities (like going to the pharmacy, buying grocery at the supermarket, paying the water bill) suggested that an ecologically valid intervention has more impact than conventional methods in cognitive rehabilitation of stroke patients (31). Also, these VR-based systems allow the integration of motor training (32) and recent studies have already shown benefits of performing simultaneous motor and cognitive training with stroke patients using VR (33,34). Yet, there is still an insufficient number of rigorous trials to clinically validate VR methods (14) and there are difficulties associated with the adoption of new technologies (35), which results in a low adoption by health professionals who still prefer paper-and-pencil interventions.

In general, existing ecologically-valid VR-based environments are simulations of cities (31,36–40), kitchens (41–47), streets (48–53), supermarkets (54–58), malls and other shopping scenarios (59–63). Of these, only rare cases take into account training personalization according to patient cognitive profile and session-to-session adaptation (31,38,40,43). Additionally, results of studies comparing VR cognitive interventions with standard occupational therapy (OT) or paper-and-pencil tasks are fundamentally biased as control interventions are planned and delivered according to health professionals' clinical experience. Hence, even if rehabilitation sessions last the same, these interventions are not equivalent as they are delivered with uncontrolled difficulty levels and cognitive demands.

Here we try to address some of the existing limitations in the validation of VR-based cognitive rehabilitation tools. In this study we compared two task content equivalent rehabilitation tools developed under the same personalization and adaptation framework (25): the TG and the Reh@City v2.0. This framework allows us to make sure that both tools deliver the same controlled adaptation and personalization of difficulty levels, and address the same cognitive demands. Hence, this comparison allows identifying the specific impact of increasing ecological validity of training through VR simulations of ADLs over the same training delivered through clinically accepted paper-and-pencil equivalent tasks. In addition, we also compared them to a group undergoing treatment as usual (TAU). These findings will further inform on the specific benefits of ecologically valid environments delivered though VR and encourage the adoption of these technologies by health professionals.

2. Methods

2.1 Participants and trial design

Participants were selected based on the following inclusion criteria: no more than 75 years old; first stroke episode and at least at 6 months post-stroke (chronic phase); no hemi-spatial neglect as assessed by the clinicians with the Line Bisection test (64); capacity to be seated; minimum of 2 years of schooling and motivation to participate in the study. Patients with more than two standard deviations below the mean score for age and education in the Montreal Cognitive Assessment (MoCA) (65,66) were excluded to ensure uniformity and enough cognitive capacity to participate in the rehabilitation interventions. Patients with severe depressive symptomatology, as assessed by the Beck Depression Inventory II (67,68), were also excluded because its impact on cognitive functioning. Additionally, patients could not have been undergoing OT at least two months before the study. The study was previously approved by the Madeira Health Service Ethical Committee (reference number: 13/2016), and all the patients gave informed consent previous to participation.

For this study, two samples totaling 48 stroke patients were recruited. The first sample (*Intervention*) was selected from a list of 334 stroke patients enrolled in the cerebrovascular accidents appointment list from the Physical Medicine and Rehabilitation department of the Madeira Health Service (Portugal). They were contacted by phone by one of the researchers, and 44 declined to participate, 146 patients were excluded for not meeting the inclusion criteria and 108 were excluded for other reasons, such as transportation problems or lack of response after three phone calls. Overall, 36 patients were included meeting all inclusion criteria and were allocated to one of the two interventions (TG or Reh@City v2.0), by the two psychologists involved in the data collection. Group allocation was randomized (through a simple randomization method using a web-based application that generates a random allocation sequence) among the different rehabilitation units working under the Physical Medicine and Rehabilitation department (Figure 1). Then, a convenience sample of 12 stroke patients *(treatment as usual - TAU)* was recruited from a total of 96 patients undergoing OT from the OT unit from the Physical Medicine and Rehabilitation department, to compare their impact with TAU. All participants of both samples met the same inclusion and exclusion criteria.

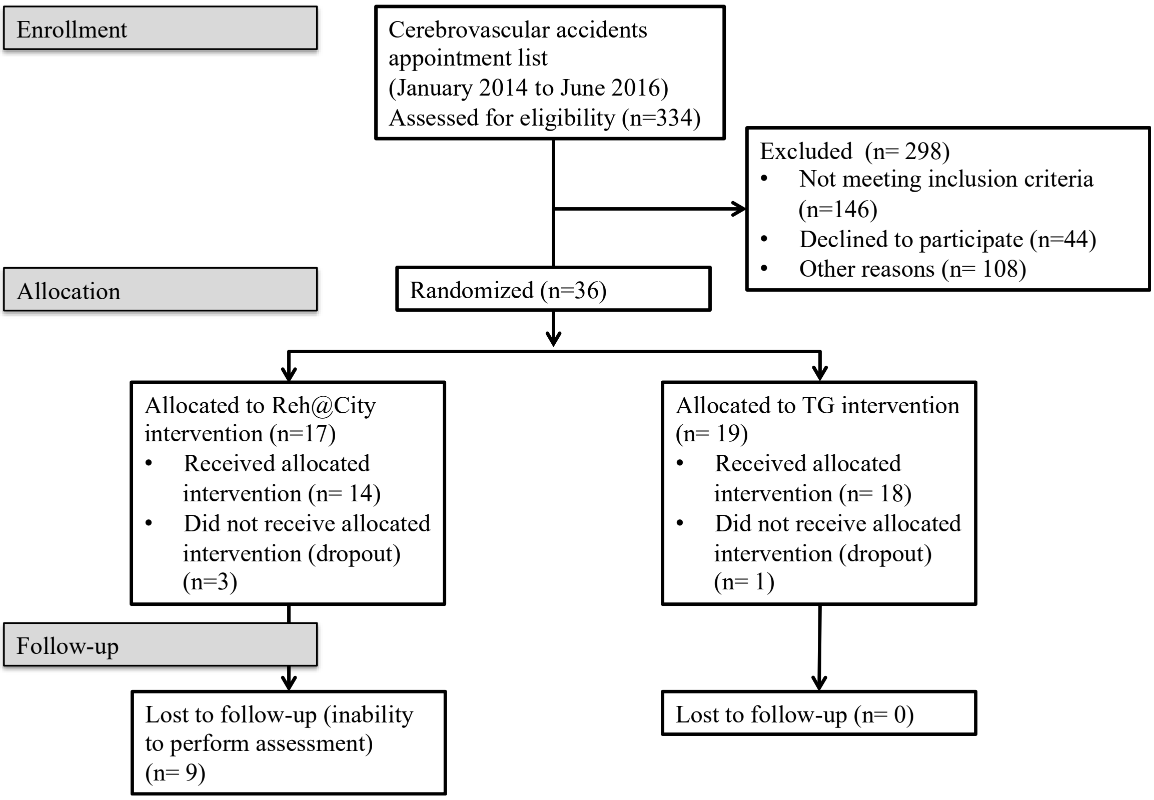


Figure 1: Protocol of the intervention.

2.2 Intervention protocol

The study started in January 2017 and stopped in December 2018, since the authors defined the maximum of two years for data collection. We performed a randomized controlled trial (RCT) comparing both TG and Reh@City v2.0 interventions in the *Intervention* sample, and then compared them to the *TAU* sample. From *Intervention* sample, 19 participants were allocated to the TG group (one dropped out) and 17 allocated to the Reh@City v2.0 group (three dropped out). Concerning the TAU sample, we recruited 12 participants (one dropped out and one passed away). All patients went through neuropsychological assessment pre and post-intervention and at two months follow-up. Each one of the assessment moments had an approximate duration of 90 min. The TAU group did not go through follow-up neuropsychological assessment because we could not guarantee, as ambulatory inpatients, that they could stop intervention during that time.

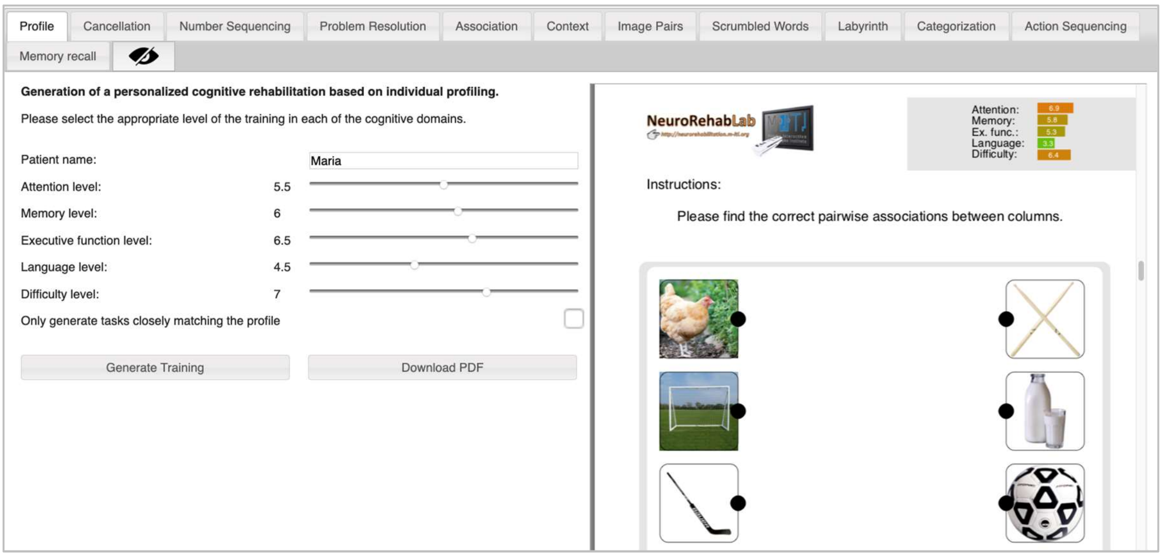
The intervention personalization was done through the characterization of each participant with the MoCA (65, 66) assessment results: the *Attention* parameter was defined from MoCA's attention component score [0-6]; the delayed recall and orientation scores [0-11] was used to parameterize *memory; executive functions* was parameterized through the sum of the visuospatial, executive, and abstraction MoCA subscores [0-7]; MoCA's naming and the language scores [0-6] was used to parameterize *language;* and the total score [0-30] was used to parameterize the overall *difficulty.*

Two psychologists performed all the assessments. The same two psychologists and one occupational therapist supervised the interventions sessions. Accordingly, in this study, only participants were blinded.

2.3 Interventions description

2.3.1 Paper-and-pencil intervention: the Task Generator

The TG is a free and worldwide accessible tool that is able to generate personalized paper-and-pencil cognitive rehabilitation programs in PDF format, composed by a set of 11 tasks gathered from clinical settings and parameterized through a participatory process with rehabilitation experts (26): Cancellation; Numeric Sequences; Problem Resolution; Association; Comprehension of Contexts; Image Pairs; Word Search; Mazes; Categorization; Action Sequencing; and Memory of Stories. After the characterization of each participant, the MoCA assessment data was normalized on a 1 to 10 scale, and a full training program was generated (Figure 2).



Generation of a personalized cognitive rehabilitation based on individual profiling.

Please select the appropriate level of the training in each of the cognitive domains.

Patient name: Maria
Attention level: 5.5
Memory level: 6
Executive function level: 6.5
Language level: 4.5
Difficulty level: 7
Only generate tasks closely matching the profile ☐

Attention: 6.9
Memory: 5.8
Ex. func.: 5.3
Language: 3.3
Difficulty: 6.4

Instructions:

Please find the correct pairwise associations between columns.

Figure 2: TG training personalization parameters (on the left) and Association task generation example (on the right).

When the patient finished the set of 11 tasks, a score was computed using a 0% to 100% scale. Consistent with previous adaptive systems for stroke rehabilitation (69), if the mean performance was higher than 70%, the difficulty was increased by 0.5 in the next set of exercises, and if performance was from 0% to 50%, the difficulty parameter was reduced by 0.5.

2.3.2 VR-based Intervention: the Reh@City v2.0

Our VR-based intervention consisted of the same TG paper-and-pencil tasks contextualized in different locations of a virtual city with streets, sidewalks, buildings, shops, and parks – the Reh@City v2.0 (70) (Table 1).

Table 1: TG paper-and-pencil tasks correspondence with Reh@City v2.0 VR tasks.

Task Generator	**Reh@City v2.0**
Cancellation	Buy/collect items at the supermarket, pharmacy, and post-office
Numeric Sequences	Find bank code
Problem Resolution	Choose the correct supermarket invoice
Association	Cards game at the park
Comprehension of Contexts	Not applicable
Image Pairs	Cards game at the park
Word Search	Not applicable
Mazes	Find the best route to the next destination in the virtual city
Categorization	Select a category of items in the clothing shop
Action Sequencing	Organize the steps for an action in the home kitchen, living room or bathroom
Memory of Stories	Memorizing verbal information from a newspaper at the kiosk for a later “true or false” recall

Reh@City v2.0 provides a more ecological training experience since patients are required to solve cognitive tasks through familiar ADL’s in a variety of commonplaces: for instance buy food in a supermarket (Figure 3a); pick up a package in the post office; pay the electricity at the bank ATM (Figure 3b); buy pain killers in the pharmacy; collect shirts in the clothing shop; play a game in the park (Figure 3c); read the newspaper in the kiosk and set the table at home (Figure 3d). These places display billboards and real products of actual spaces and trademarks commonly found in Portugal to help the patient relate the VR tasks to the real world. In addition, consistent with the actual simulated ADLs and to increase the ecological validity of the training, patients were also required to use their paretic arm to solve the tasks.

Figure 3: Reh@City v2.0 task examples: a) buying food in the supermarket; b) making payments at the bank ATM; c) playing a cards game at the park and; d) setting the table at home.

Because we were generally dealing with people of older age and low computer literacy, the interaction with the virtual environment was simplified and city was designed to have only square or rectangular building blocks and perpendicular street intersections, as well as simplified simulated environments. This simplified arrangement also allowed a more precise control of difficulty parameterization (Figure 4).

Figure 4: Reh@city v2.0 three-dimensional street view. Users are given goal instructions supported with a mini-map indicating the optimal path and a street arrow. Time and point counters are used to provide feedback on performance.

2.3.3 Treatment as Usual (TAU)

The TAU intervention consisted of ADL's training with an occupational therapist. The intervention was time-matched with the TG and Reh@City v2.0 groups, comprising twelve OT sessions of thirty minutes, three times per week.

2.4 Experimental setup

2.4.1 Task Generator (TG)

The TG is an online application, accessible at neurorehabilitation.m-iti.org/TaskGenerator, and does not require to be installed on the computer. The only required software was a PDF reader to open the downloaded paper-and-pencil cognitive training tasks. After printed, the tasks were solved on a table with a pencil having the user seated.

2.4.2 Reh@City v2.0

Reh@City v2.0 was installed on a PC (OS: Windows 7, CPU: Intel core 2 duo E8235 at 2.80 GHz, RAM: 4 Gb, Graphics: ATI mobility Radeon HD 2600 XT). Given the potential benefits reported in the literature of combining motor and cognitive rehabilitation through VR (32–34), Reh@City v2.0 implies the use of the paretic arm to solve its tasks. The user worked on a tabletop, facing an LCD monitor (24″) and moved a customized handle with a tracking pattern on the surface of the table with his/her paretic arm (Figure 5). 2D upper limb reaching movements were captured through a camera-based Augmented Reality (AR) pattern tracking software (AnTS) (71) connected to a PlayStation Eye camera (Sony Computer Entertainment Inc., Tokyo, Japan). For adapting the interaction to individual users, the Reh@City v2.0 implemented a built-in calibration function that normalizes the motor effort required in the task to the active range of movement of the user. The movements of the user are then mapped onto the movements of a virtual arm (in indoor tasks) or as movement directions (during outdoor navigation) in the Reh@City v2.0 environment.

Figure 5: Reh@City v2.0 experimental setup. The user faces an LCD monitor and moves a handle on the surface of the table with his/her paretic arm to interact with the virtual content.

2.5 Outcome Measures

2.5.1 Primary outcome measure: general cognitive functioning

As primary outcome measure we used the MoCA (65,66), which has been reported to have a good sensitivity and specificity in screening for cognitive impairment after stroke (72). In addition, the decline in MoCA scores (reduction ≥ 2 points) was found to be associated with the decline in neuropsychological diagnosis transitional status on a sample of 275 stroke patients (73).

2.5.2 Secondary outcome measures

As secondary outcome measures, we selected specific attention, memory, executive functions, and language assessments. To assess attention we used the Trail Making Test A and B (TMT A and B) (74,75), a very popular neuropsychological test that provides information on visual search, visual scanning, selective and divided attention, processing speed, mental flexibility, and also executive functioning. In part A, circles numbered from 1 to 25 need to be connected in numerical order. In part B, numbers from 1 to 13 and letters from A to L need to be connected alternating numbers and letters in ascending order. The memory assessment was performed with the Verbal Paired Associates from the Wechsler Memory Scale-III (WMS-III) (76). To assess executive functions, namely working memory and processing speed, we used the Digit Span (forward and backward recall conditions) also from the WMS-III, and the Symbol Search and the Digit Symbol (Coding and Incidental learning pairing conditions) from the Wechsler Adult Intelligence Scale III (WAIS) (77). Finally, we assessed language through the Vocabulary from WAIS-III, which provides information about verbal comprehension.

Additionally, we also measured the perceived impact of persisting problems with cognition, as assessed by the Patient-Reported Evaluation of Cognitive State (PRECiS) (78,79), which includes 27 core items asking respondents about the impact of cognition on four conceptual dimensions: skills, family and life, mood and sense of self.

Finally, at the end of the Reh@City v2.0 intervention, we used the System Usability Scale (SUS) (80), to assess satisfaction and usability with the Reh@City v2.0 system. Final scores for the SUS can range from 0 to 100, where higher scores indicate better usability: 90s is exceptional, 80s is good, and 70s is acceptable (80). The questionnaire is technology agnostic, making it adaptable enough to assess a wide range of technologies.

2.6 Statistical analysis

All statistical analyses were performed using SPSS software (version 20, SPSS Inc., Chicago IL, USA). As a criterion for significance, we used an α of 0.05. Normality of data was assessed with the Kolmogorov-Smirnov (KS) test. As some data were not normally distributed, nonparametric tests were used to evaluate the inter-group and intra-group differences. The Wilcoxon signed-rank test (W) was used to analyze the within group changes over time, while the two-tailed Mann-Whitney (MW) test was used to compare the between-group differences from baseline to the end of the study. Differences between groups were measured with the chi-squared test (χ^2). Effect sizes (r) were computed as $Z/\sqrt{N}$ on the pairwise comparisons. The criteria for interpretation of the effect was 0.1 = small, 0.3 = medium, and 0.5 = large.

3. Results

3.1 Sample description

The *intervention* sample consisted of thirty-two patients with stroke randomly distributed in two groups. The Reh@City v2.0 group comprised fourteen (5 male, 9 female) senior (*M*=59.1 years old, *SD*=11.8) patients with stroke (11 right hemisphere, 3 left hemisphere; 12 ischemic, 2 hemorrhagic), with an average of 45.9 ± 43.6 months post- stroke and a mean of 8 ± 5.3 years of schooling. The TG group comprised eighteen (11 male, 7 female) senior (*M*=65 years old, *SD*=6.2) patients with stroke (9 right hemisphere, 6 left hemisphere, 3 not specified; 14 ischemic, 3 hemorrhagic, 1 not specified), with an average of 21.3 ± 12.9 months post-stroke and a mean of 5.5 ± 3.2 years of schooling. The TAU sample comprised ten (7 male, 3 female) senior (*M*=61.8 years old, *SD*=13.9) patients with stroke (6 right hemisphere, 4 left hemisphere; 6 ischemic, 4 hemorrhagic), with an average of 43.3 ± 36.6 months post- stroke and a mean of 8.3 ± 5.6 years of schooling. The chi-squared test revealed no differences between groups in the demographic characteristics and in all baseline outcome measures (Table 2).

Table 2: Demographic characteristics (presented as Means ± SD's) of the three groups and differences between groups measured by the chi-squared test (χ^2).

	Reh@City v2.0 (N=14)	Task Generator (N=18)	Occupational Therapy (N=10)	χ^2	*p*
Age (years)	59.14 ± 11.81	65.00 ± 6.20	61.80 ± 13.88	2.527	.283
Gender (M/F)	5/9	11/7	7/3	3.202	.202
Schooling (years)	8.00 ± 5.32	5.50 ± 3.15	8.25 ± 5.64	1.335	.513
Stroke type (I/H/NS)	12/2/0	14/3/1	6/4/0	1.975	.372
Side of lesion (R/L/NS)	11/3/0	9/6/3	6/4/0	3.407	.182
Time post-stroke (months)	45.93 ± 43.56	21.33 ± 12.88	43.30 ± 36.56	2.114	.348

Sex: F, female; M, male; Schooling is presented in years; Type of stroke: I, ischemic; H, hemorrhagic; NS, not specified; Side of lesion: L, left; R, right; NS, not specified; Time post-stroke is presented in months.

According to the Kolmogorov-Smirnov (KS) test, data were normally distributed in all groups for age ($\text{KS}_{\text{Reh@City}} = .706, p = .701$; $\text{KS}_{\text{TG}} = .772, p = .590$; $\text{KS}_{\text{TAU}} = .671, p = .759$) and time post-stroke ($\text{KS}_{\text{Reh@City}} = .791, p = .559$; $\text{KS}_{\text{TG}} = .795, p = .553$; $\text{KS}_{\text{TAU}} = .861, p = .449$). The type of stroke had a normal distribution in the TAU group ($\text{KS}_{\text{Reh@City}} = .791, p = .559$; $\text{KS}_{\text{TG}} = 1.966, p = .001$; $\text{KS}_{\text{TAU}} = 1.204, p = .110$). The side of lesion was normally distributed in both TAU and TG groups ($\text{KS}_{\text{Reh@City}} = 1.790, p = .003$; $\text{KS}_{\text{TG}} = 1.305, p = .066$; $\text{KS}_{\text{TAU}} = 1.204, p = .110$). The number of years of schooling distribution was normal in both Reh@City v2.0 and TAU groups ($\text{KS}_{\text{Reh@City}} = 1.292, p = .071$; $\text{KS}_{\text{TG}} = 1.720, p = .005$; $\text{KS}_{\text{TAU}} = .858, p = .453$). Data were not normally distributed for gender in any of the groups ($\text{KS}_{\text{Reh@City}} = 1.521, p = .020$; $\text{KS}_{\text{TG}} = 1.663, p = .008$; $\text{KS}_{\text{TAU}} = 1.368, p = .047$).

3.2 Primary outcome measure

3.2.1 MoCA - General cognitive functioning

We analyzed the global cognitive functioning, as assessed by the MoCA, of the three groups in the pre and post intervention assessments, and follow-up for the Reh@City v2.0 and TG groups (Table 3).

A Wilcoxon test for within-groups differences revealed that only the Reh@City v2.0 group presented significant statistical improvements between pre and post assessment moments in MoCA [Pre: Mdn= 23, IQR= 19.8–26; Post: Mdn= 25, IQR= 23–27.3 ($W_{(14)} = 64.00$, $Z = -2.777$, $p = .005$, $r = .74$)]. In the subdomains analysis, we found significant improvements in visuospatial ability and executive functioning [Pre: Mdn= 3.5, IQR= 2.8–4; Post: Mdn= 4, IQR= 3–5 ($W_{(14)} = 41.00$, $Z = -2.310$, $p = .021$, $r = .62$)] and attention [Pre: Mdn= 4, IQR= 2.8–5.3; Post: Mdn= 5.5, IQR= 3–6 ($W_{(14)} = 28.00$, $Z = -2.460$, $p = .014$, $r = .66$)]. Concerning the TG group, the only significant change was in the MoCA orientation subdomain [Pre: Mdn= 6, IQR= 5–6; Post: Mdn= 6, IQR= 6–6 ($W_{(18)} = 15.00$, $Z = -2.121$, $p = .034$, $r = .57$)].

A Wilcoxon test for within-groups differences revealed that only the Reh@City v2.0 group presented significant statistical improvements between pre and post assessment moments in MoCA [$W_{(14)} = 64.00$, $Z = -2.777$, $p = .005$, $r = .74$ (Pre: Mdn= 23, IQR= 19.8–26; Post: Mdn= 25, IQR= 23–27.3)]. In the subdomains analysis, we found significant improvements in visuospatial ability and executive functioning [$W_{(14)} = 41.00$, $Z = -2.310$, $p = .021$, $r = .62$ (Pre: Mdn= 3.5, IQR= 2.8–4; Post: Mdn= 4, IQR= 3–5] and attention [$W_{(14)} = 28.00$, $Z = -2.460$, $p = .014$, $r = .66$ (Pre: Mdn= 4, IQR= 2.8–5.3; Post: Mdn= 5.5, IQR= 3–6)]. Concerning the TG group, the only significant change was in MoCA orientation [$W_{(18)} = 15.00$, $Z = -2.121$, $p = .034$, $r = .57$ (Pre: Mdn= 6, IQR= 5–6; Post: Mdn= 6, IQR= 6–6)].

A Mann-Whitney test indicated that the Reh@City v2.0 group improved significantly more than the TG group, in terms of general cognitive functioning, as assessed by the MoCA, from baseline to post-intervention [Reh@City v2.0: Mdn= 2, IQR= 0–3; TG: Mdn= -1.5, IQR= -3.25–2; TAU: Mdn= -.50, IQR= -2.25–2.50 ($U = 65.00$, $Z = -2.334$, $p = .020$, $r = .41$)]. The Reh@City v2.0 also presented significantly higher scores, comparing with the TAU group, in the MoCA visuospatial ability and executive functioning domain post-intervention [Reh@City v2.0: Mdn= 1, IQR= 0–1; TG: Mdn= 0, IQR= -.25–1; TAU: Mdn= 0, IQR= -1–.25 ($U = 33.50$, $Z = -2.245$, $p = .031$, $r = .46$)].

We analyzed the global cognitive functioning, as assessed by the MoCA, of the three groups in the pre and post intervention assessments and follow-up of the Reh@City v2.0 and TG groups (Table 3).

Table 3: MoCA scores (presented as Medians and IQR) pre and post intervention and follow-up highlighted for within-groups significant differences and marked with an asterisk for between-groups significant differences.

	Reh@City v2.0			Task Generator			Occupational Therapy	
	Pre	Post	FU	Pre	Post	FU	Pre	Post
Total	23 (19.8-26)	**25 (23-27.3)***	28 (22.5-28.5)	21 (18.8-24.3)	21 (16.8- 23.3)	23 (19.8-25.3)	24 (18.8-26.5)	23 (20.3-26)
Visuo-Executive	3.5 (2.8-4)	**4 (3-5)***	4 (4-5)	3.5 (2-4)	4 (3-4)	4 (2.8-5)	4 (2.5-5)	3.5 (2-4.3)
Naming	3 (2-3)	3 (2.8-3)	3 (1.5-3)	2.5 (2-3)	2 (1-3)	3 (2-3)	3 (3-3)	3 (2.8-3)
Attention	4 (2.8-5.3)	**5.5 (3-6)**	5 (3-6)	4 (2-5.3)	4 (2.8-5)	4 (3-5.2)	4.5 (3.8-5.3)	4.5 (2.8-6)
Language	2 (1.8-3)	2 (2-3)	3 (2-3)	2 (2-3)	2 (1-2)	2 (1-2)	2 (1.8-2.3)	2 (2-2.3)
Abstraction	2 (1-2)	2 (1-2)	2 (1-2)	1 (1-2)	2 (0-2)	1 (1-2)	1 (1-2)	2 (1.8-2)
Memory	3 (1-3.5)	3 (2-4)	4 (2.5-5)	2 (0-3.3)	.50 (0-2)	2.50 (1.8-3.2)	2 (.8-4)	2.5 (.8-4.3)
Orientation	6 (6-6)	6 (6-6)	6 (6-6)	6 (5-6)	**6 (6-6)**	6 (6-6)	6 (6-6)	6 (5.8-6)

3.3 Secondary outcome measures

3.3.1 TMT A & B - Attention

We computed the TMT A and TMT B performance for the three groups, in terms of errors and completion time, pre, post-intervention and follow-up (Table 4). Only the TG group showed a significant improvement in the reduction of time to completion of the TMT A test pre to post-intervention [Pre: Mdn= 84, IQR= 59.5–114.3; Post: Mdn= 72, IQR= 58.8–99.5 ($W_{(18)} = 18.00$, $Z = -2.588$, $p = .010$, $r = .61$)].

Table 4: TMT A and B scores (presented as Medians and IQR) pre and post intervention and follow-up highlighted for within-groups significant differences.

	Reh@City v2.0			Task Generator			Occupational Therapy	
	Pre	Post	FU	Pre	Post	FU	Pre	Post
A time	72.5 (49.5-97.5)	65 (51-86.3)	70 (30.5-84)	84 (59.5-114.3)	**72 (58.8-99.5)**	76.5 (59.3-114.3)	57 (36.8-109.8)	51 (36.8-120.8)
A errors	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-.50)	0 (0-.50)	0 (0-0)
B time	195 (130.8-360)	200 (135.5-241)	190 (61.5-360)	209.5 (123.3-256.5)	236 (152-360)	202 (112.3-360)	123 (68.8-211.5)	107.5 (80.5-165)
B errors	0 (0-3)	0.5 (0-1.25)	1 (0-4.5)	3 (1.5-6)	3 (1-4.5)	2.5 (0-3.8)	1.5 (0-5.3)	2 (0-6)

3.3.2 WMS-III Verbal Paired Associates - Memory

Table 5 describes the Verbal Paired Associates test performance for the three groups pre, post-intervention and follow-up. In this learning and memory test, we found significant improvements within the Reh@City v2.0 group for the retention [Pre: Mdn= 75, IQR= 0–100; Post: Mdn= 100, IQR= 74.1–100 ($W_{(14)} = 36.00$, $Z = -2.524$, $p = .012$, $r = .67$)] and recognition [Pre: Mdn= 24, IQR= 21.8–24; Post: Mdn= 24, IQR= 24–24 ($W_{(14)} = 21.00$, $Z = -2.214$, $p = .027$, $r = 59$)] scores post-intervention. In the TG group improvements were only significant for the retention score in both post-intervention [Pre: Mdn= 0, IQR= 0–56.3; Post: Mdn= 82.9, IQR= 26.5–100 ($W_{(18)} =$

118.00, $Z = -2.602$, $p = .009$, $r = .61$)] and follow-up [Pre: Mdn= 0, IQR= 0–56.3; FU: Mdn= 82.9, IQR= 37.5–100 ($W_{(18)} = 95.00$, $Z = -2.776$, $p = .006$, $r = .65$)].

Table 5: WMS-III Verbal Paired Associates scores (presented as Medians and IQR) pre and post intervention and follow-up highlighted for within-groups significant differences.

	Reh@City v2.0			Task Generator			Occupational Therapy	
	Pre	Post	FU	Pre	Post	FU	Pre	Post
Learning	2 (.75-4)	1.5 (1-4)	5 (1-6)	1 (0-2)	1 (.75-2.3)	1.50 (8-4)	2 (.75-4.3)	2 (1-4.25)
Retention	75 (0-100)	**100 (74.1-100)**	83.3 (25-93.8)	.00 (0-56.3)	**82.9 (26.5-100)**	**82.9 (37.5-100)**	36.9 (0-81.5)	71.7 (0-89.3)
Recognition	24 (21.8-24)	**24 (24-24)**	24 (24-24)	23 (19.8-24)	24 (21-24)	24 (23.8-24)	23.5 (23-24)	24 (23.8-24)

3.3.3 WAIS-III Digit Symbol, Symbol Search and Digit Span - Executive Functions

Table 6 describes the executive functioning outcome measures for the three groups pre, post-intervention and follow-up. The Reh@City v2.0 group showed improvements in the Coding task post-intervention [Pre: Mdn= 28.5, IQR= 23.5–36.8; Post: Mdn= 33, IQR= 26.8–47 ($W_{(14)} = 87.00$, $Z = -2.171$, $p = .030$, $r = .58$)]. The TG group had significant improvements in the Symbol Search at follow-up [Pre: Mdn= 12, IQR= 7.8–13.5; FU: Mdn= 15, IQR= 9–20.3 ($W_{(18)} = 101.00$, $Z = -2.340$, $p = .019$, $r = .55$)].

Table 6: WAIS-III Digit Symbol, Symbol Search and Digit Span scores (presented as Medians and IQR) pre and post intervention and follow-up highlighted for within-groups significant differences.

	Reh@City v2.0			Task Generator			Occupational Therapy	
	Pre	Post	FU	Pre	Post	FU	Pre	Post
Coding	28.5 (23.5-36.8)	**33 (26.8-47)**	33 (19-50)	21.5 (11.8-33)	26.5 (18.8-38.3)	27 (16.8-34.3)	26 (16-37.5)	28.5 (20.8-36.8)
Incidental learning pairing	3 (.0-10.5)	6.5 (4-11.5)	10 (3-16)	4 (1.5-8.8)	6 (.8-10.5)	8 (2-14)	4 (1.5-8)	5 (2-14)
Symbol search	13.5 (9.8-20.5)	17.5 (10.3-24)	17 (10-25.5)	12 (7.8-13.5)	14 (10-16.5)	**15 (9-20.3)**	14.5 (10.3-19.8)	14 (10.8-19.8)
Digit span	11 (10-13)	10 (8.8-13)	11 (10.5-13.5)	10 (8-11)	10.5 (8.8-12)	10 (9.5-13.3)	11 (10.5-13.3)	10.5 (9-12.5)

3.3.4 WAIS-III Vocabulary - Language

The analysis of the language outcome measure for the three groups pre, post-intervention and follow-up revealed that only the TG group showed improvements in the Vocabulary assessment at follow-up [Pre: Mdn= 19.5, IQR= 13–28.5; FU: Mdn= 24.5, IQR= 16.5–30.3 ($W_{(18)} = 166.00$, $Z = -3.514$, $p < .001$, $r = .83$)] (Table 7).

Table 7: WAIS-III Vocabulary score (presented as Medians and IQR) pre and post intervention and follow-up highlighted for within-groups significant differences.

	Reh@City v2.0			Task Generator			Occupational Therapy	
	Pre	Post	FU	Pre	Post	FU	Pre	Post
Vocabulary	29 (21-34)	25.5 (12.8-30.3)	22 (13.5-40)	19.5 (13-28.5)	20.5 (12.8-30.3)	**24.5 (16.5-30.3)**	31 (15.5-38.8)	31 (22.8-39.3)

3.3.5 Patient-Reported Evaluation of Cognitive State

When analyzing the answers of the three groups pre, post-intervention and follow-up to the PRECiS questionnaire, only the Reh@City v2.0 group revealed a significant self-perceived decrease in the stroke cognitive deficits impact post intervention [Pre: Mdn= 13.5, IQR= 7–23.8; Post: Mdn= 12, IQR= 3.8–21.3 ($W_{(14)} = 13.00$, $Z = -2.041$, $p = .041$, $r = .55$)] (Table 8).

Table 8: PRECiS score (presented as Medians and IQR) pre and post intervention and follow-up highlighted for within-groups significant differences.

	Reh@City v2.0			Task Generator			Occupational Therapy	
	Pre	Post	FU	Pre	Post	FU	Pre	Post
PRECiS	13.5 (7-23.8)	**12 (3.8-21.3)**	13 (0-24.5)	28.5 (6-47)	18.5 (8.5-44.8)	13.5 (5.5-30.3)	18 (7-25.5)	15 (7.5-35.5)

3.4 Usability

Observational information and subjective statements from the participants were consistent with the SUS scores, which reported acceptable to good levels of usability and satisfaction for the Reh@City v2.0 (*Mdn* = 75/100, IQR = 71.3–81.3).

4. Discussion

In the last years there has been significant growth in the evidence for post-stroke cognitive rehabilitation (14,15), with a number of studies proposing ecologically valid VR-based simulations of ADL's as the most promising training solutions (28,29). However, an important number of the developed systems have not been field tested (40), have only gone through studies with a small number of participants (31,38) and/or with healthy control groups (81). Additionally, none of these VR-based ADL's simulations are compared with widely used and clinically accepted paper-and-pencil tasks, being always compared with non-equivalent interventions as OT (82). Our RCT, is the first to implement an adaptive paper-and-pencil training and compare it with a content equivalent VR-based ADL's simulation, by using the same tasks, personalization and difficulty adaptation framework within a longitudinal clinical intervention. In addition, this RCT was compared to a TAU group undergoing OT, which is the conventional treatment provided by the health services in Portugal.

4.1 Primary outcome measure

The Reh@City v2.0 group improved in the MoCA general cognitive functioning and in its attention, visuospatial ability and executive functioning subdomains. The TG group improved in the MoCA orientation domain. In a between groups comparison, the Reh@City v2.0 group had a higher impact in the general cognitive functioning comparatively to the TG group and in the visuospatial ability and executive functioning, comparatively to the TAU group. Although with a different cognition screening measure, these results are coherent with the Reh@City v1.0 study, where the Reh@City v1.0 group improved in the general cognitive functioning, attention, memory and visuospatial abilities and was superior between groups in general cognitive functioning and attention (31).

4.2 Secondary outcome measures

The Reh@City v2.0 intervention group had a significant impact in verbal memory (as assessed by the retention and recognition from the Verbal Paired Associates test - WMS-III), and processing speed (as assessed by the Digit Symbol Coding task - WAIS-III), which is superior to what we have found in the Reh@City v1.0 study, where we had improvements in an executive functioning measure (31).

The TG group improved in verbal memory (as assessed by the retention from the Verbal Paired Associates test - WMS-III) and processing speed (as assessed by the TMTA task execution time) subdomains. At follow-up, participants who underwent the TG intervention maintained the verbal memory benefits with new improvements in the sustained attention and processing speed (as assessed by the Symbol Search task – WAIS-III) and language (as assessed by the Vocabulary – WAIS-III) domains. These findings may be related to the fact that the TG offers a more domain-specific training and recent evidence supports that attention, language (16), memory, executive functions and visuospatial and perceptual skills training after stroke is effective at long-term (15). Besides cognition, we assessed the intervention's impact in the self-perceived cognitive deficits. Only the Reh@City v2.0 group had a significant reduction in the self-perceived cognitive deficits in different aspects of their everyday life, measured by the PRECIS questionnaire. This result provides further support to existing literature that states that comprehensive neuropsychological rehabilitation is effective to reduce cognitive and functional disability after stroke (16); and that the combined cognitive and motor training has more impact, than motor training only, in ADL's performance (32). Also, this result is in line with the Reh@City v1.0 study, where we have found significant improvements in a self-reported general health status questionnaire (31).

Finally, the interaction with our system was reported as very positive, with high levels of engagement and motivation, which is essential to enhance adherence to treatment. The acceptable to good usability and satisfaction scores obtained with the SUS confirmed these observations.

4.3 Limitations

Some limitations of our study must be considered when interpreting the results. Concerning the sample, although 42 stroke participants is a large sample when compared to previous similar clinical trials (31,38), the TAU group was considerably smaller than the RCT groups. Also, in the Reh@City v2.0 group, most participants were lost at follow-up. Hence, the comparison between TG and Reh@City v2.0 at this assessment moment should be considered with caution. Furthermore, the intervention was not blind since the same persons performed the assessments and interventions, except for the intervention for the TAU group, which was executed by the occupational therapists of the Physical Medicine and Rehabilitation department of the Madeira Health Service. Finally, there might have been learning effects of the cognitive assessment tools since only the MoCA had parallel versions for multiple assessments. Yet, even if a learning effect existed, this would apply to the three groups, and the comparison would still hold valid.

4.4 Conclusions

The results of this one-month longitudinal study showed a positive impact of a rehabilitation training with the Reh@City v2.0, an ecologically valid VR ADL's simulations, in general cognitive functioning, visuospatial ability and executive functioning, attention, verbal memory and processing speed, generalized for other health and life aspects measured by the self-perceived impact of cognitive deficits scale. This generalization did not happen in the TG group that only revealed similar cognitive impact in the orientation, processing speed and verbal memory domains. The TG intervention sustained impact at follow-up, maintaining processing speed and verbal memory improvements and revealing a new one in language. As expected, OT was shown to be an insufficient intervention for cognitive deficits after stroke and did not reveal any significant improvement in the outcome measures. Finally, by comparing interventions between themselves, we have found Reh@City v2.0 to be superior in general cognitive functioning, visuospatial ability and executive functioning. Only the intervention with TG allowed cognitive gains to last over time. However, these results need to be considered with caution given the dropout at follow-up in the Reh@City v2.0 group.

Overall, our results contribute with new evidence about the impact of ecological validity - using personalization and adaptation in VR simulations of ADL's and paper-and-pencil tasks - in the rehabilitation of cognitive deficits, which can facilitate the adoption of these innovative tools by health professionals in their daily practice. Nevertheless, there is still a need for further research considering other clinical populations, as well as the implementation of a wider variety of cognitive training tasks.

List of abbreviations

ADL's: Activities of Daily Living

KS: Kolmogorov-Smirnov

MoCA: Montreal Cognitive Assessment

MW: Mann-Whitney

OT: Occupational Therapy

PRECiS: Patient-Reported Evaluation of Cognitive State

RCT: Randomized Controlled Trial

SUS: System Usability Scale

TAU: Treatment as Usual

TG: Task Generator

TMT: Trail Making Test

VR: Virtual Reality

W: Wilcoxon

WAIS: Wechsler Adult Intelligence Scale

WMS: Wechsler Memory Scale

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6. Comparing adaptive cognitive training in virtual reality and paper-and-pencil tasks in a sample of stroke patients [11, 12]

Abstract

The growing number of people with cognitive deficits creates an urgent need for new cognitive training solutions. Paper-and-pencil tasks are still widely used for cognitive rehabilitation despite the proliferation of new computer-based methods, like VR-based simulations of ADL's. The health professionals' resistance in adopting new tools might be explained by the small number of validation trials. Studies have established construct validity of VR assessment tools with their paper-and-pencil version by demonstrating significant associations with their traditional construct-driven measures. However, adaptive rehabilitation tools for intervention are mostly not equivalent to their counterpart paper-and-pencil versions, which makes it difficult to carry out comparative studies. Here we present a 12-session intervention study with 31 stroke survivors who underwent different rehabilitation protocols based on the same content and difficulty adaptation progression framework: 17 performed paper-and-pencil training with the Task Generator and 14 performed VR-based training with the Reh@City. Results have shown that both groups performed at the same level and there was not an effect of the training methodology in overall performance. However, the Reh@City enabled more intensive training, which may translate in more cognitive improvements.

***Keywords* -** cognitive rehabilitation, paper-and-pencil, virtual reality, personalization.

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[11] Faria, A. L., Paulino, T., & Bermudez i Badia, S. (2019, July). *Comparing adaptive cognitive training in virtual reality and paper-and-pencil in a sample of stroke patients*. Paper presented at the IEEE International Conference on Virtual Reality. Tel Aviv, Israel, 27.

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Introduction

Cognitive deficits affect a person's capability to live independently and are present in 3-19% of people older than 65 years [1]. Between 2015 and 2050, the proportion of the world's older adults is estimated to almost double from about 12% to 22% [2]. This will raise the numbers of age-associated diseases, like stroke and dementia, which already have 15 and 50 million new cases every year, respectively [3], [4]. These facts created an urgent need for intensive and personalized cognitive training solutions to maximize neural plasticity and, consequently, improve functional independence [5].

Cognitive exercises, including computer-based programs, have been used to improve specific neuropsychological processes, predominantly attention, memory, and executive functions [6], [7]. Despite many descriptions of particular programs and interventions, limited data on the effectiveness of cognitive rehabilitation is available because of the heterogeneity of participants, interventions, and outcomes [8]. In what concerns interventions, still today, paper-and-pencil tasks are the most commonly used methods to train cognitive functions in clinical settings [9]. Although with established clinical validity and reduced cost [10], paper-and-pencil methods are mostly planned and delivered based on the clinician experience and lack a solid theoretical framework for intervention personalization [11]. Additionally, rehabilitation with these tasks has shown to have a limited transfer to performance in activities of daily living (ADL) [9].

Over the last years, rehabilitation tools based on virtual reality (VR) have been developed and validated as promising solutions to improve cognitive functions [12], [13]. VR-based methods have shown potential to be ideal environments to incorporate cognitive tasks within the simulation of ADL's [14], [15], [16] offering immersive and ecologically valid experiences capable of promoting enjoyment and adherence [17]. However, there is still an insufficient number of trials to clinically validate these methods [18], which together with the difficulties in adopting new technologies [19], limits the acceptance of these methods by health professionals who choose to continue performing paper-and-pencil interventions.

Regardless of the purported advantages of virtual environments, there are several critical areas that require further development. One area of note is the need to bridge widely accepted paper-and-pencil methodologies with VR-based ADL's simulations. In the field of cognitive assessment, a considerable number of studies have compared VR neuropsychological assessment tools with their paper-and-pencil original versions [20]. Raspelli and colleagues (2012) evaluated a virtual version of the Multiple Errands Test (MET), the Virtual Multiple Errands Test (VMET), with the purpose of establishing ecological and construct validity as an assessment tool for executive functions. The MET consists of tasks that abide by certain rules and is performed in a shopping mall-like setting where there are items to be bought and information to be obtained. The study population included post-stroke participants and healthy adults. Correlations between VMET variables and some traditional executive functions paper-and-pencil measures provided preliminary support for its ecological and construct validity [21]. Nir-Hadad and colleagues (2015) examined the discriminant, construct-convergent and ecological validity of the Adapted

Four-Item Shopping Task, an assessment of the shopping Instrumental Activity of Daily Living (IADL). Stroke and healthy participants performed the shopping task in both the Virtual Interactive Shopping environment and a real shopping environment. The shopping task outcomes were compared to paper-and-pencil measures of executive functions. The findings provided initial support for the validity of the Adapted Four-Item Shopping Task as an IADL assessment that requires the use of executive functions for people with stroke [22]. Vourvopoulos and colleagues (2014) developed a VR-based simulation of activities of daily living (ADLs) within a city where stroke participants had to accomplish several goals; and found a strong correlation between the VR score and the Mini-Mental State Examination cognitive screening test for clinical assessment of cognitive function in several domains [23]. Parsons and colleagues (2018) compared the performance of healthy participants on a virtual apartment-based Stroop with traditional (multi-item) and computerized (single item) modalities. Results suggested the potential of the Virtual Apartment Stroop task to distinguish between prepotent response inhibition and resistance to distractor inhibition in young adults [24]. Costa and colleagues (2018) compared the performance obtained on the assessment of perception of spatial abilities in an immersive VR spatial task and its correspondent paper-and-pencil version and found that the VR task is ecologically more valid since it is closer to real life [25].

The previously referred studies lead us to conclude that researchers of VR-based cognitive assessments have sought to establish construct validity by demonstrating significant associations between construct-driven virtual environments with other traditional construct-driven measures [10]. So, how can we validate VR-based cognitive rehabilitation? There is a rising number of VR-based rehabilitation tools, most of them incorporating personalization and adaptation, but no study has explored associations between adaptation in traditional paper-and-pencil and VR training. This comparison is challenging since interventions are planned and delivered according to health professionals' clinical experience, which involves a large variety of paper-and-pencil tasks with different difficulty levels and customizable or adaptive VR systems. One solution would be to have an objective difficulty adaptation framework to be applied in a set of paper-and-pencil training tasks and then compare it with content equivalent VR-based tasks using the same difficulty adaptation framework. This comparison would allow identifying the specific contributions of VR over clinically accepted paper-and-pencil, which could promote the adoption of VR technologies by health professionals.

Based on the NeuroRehabLab's cognitive rehabilitation adaptation framework, which established quantitative and task-specific guidelines to personalize training difficulty to the patient profile [26], we developed two content equivalent tools and clinically validated them with stroke patients: a web-based paper-and-pencil Task Generator [27] and a VR-based simulation of different ADL's, the Reh@City v2.0 [28]. To compare these two rehabilitation methods, we performed an intervention study with stroke survivors in order to explore three main questions:

a) Are paper-and-pencil and VR training performances equivalent?
b) Is performance modulated by the difficulty adaptation or the training methodology?
c) Which training method is more intensive?

Methods

A. Participants

Participants were selected in the Physical Medicine and Rehabilitation department from the Madeira Health Service (Portugal). In total, we have selected 35 outpatients based on the following inclusion criteria: no more than 75 years old; first ischemic stroke episode and at least at 6 months post-stroke (chronic phase); self-reported cognitive complaints; no hemi-spatial neglect as assessed by the clinicians with the Line Bisection test [29]; capacity to be seated and ability to read and write. The study was approved by the Madeira Health Service Ethical Committee (reference number: 13/2016), and all the participants gave informed consent before participation.

Table I presents the mean values (standard deviations) of the demographic characteristics (age, gender, education) and clinical information (stroke type and location and time post-stroke) for the two groups. No differences between groups were found with the Mann-Whitney test.

Table I. Demographics characteristics of the participants.

	Reh@City (N=14)	**Task Generator (N=17)**	**MW**	**p.**
Age (years)	59.14 ± 11.81	65.00 ± 6.20	83.500	.107
Gender (M/F)	5/9	11/7	94.000	.235
Education (years)	8.00 ± 5.32	5.50 ± 3.15	100.500	.338
Stroke type (I/H/NS)	12/2/0	14/3/1	115.000	.694
Stroke localization (R/L/NS)	11/3/0	9/6/3	85.500	.125
Months post-stroke	45.93 ± 43.56	21.33 ± 12.88	89.500	.168

B. Protocol

An intervention study was performed between June 2016 and January 2019. A total of 35 stroke survivors met the eligibility criteria and had shown motivation to participate. Intervention allocation was made through randomization of the Madeira island counties: participants from Porto Moniz, Calheta, Ribeira Brava, Santana, Câmara de Lobos, and west Funchal would perform the paper-and-pencil intervention and; participants from São Vicente, Ponta do Sol, Santa Cruz, Machico and east Funchal would perform the VR intervention. When recruitment stopped, there were 18 participants in the paper-and-pencil group, and 17 in the VR one (Figure 1).

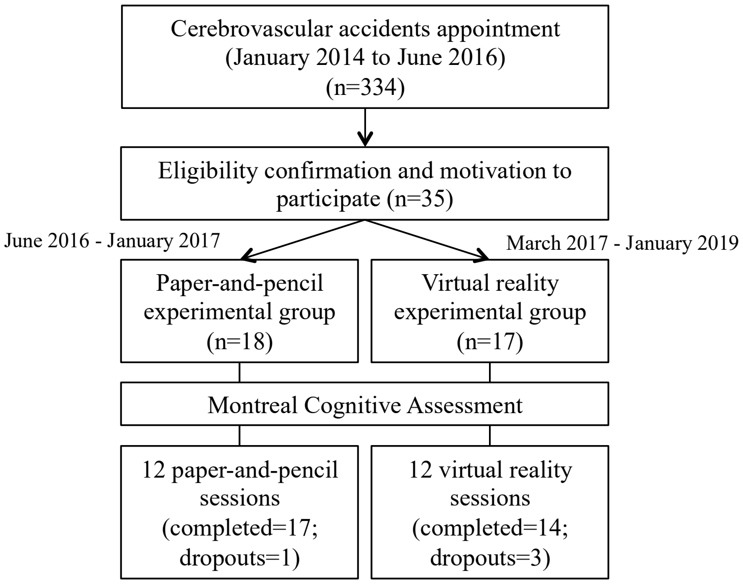


Figure 1. Diagram showing an overview of the intervention study.

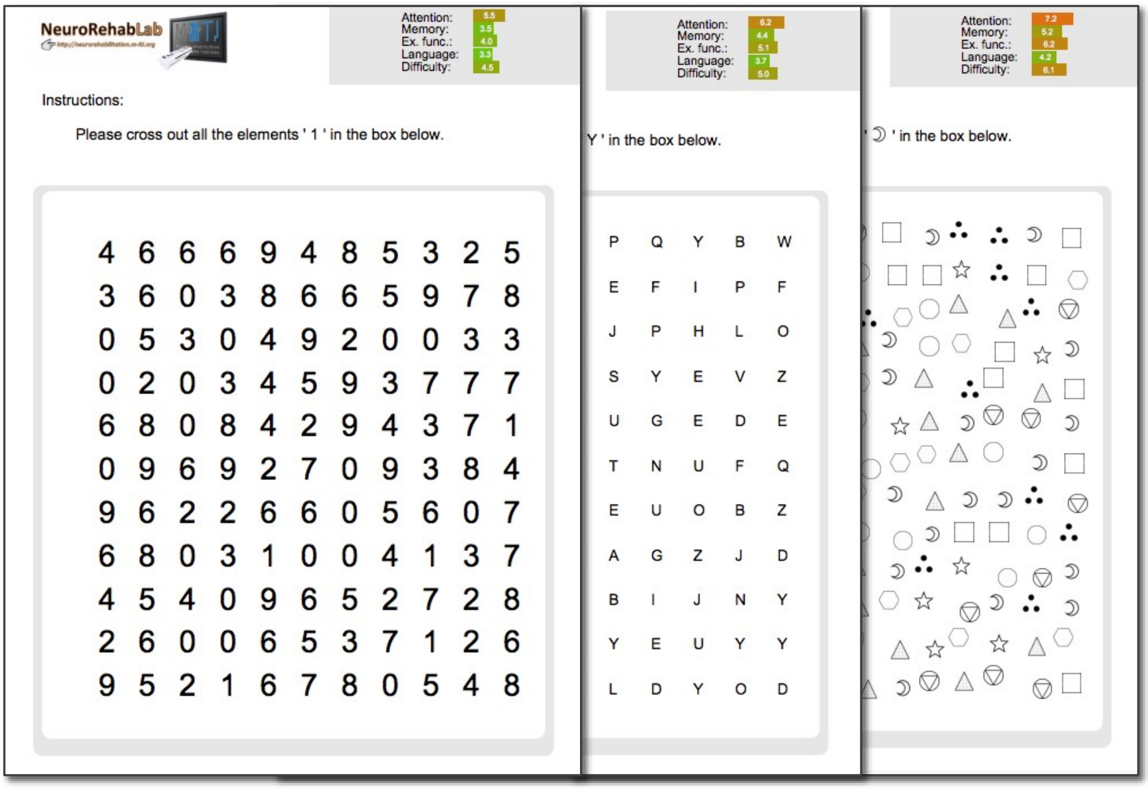
All participants were assessed through the Montreal Cognitive Assessment (MoCA) [30] before and after the intervention. Each participant went through a set of 12 30-minute sessions with a frequency of 3 per week. On each session, the participant was assigned a set of cognitive tasks individually personalized according to the participant cognitive levels previously assessed through the MoCA. There was no predefined number of tasks that the participant had to complete; tasks were performed on each session at the participant's own pace. On both groups, the intervention consisted of fulfilling tasks, and at the end of each set, the difficulty level for the following set of tasks was calculated based on the participant's performance. If the user obtained an average performance lower than 50%, the difficulty was reduced in 0.5 points (out of 10), if higher than 70%, the difficulty was increased in the same amount; otherwise, the difficulty value remained the same. This difficulty parameter is further explained in the next subsection.

C. Tools

Two tools were developed to create personalized cognitive rehabilitation: a web tool that generates paper-and-pencil tasks named the Task Generator (TG) [27] and the Reh@City v2.0 (RC) [28], a virtual reality system that integrates the simulation of tasks based on ADL's on a virtual environment. The two tools are described as follows:

Task Generator: The TG [27] is a web-based tool that allows the automatic generation of paper-and-pencil cognitive tasks tailored for each user profile. The TG consists of 11 cognitive tasks: cancellation (example on Figure 2), numeric sequences, problem resolution, association, comprehension of contexts, image pairs, word search, mazes, categorization, action sequencing, and memory of stories. A brief description of each task can be found in Table II(A). The personalization of tasks depends on the user levels of the following cognitive domains: attention, memory, executive function, and language. These levels are found through the MoCA with values varying between 1 and 10 with 0.5 intervals, where 10 represents the highest value that is possible to score. For instance, the maximum value that is possible to achieve on the attention domain of the MoCA is 6; this result is then normalized to the TG scale, corresponding to the maximum value of 10.

The process is similar for the remaining domains: memory, executive function, and language, which can hold the maximum values of 11, 7, and 6, respectively. The user profile levels are manually set using sliders for each domain. One additional parameter, the difficulty, is used to adjust the cognitive tasks based on user performance. The initial value of the difficulty is found by normalizing the MoCA's total score to the 10-point TG scale. This value varies over sessions based on the average scores obtained on each set of tasks, which needs to be manually calculated.



NeuroRehabLab

Attention: 5.5
Memory: 3.5
Ex. func.: 4.0
Language: 3.3
Difficulty: 4.5

Instructions:

Please cross out all the elements ' 1 ' in the box below.

4 6 6 6 9 4 8 5 3 2 5
3 6 0 3 8 6 6 5 9 7 8
0 5 3 0 4 9 2 0 0 3 3
0 2 0 3 4 5 9 3 7 7 7
6 8 0 8 4 2 9 4 3 7 1
0 9 6 9 2 7 0 9 3 8 4
9 6 2 2 6 6 0 5 6 0 7
6 8 0 3 1 0 0 4 1 3 7
4 5 4 0 9 6 5 2 7 2 8
2 6 0 0 6 5 3 7 1 2 6
9 5 2 1 6 7 8 0 5 4 8

Attention: 6.2
Memory: 4.4
Ex. func.: 5.1
Language: 3.7
Difficulty: 5.0

Y ' in the box below.

P Q Y B W
E F I P F
J P H L O
S Y E V Z
U G E D E
T N U F Q
E U O B Z
A G Z J D
B I J N Y
Y E U Y Y
L D Y O D

Attention: 7.2
Memory: 5.2
Ex. func.: 6.2
Language: 4.2
Difficulty: 6.1

' ☽ ' in the box below.

Figure 2. TG Cancellation tasks with different difficulty adaptations.

Reh@City v2.0: The RC [28] system is a virtual environment that consists of a city with different locations where the user can perform cognitive tasks equivalent to the ones generated by the TG [33]. Like in the TG, tasks are personalized for each user profile based on the MoCA's results of the same cognitive domains: attention, memory, executive function, and language. MoCA's results are also normalized to the same scale used in the TG (from 1 to 10, with 0.5 intervals). The RC performs the normalization process automatically without the need for manual calculation. The RC system is also able to save the user levels avoiding the need for configuration on each intervention session. The cognitive tasks are spread over eight locations in the city: bank, clothes shop, home, kiosk, park, supermarket, post office, and pharmacy. The RC tasks were ideated to be as equivalent as possible to the ones found in the TG. Eight tasks have been implemented, and a brief description of each one can be found in Table II(B). Tasks are presented as requests that the participant needs to fulfill. Each task starts by navigating to a specific location and then executing the task on that location. The process is repeated until all expected locations to complete tasks have been visited. RC automatically adjusts each set of tasks based on user performance using the principles mentioned in the protocol subsection of this paper. Each set consists of 7 tasks plus the navigation in the city, which is equivalent to the mazes task in the TG.

Table II. Cognitive tasks description of each tool: (a) Task generator and (b) Reh@City

Task	**(A) Task Generator**	**(B) Reh@City**
Cancellation	Find a specific letter, number, or symbol on an assorted sheet	Find specific items at the pharmacy or post office
Numeric Sequences	Fill in the missing numbers on numeric sequences	Fill in the missing numbers on a numeric sequence at the ATM
Problem resolution	Solve mathematical calculations	Choose the correct invoice after shopping at the supermarket
Association	Match related image pairs	Not applicable
Comprehension of contexts	Mark true or false on affirmations concerning a given contextual image	Not applicable
Image pairs	Memorize a set of image pairs and recall each pair when not visible	Find matching cards in a memory game at the park
Word search	Find words on a sheet of assorted letters	Not applicable
Mazes	Find the correct path from the entry to the exit	Navigate in the city through the shortest path till finding a given location
Categorization	Name the category of each image on a set of images	Select items of a given category at the clothes shop

Task	(A) Task Generator	(B) Reh@City
Action sequencing	Order a set of actions in a manner that makes sense	Select the steps in the right order to accomplish a given task at home
Memory of stories	Read a story and then afterward answer a set of questions concerning the story	Read the text of a newspaper at the kiosk and then answer a set of questions when reaching the next location

Contrary to the TG, the RC allows evolving to difficulty levels above the maximum value of the scale, which is 10. In these circumstances, removing "helpers" that assist the participant when performing the tasks increases the difficulty. For instance, when reaching level 10, the task request is only visible for a few seconds, the participant needs to memorize what task needs to fulfill. At level 10.5 a mini-map that enables to have a broader overview of the path is no longer visible, and at level 11, city signs that indicate directions to the locations are removed. Figure 3 indicates the helpers that have been mentioned.

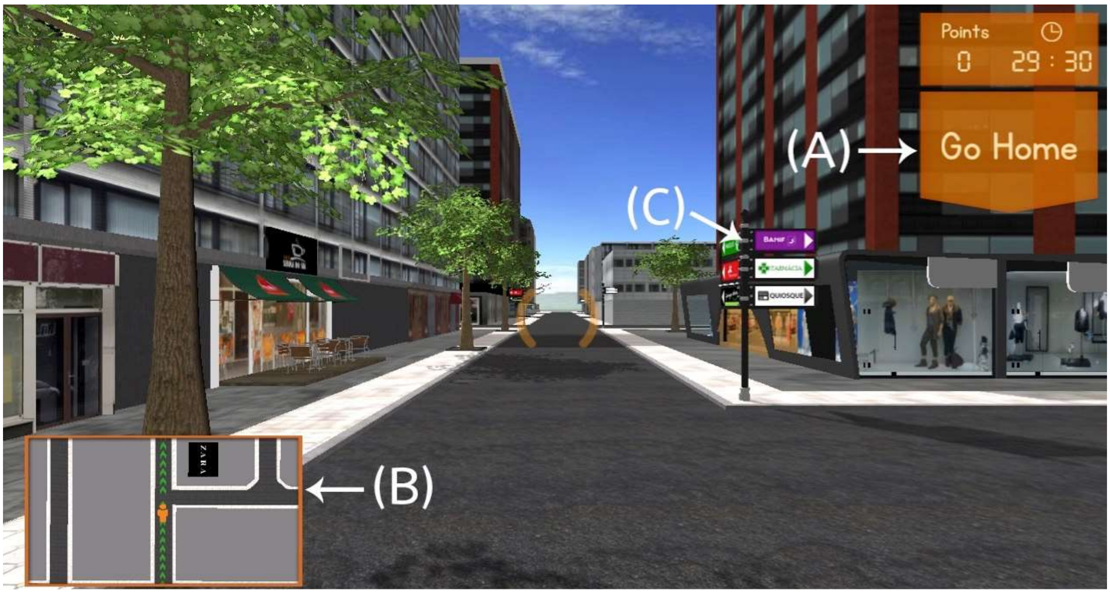


Figure 3. RC street showing helpers that are removed after difficulty level 10: (A) Task request text, (B) mini-map, and (C) city signs.

For instance, the cancellation task, in the TG consists of a set of numbers, letters or symbols where the participant is required to circle or cross a specific given item. The number of items and if they are organized or not are set by the difficulty level. Figure 2 shows some examples of paper-and-pencil tasks generated by the TG tool. In RC, the cancellation task can be found in two different locations: the pharmacy and the post office. A set of shelves with products are presented, and similarly, the participant is required to find one or more items. Items are randomly displayed on the shelves; the number of items is also set by the difficulty level (Figure 4).

Figure 4. Cancellation task at the pharmacy location in RC.

D. Data Analysis

Data from the TG was manually inserted in table sheets with the information of each session per participant including the difficulty level, and the percentage of performance obtained on each task. The RC automatically generated log files in CSV and XML formats, which enabled easy importing into Excel table sheets. RC creates two types of files, one ready for analysis with data summaries, and a highly detailed type of log files with data saved at the software frame rate (mostly 30FPS). These data had to go through a manual verification and rectification process because, during the intervention, the software crashed a few times. After this initial process, the means per participant considering the performance obtained on each task, on each set of tasks, in all intervention tasks (overall performance), the number of tasks performed, and the difficulty level evolution over sessions was computed for both groups. To compare the intensity of training in both methodologies, we used the number of tasks sets, the highest difficulty level achieved, and the total number of tasks performed by each participant. All statistical analyses were performed using SPSS software (version 20, SPSS Inc., Chicago IL, USA). As a criterion for significance, we used an α of 0.05. Normality of data was assessed with the Kolmogorov-Smirnov (KS) test. As some data were not normally distributed, the Mann-Whitney (MW) test was used to compare the between-group differences from baseline to the end of the study. To analyze the effect of the difficulty adaptation and the training methodology in performance we did a general linear model univariate analysis. Since we only had homogeneity of variances, as assessed by the Levene's test, for the overall performance and not for all training tasks, we did not perform a general linear model multivariate analysis to analyze each task performance separately. Instead, we have compared them through a non-parametric Mann-Whitney analysis.

Results

a) Are paper-and-pencil and VR training performances equivalent?

Regarding the twelve training sessions overall performance, no significant statistical differences were found (U=91.000, Z=-1.111, p=.266) between the two groups (TG: Mdn=79.91, IQR=72.11-86.12; RC: Mdn=77.63, IQR=71.09-81.47) (Figure 5).

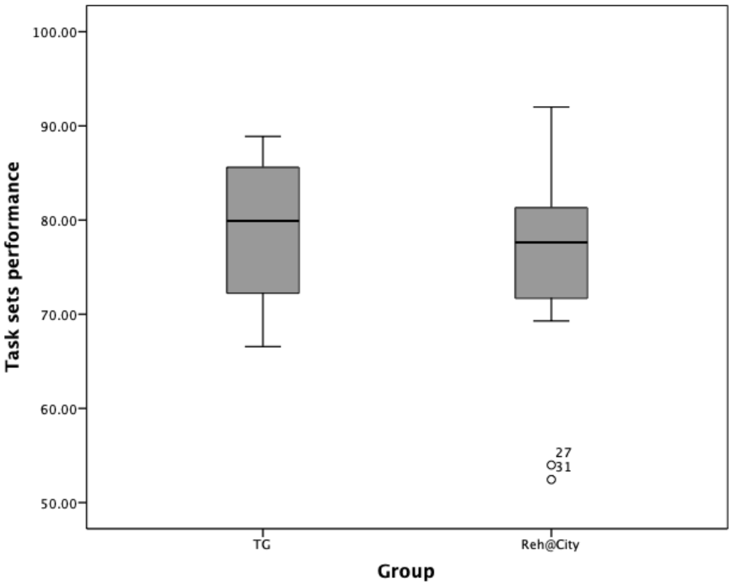


Figure 5. Comparison of the overall task performance per training modality.

b) Is performance modulated by the difficulty adaptation or the training methodology?

A Levene's test showed that the variances for performance (F(1,204)=.838, p=.361) and difficulty adaptation (F(1,204)=.113, p=.737) were equal between groups. After complying with the homogeneity assumption, we performed a general linear model univariate analysis. According to the obtained results the main effect of the adapted difficulty was significant (F(10)=1.992, p=.036) but not the training methodology (TG versus RC) (F(1)=.079, p=.779). The interaction of these two factors was also not significant, F(10,1)=.621, MS=109.710, p=.795. Concerning performance by each task separately, no significant differences were found for the Numeric Sequences, Mazes, Categorization, and Memory of Stories. However, the Mann-Whitney test indicated that the participants who went through the TG intervention achieved a significantly higher performance in both Cancellation ($U = 66.000$, $Z = -2.167, p = .030$) and Action Sequencing ($U = 55.000$, $Z = -2.555, p = .011$) tasks. On the other hand, the participants who performed the RC training performed significantly better in the Problem Resolution ($U = 24.000$, $Z = -3.773, p < .001$) and Image Pairs tasks ($U = 69.000$, $Z = -1.985, p = .047$). In these four tasks where there were statistical differences (Table III), the TG group had higher performances for the Cancellation and Action Sequencing tasks while the RC group had higher performances for the Problem Resolution and Image Pairs task. So, there is no clear specific preference for any approach, which is consistent with the lack of significant differences between overall performances in both training methodologies.

Table III. Results of the Mann-Whitney test on median scores of performance obtained on each task (IQR between brackets).

	Task Generator	**Reh@City**	**MW**
Cancellation	99.75 (96.42-100)	89.44 (68.17-100)	.030*
Numeric Sequences	89.00 (77.89-93.38)	83.95 (61.50-90.48)	.204
Problem Resolution	44.45 (27.21-59.45)	81.53 (71.43-94.64)	<.001*
Association	100 (92.82-100)	Not applicable	Not applicable
Comprehension of Contexts	88.09 (82.43-93.40)	Not applicable	Not applicable
Image Pairs	54.67 (29.80-64.59)	66.34 (60.24-73.97)	.047*
Word Search	93.33 (88.25-99.00)	Not applicable	Not applicable
Mazes	83.33 (69.50-100)	88.59 (78.90-96.40)	.719
Categorization	92.85 (79.14-95.66)	86.02 (76.68-91.97)	.321
Action Sequencing	83.34 (59.92-100)	67.86 (35.42-73.56)	.011*
Memory of Stories	72.50 (59.49-83.96)	73.96 (61.67-85.73)	.648

* Statistically significant difference.

Note: Association, Comprehension of Contexts and Word Search tasks are only available in the TG tool.

c) Which training modality is more intensive?

Both groups evolved in difficulty level in similar ways. However, the RC group evolved slightly faster and attained higher levels (Figure 6).

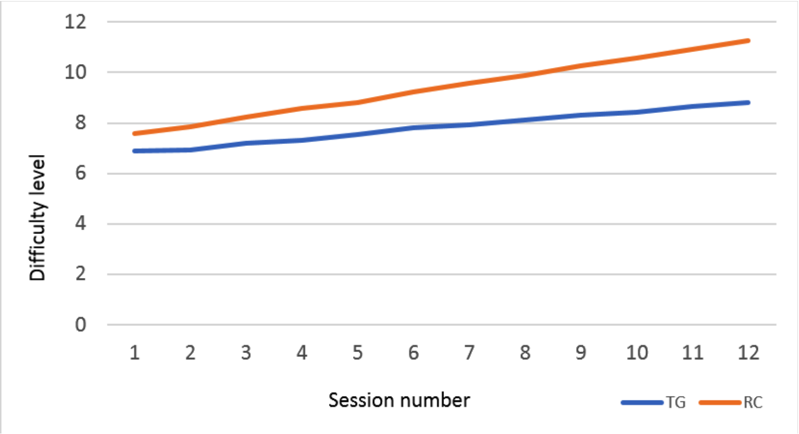


Figure 6. Comparison of the means of difficulty evolution over the 12 sessions of the TG and the RC.

As descibed before, RC allows progression to higher levels than 10 while in the TG, even if the participant could further progress, there is a ceiling effect and training can only be generated until the maximum level of 10. However, only two out of seventeen participants of the TG group managed to reach the maximum difficulty and were limited in progressing in the last training sessions. While in the RC group, eleven out of fourteen managed to surpass the difficulty level of 10.

According to Table IV, the three task performance parameters (number of sets, last set difficulty, the total number of tasks) are higher in the VR training modality and significantly different from the paper-and-pencil one. The RC allows solving more tasks and subsequently completing more task sets, which results in a more progressive difficulty adaptation for the same amount of time.

Table IV. Results of Mann-Whitney test on median scores of task performance parameters (IQR between brackets)

	Task Generator	**Reh@City**	**MW**
Number of task sets	5 (5-6)	10 (9-13.50)	< .001*
Last set difficulty	9 (7.75-9.75)	11.50 (10.25-12.13)	.001*
Total number of tasks	54 (49.5-64.5)	82.5 (68.75)	.001*

* Statistically significant difference.

Discussion

Paper-and-pencil tasks are still widely used in cognitive rehabilitation despite the proliferation of computer-assisted [6], [7] and other multimedia methods, like VR-based simulations of ADL's [14], [15], [16]. This might be due to a reduced number of trials validate these methods [18] and by the difficulties in new technologies adoption by health professionals [19]. A significant number of studies has established construct validity of VR neuropsychological assessment tools with their paper-and-pencil version [17] by demonstrating significant associations with their traditional construct-driven measures [10]. Unfortunately, the clinical validation of a VR-based rehabilitation system is limited if only assessed by baseline and post-intervention neuropsychological outcome measures, which are paper-and-pencil based and lack ecological validity [9]. Hence, the specific role of adaptation in VR and paper-and-pencil cognitive rehabilitation remains unexplored. To our knowledge, no other study exists comparing VR and with widely accepted paper-and-pencil in an adaptive rehabilitation protocol.

Here we presented a comparison of two content equivalent rehabilitation methodologies based on the same difficulty adaptation framework [26]: a web-based paper-and-pencil Task Generator and a VR-based simulation of different ADL's, the RC. The original paper-and-pencil tasks inspired tasks in RC. Sometimes, enhancing the ecological validity of some tasks in VR required adjusting some elements according to what was possible. For instance, the number of targets and distractors in a cancellation task. However, the training adaptation was implemented in the very same way and using the same computing models and difficulty progression rules. A twelve-session intervention study with stroke patients has led us to three main conclusions concerning the content equivalence of both training modalities.

First, according to the overall training performance comparison and despite the differences in training, the personalization and adaptation framework used led to similar cognitive training performances. Hence, there were no differences between groups, meaning that both tools delivered adaptive content of equivalent difficulty.

Second, we wanted to understand if performance was modulated by the implemented adaptation of task difficulty or by the training technology used, being it paper-and-pencil or VR. Our results show a significant effect on the performance of the difficulty adaptation but not of the training methodology, which further strengthens the equivalence of both training methodologies. By specifically comparing both groups' individual tasks performance, we have found significant differences that were consistent with the implementation adjustments we had to perform in VR. For instance, the performance obtained in the Cancellation task was significantly higher in the TG group, this may be due to the number of elements and targets which was much reduced in the RC. To illustrate this discrepancy, the same task with the same level of difficulty, in the RC could have only one target among 20 distractors. While in the paper-and-pencil task would have 15 targets among 120 distractors, by failing to find the correct target in the RC would lead to 0% performance, while by failing one in the TG task would not translate in the same percentage in performance. In the Problem Resolution task, the RC group obtained significantly higher performance. This is due to the number of calculations to solve equivalent tasks, which is also reduced in the RC. The Image Pairs task performance was also significantly higher in the RC group, this may be due to the task itself, which is slightly different in each method: in the TG, the participant was required to remember the pairs of unrelated images, and on the RC, is required to find identic pairs of images in a game. Finally, in what concerns the Action Sequencing task, the TG group performed at a higher level because there was no strict rule in how to order the actions, as long as the ordering was logic, as opposed to RC, where tasks were required to be selected in a specific programmed order. If one step failed, it counted immediately to the overall task performance. However, despite these implementation differences, they did not have a statistical impact on overall performance.

Third and last, our findings, concerning the training intensity of each methodology, show that the VR-based group performed a larger number of tasks and therefore also more task sets and finished at higher difficulty levels. This could lead us to conclude that VR allows a more effective training by enabling more repetitions in the same amount of time, turning the training more intensive. However, these results can also be interpreted by the implementation' discrepancies. Not all the TG tasks have been implemented in the RC, the result in terms of the number of sets was expected since the participant had three tasks less to accomplish to complete each set. Regarding the higher level of difficulty attained by the RC group, this can be influenced by multiple factors such as an easier interaction in VR compared to paper-and-pencil, motivational factors of gaming in VR, computer automation of task delivery and also by embedding tasks in ecologically meaningful contexts.

Conclusion

The presented study, besides its limitations, is the first to compare adaptive paper-and-pencil training with content equivalent VR-based ADL's simulation, by using the same personalization and difficulty adaptation framework within a longitudinal clinical intervention.

Findings of this study support that despite the necessary differences in task implementations, both groups performed at the same level and there was not an effect of the training methodology in overall performance. Moreover, our results contribute with new evidence and provide a further understanding of the impact of using adaptation in VR simulations of ADL's in the rehabilitation of cognitive deficits, instead of paper-and-pencil. Although there are not established clinically important differences for cognitive assessment and rehabilitation outcome measures, we can conclude that the RC offered a more intensive training leading to more task repetitions and higher difficulty adaptation progression, which we believe can be translated in more cognitive improvements.

Nevertheless, there is still a need for further research considering larger samples and more comparative studies with other cognitive rehabilitation tasks.

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Conclusions

This work aimed to contribute with new knowledge and tools to the field of cognitive rehabilitation after stroke. More specifically, the primary goals were to develop a framework with objective guidelines and to design innovative and clinically effective cognitive rehabilitation tools. Here we briefly review the work presented in this thesis, highlight the most relevant findings, and discuss our contributions and limitations:

1. An objective and quantitative framework for the personalization of multiple cognitive domains (attention, memory, language, and executive functions), derived from expert knowledge and materialized in two cognitive rehabilitation tools.

The latest technological advances have allowed improved information and communication technologies (ICT's) applications for cognitive rehabilitation, and it has been shown that they can be effective rehabilitation tools for clinicians (Tedim Cruz et al., 2014). However, the lack of a precise design methodology that can guide their development remains one of the main limitations in this research field. In an attempt to tackle this limitation, data mining techniques have been used to predict the cognitive rehabilitation outcomes in a sample of acquired brain injury patients (Solana et al., 2015). Although it was an important contribution, it is argued that, in the development of novel rehabilitation tools, rehabilitation experts' input should be taken into account (Lange et al., 2012). As an answer to this need, the primary goal of Part I of this thesis was to propose a general framework to guide in the design of future cognitive rehabilitation tools, with objective and expert-based guidelines.

In Chapter 1 we presented the study (Faria, Pinho, & Bermúdez i Badia, 2018) where we describe the development process of this design framework, which combines concepts from educational psychology and a participatory design strategy with stakeholders. The process started with the identification of 11 clinically accepted standard paper-and-pencil tasks, currently used for cognitive rehabilitation, and their operationalization with different parameters, which resulted in 67 tasks rated by 20 rehabilitation experts according to its difficulty and impact on cognitive functions. Through a computational modeling of this data, we identified the parameters that significantly affected cognitive functions and proposed specific models for each task. This methodology provided us with quantitative guidelines for the development of personalized cognitive rehabilitation tools. This is to the best of our knowledge, the first of its kind and also the first to be implemented in two different ICT based solutions, and validated in a RCT. Although the proposed methodology was applied to post-stroke cognitive rehabilitation in this thesis, it can be generalized to other neurologic or psychiatric clinical conditions in which patients would benefit from personalized cognitive rehabilitation or stimulation. We validated the proposed framework with an example case: a web-based tool for the generation of personalized paper-and-pencil cognitive training tasks: the Task Generator (TG), and later on with Reh@City v2.0.

2. A clinical evaluation of the TG with twenty stroke patients showed that, by enabling the adaptation of task parameters and difficulty levels according to patient cognitive assessment, this tool provides a comprehensive cognitive training.

To evaluate the personalization of the TG tasks according to our proposed framework, we performed a feasibility study (Faria & Bermúdez i Badia, 2018), presented in Chapter 2. To assess the proposed TG adaptation to each patient's needs we measured how accurate is the generated profile of cognitive demands of each task was. An evaluation with 20 stroke patients has led us to four main conclusions concerning the feasibility of this web-based tool: 1) although moderately correlated, the TG training performance was higher and statistically different from the patients general cognitive functioning, as assessed by the MoCA, which leads us to conclude that performance is successfully modulated by the TG adaptation mechanisms; 2) more difficult tasks were assigned to the patients that could perform at higher levels, indicating that our personalization adapts to each patient's skillset, providing an individualized challenge level; 3) there were moderate and strong correlations between attention, memory, executive functions and language assessment scores with the TG performance in the corresponding domains, which supports the task profiling, that is, the methodology used to quantify how each task impacts demands on each domain and; 4) the TG was very well received by patients and rehabilitation professionals, who showed interest and motivation to use it in the future.

Given the encouraging results of this study, we have performed a longitudinal clinical trial to measure the impact of intensive cognitive training with the TG, which was presented in Chapter 6 of this thesis and will be discussed afterward. Furthermore, as current work, we are working in a TG tablet version that allows remote monitoring by the rehabilitation professionals and automatic personalization through artificial intelligence and machine learning algorithms.

3. Viability of Virtual Reality (VR) as a tool to combine motor and cognitive training.

After a stroke, it is of major importance to initiate an intensive rehabilitation process with personalized objectives in order to maximize neuroplasticity and, consequently, recovery (Ganguly, Byl, & Abrams, 2013). Fortunatelly, damaged cortical networks can be re-organized through the persistent repetition of learning situations (Alia et al., 2017). However, conventional stroke rehabilitation strategies, based on these principles, are labor and resource-intensive, may be demotivating and can result in reduced effectiveness (Langhorne, Coupar, & Pollock, 2009). These limitations have inspired the development of VR tools to increase treatment adherence and enhance the effectiveness of conventional approaches. VR technology provides one of the most advanced interactions between humans and computers and, in the last years, interest in its application to rehabilitation has increased substantively (Laver et al., 2018). Specifically, training both cognitive and motor domains by means of gaming approaches is gaining clinical acceptance because of the ability of these tools to promote sustained movement practice (Tieri, Morone, Paolucci, & Iosa, 2018). Moreover, activities of daily living (ADL's) are rarely exclusively motor or cognitive but a combination of both.

The relationship between cognitive and motor deficits is increasingly being revealed, and cognitive effort appears to contribute to motor recovery (Faria, Vourvopoulos, Cameirão, Fernandes, & Bermúdez i Badia, 2014; Verstraeten, Mark, & Sitskoorn, 2016). In the past, the practice of activities that require more cognitive demands was already unveiled to be more effective for motor learning compared to those that require less cognitive demands (Hochstenbach, Mulder, Limbeek, Donders, & Schoonderwaldt, 1998). As such, we investigated the learning potential of patients with post-stroke cognitive and motor impairments by developing and validating a rehabilitation strategy that combines cognitive and motor intensive training: the Reh@Task (Faria, Cameirão, et al., 2018).

In chapter 3, we (Faria, Cameirão, et al., 2018) presented a randomized controlled trial (RCT) with a VR cognitive and motor training task, the Reh@Task, consisting on a 1-month intervention with 24 chronic stroke survivors. The Reh@Task group combined arm-reaching movements with memory and attention training, which was inspired in traditional cancellation paper-and-pencil tasks; and the control group performed standard occupational rehabilitation. All patients underwent conventional occupational therapy; only the VR group had time-matched specific training with the Reh@Task. The main hypothesis was that, combining both motor and cognitive components, would impact its ecological validity. Also, the Reh@Task difficulty progression from session to session was based on the computational models derived from the framework presented above (Faria, et al., 2018), providing personalization to the cognitive training in memory and attention. Motor and cognitive abilities were assessed at baseline, end of treatment (1 month) and at a 1-month follow-up through the MoCA (Nasreddine et al., 2003; Portuguese version Freitas, Simões, Alves, & Santana, 2011), Single Letter Cancellation (Diller, 1974), Digit Cancellation (Mohs et al., 1997), Bells Test (Gauthier, Dehaut, & Joanette, 1989), Fugl-Meyer Assessment Test (Fugl-Meyer, Jääskö, Leyman, Olsson, & Steglind, 1975), Chedoke Arm and Hand Activity Inventory (Barreca et al., 2004), Modified Ashworth Scale (Bohannon & Smith, 1987), and Barthel Index (Mahoney & Barthel, 1965).

Overall, results supported the viability of rehabilitation solutions that combine motor and cognitive training, such as the Reh@Task. Both groups improved in motor function over time, but the Reh@Task group exhibited significantly higher between-group outcomes in the arm subpart of the Fugl-Meyer Assessment Test. Improvements in cognitive function were significant and similar in both groups. The analysis of the scores over time for each group, considering the three evaluation moments (baseline, end of treatment, and follow-up), showed a significant impact on MoCA total score and some of its subdomains (Reh@Task group: memory and orientation; control group: language and memory). Concerning the paper-and-pencil cancellation tests, both groups improved over time in the Bells test; the control also improved in the Digit Cancellation.

These data support a more considerable impact of the Reh@Task on motor function than in cognitive function when compared to control. One possible reason could be the limited number of cognitive tasks that only targeted attention and memory. Also, regarding the cognitive outcome measures, the use of screening instruments, as the MoCA may lack sensitivity to capture small improvements. Finally, the Reh@Task has limited ecological validity. Despite being integrative motor and cognitive, it is still far from real motor-cognitive tasks performed in ADLs. Previous work using VR cognitive training of ADLs in simulated environments like a virtual mall showed the translation of competences to real-world ADLs (Rand, Rukan, Weiss, & Katz, 2009). The importance of such approaches can also be seen in a recent study with chronic stroke survivors that used a VR scenario for motor training based on the execution of virtual ADLs (Adams et al., 2018). After eight weeks of treatment, a group of 15 patients showed a mean improvement of ~6 points in FM-UE, which is superior to what we have observed in this study. Nevertheless, this work was a valuable step toward designing more effective rehabilitation technologies that combine motor and cognitive training relying on VR and inspired the development of the Reh@City.

4. Cognitive rehabilitation through the Reh@City, an ecologically valid VR simulation for the training of ADL's, has more impact than standard methods.

Current cognitive rehabilitation practices tend to be directed towards specific cognitive domains like attention, executive functions, visuospatial ability, memory and/or language (Cumming, Marshall, & Lazar, 2013). However, an important concern is how effectively the improvements of these abilities that are trained separately generalize, leading to sustained improvement in everyday functioning (Karbach & Verhaeghen, 2014). When we consider the cognitive domains required for ADLs, such as a efficacious meal preparation (identify the needed ingredients, write a shopping list and preparing the meal through the correct steps) we acknowledge that multiple dimensions of cognition are involved, suggesting the need to be rehabilitated as a whole (Wilson, Herbert, & Shiel, 2004). Unfortunately, there is insufficient evidence to determine if and how the ecological validity of current cognitive rehabilitation methods impacts recovery (Aminov, Rogers, Middleton, Caeyenberghs, & Wilson, 2018; Heugten, Gregório, & Wade, 2012; Parsons, 2016a; Rogers, Foord, Stolwyk, Wong, & Wilson, 2018).

As an answer to this problem and in line with the Reh@Task findings, we developed a virtual simulation of a city - Reh@City v1.0 - where several ADLs are trained in four frequently visited places: a supermarket, a post office, a bank, and a pharmacy. To help the patient relate the VR tasks to the real world, these places display billboards and products of real spaces and trademarks commonly found in Portugal. Reh@City v1.0 enables an integrative and personalized cognitive rehabilitation process, targeting several cognitive domains such as memory, attention, executive functions and visuospatial abilities in a more ecologically valid approach (Vourvopoulos, Faria, Ponnam, & Bermúdez i Badia, 2014).

In Chapter 4 (Faria, Andrade, Soares, & Bermúdez i Badia, 2016) we presented a one-month RCT with 18 stroke patients: nine performing a VR-based intervention with the Reh@City and nine performing a conventional intervention, 20 minutes, three times per week in a total of 12 sessions. The VR intervention had levels of difficulty progression through a method of fading cues. There was a pre and post-intervention assessment in both groups with the Addenbrooke Cognitive Examination Revised (ACE-R) (Mioshi, Dawson, Mitchell, Arnold, & Hodges, 2006; Portuguese version Firmino, Simões, Pinho, Cerejeira, & Martins, 2009), the Trail Making Test A and B (TMTA and TMTB) (Reitan, 1958; Portuguese version Cavaco et al., 2013), Picture Arrangement from WAIS-III (Wechsler, 2008a) and Stroke Impact Scale 3.0 (SIS 3.0) (Vellone et al., 2015). The Reh@City v1.0 group had significant improvements in global cognitive functioning, attention, memory and visuospatial abilities, as assessed by the ACE-R; executive functions, as assessed by the Picture Arrangement Test and; emotion and overall recovery, as self-reported in the SIS 3.0. The control group only improved in memory and social participation, as self-reported in the SIS 3.0. In a between groups analysis, the Reh@City also had superior impact with improvements in ACE-R global cognitive functioning and attention scores and executive functions, as assessed by the Picture Arrangement test.

Despite statistical limitations mainly related to the small number of participants, this study was the first RCT that showed that VR-based cognitive rehabilitation in an ecologically valid context could be more effective than conventional training.

5. Cognitive rehabilitation through the Reh@City v2.0, an ecologically valid VR simulation for the adaptive training of ADL's, has a more comprehensive efficacy with improvements in different cognitive domains and self-perceived cognitive deficits impact in everyday life, than a content equivalent paper-and-pencil intervention with cognitive gains that last for longer.

Lately, there has been significant growth in the number of studies proposing ecologically valid VR-based simulations of ADL's like the most promising training solutions (Luca et al., 2018; Maggio et al., 2019). However, most of the developed systems were not clinically validated (Klinger et al., 2013), have only gone through studies with a small number of participants (Gamito et al., 2017) and/or with healthy control groups (Nir-Hadad, Weiss, Waizman, Schwartz, & Kizony, 2015). Additionally, these VR-based ADL's simulations miss a comparison with widely used and clinically accepted paper-and-pencil training, being always compared with non-equivalent interventions as occupational therapy (Faria, Andrade, et al., 2016; Faria, Cameirão, et al., 2018). In Chapter 5, we address these current limitations through an RCT that compared adaptive paper-and-pencil training (TG) with content equivalent VR-based ADL's simulation (Reh@City v2.0). We also had a control group of patients undergoing treatment as usual (TAU), which was OT (occupational therapy), the conventional treatment provided by the Madeira health service. As presented throughout this thesis, both TG and Reh@City v2.0 tools were developed with the same task contents and using the same personalization and difficulty adaptation framework. In this RCT, a total of 42 participants, 14 allocated to Reh@City v2.0, 18 to TG and 10 to OT performed twelve sessions of time-matched training with pre and post-intervention neuropsychological assessment. The Reh@City v2.0 and the TG groups also went through a follow-up neuropsychological assessment. The primary outcome was the MoCA (Nasreddine et al., 2003; Portuguese version Freitas, Simões, Alves, & Santana, 2011). The secondary outcomes included the TMTA and B (Reitan, 1958, Portuguese version Cavaco et al., 2013), the WAIS-III (Wechsler, 2008a) Symbol Seach (SS), Digit Symbol (DS) and Vocabulary, the WMS-III (Wechsler, 2008b) Verbal Paired Associates (VPA) and Digit Span and the PRECiS (Patchick, Vail, Wood, & Bowen, 2015; Portuguese version Faria, Alegria, Pinho, & Bermúdez i Badia, 2018).

Training with the Reh@City v2.0 had a positive impact on MoCA general cognitive functioning, attention and visuospatial ability and executive functioning, verbal memory as assessed with the VPA, and processing speed as measured by the DS Coding task, which generalized for the self-perceived impact of cognitive deficits from PRECiS. This generalization did not happen in the paper-and-pencil group that only revealed similar cognitive impact in the MoCA orientation score, processing speed as measured with TMTA task execution time and verbal memory as assessed with the VPA. The TG intervention sustained impact at follow-up, maintaining processing speed gains as assessed by the SS and verbal memory (VPA) improvements, revealing a new one in language (Vocabulary). As expected, OT was shown to be an insufficient intervention for cognitive deficits after stroke with no improvements in none of our outcomes measures. By comparing interventions between themselves, Reh@City v2.0 was superior in MoCA general cognitive functioning and visuospatial ability and executive functioning.

The Reh@City v1.0 RCT (Faria, Andrade, et al., 2016) had already demonstrated the benefits of an ecologically valid VR system in cognitive rehabilitation. But, the Reh@City v2.0 RCT (Faria, Pinho, & Bermúdez i Badia, submitted), contributes with new evidence and provides a further understanding of the impact of using personalization and adaptation in VR simulations of ADL's and paper-and-pencil tasks in the rehabilitation of cognitive deficits, which can facilitate the adoption of these innovative tools by health professionals in their daily practice. Concerning the study limitations, although 42 stroke participants is a large number when compared with existing clinical trials, its distribution was not balanced and, mainly, the TAU group was smaller. Also, the intervention was not blind, and the same researchers performed assessments and interventions, except for the TAU group that had an occupational therapist providing the intervention.

6. Comparatively with the Task Generator, the Reh@City v2.0 offers more intensive training leading to more task repetitions and higher difficulty adaptation progression.

A significant number of studies has established the construct validity of VR neuropsychological assessment tools with their paper-and-pencil version (Nir-Hadad et al., 2015) by demonstrating significant associations with their traditional construct-driven measures (Parsons, 2016b). Concerning the VR-based rehabilitation systems, clinical validation studies only assess the baseline and post-intervention neuropsychological outcome measures. To the best of our knowledge, no study compared VR with widely accepted paper-and-pencil tasks in an adaptive rehabilitation protocol.

For this reason, we performed an analysis of the participants' performance, both in the TG and Reh@City v2.0, during the twelve training sessions of the RCT presented in Chapter 5 (Faria, Pinho, & Bermúdez i Badia, *submitted*). In both tools, the training adaptation was implemented in the very same way and using the same computational models and difficulty progression rules (Faria, et al., 2018). As such, we wanted to answer three main questions: 1) are paper-and-pencil and VR training performances equivalent?; 2) is performance modulated only by the difficulty adaptation or also by the methodology to deliver it (paper-and-pencil vs. VR)?; and 3) which training method is more intensive?

In Chapter 6 we presented the main conclusions (Faria, Paulino, & Bermúdez i Badia, 2019) concerning the content equivalence of both training modalities. Findings support that despite the necessary differences in task implementations, both groups performed at the same level and there was not an effect of the training methodology in overall performance. Moreover, the obtained results contribute with new evidence and provide a further understanding of the impact of using adaptation in VR simulations of ADL's in the rehabilitation of cognitive deficits, instead of paper-and-pencil. Overall, we can conclude that the Reh@City v2.0 offered more intensive training leading to more task repetitions and higher difficulty adaptation progression, which we believe translated in more cognitive improvements.

Practical applications

All three cognitive rehabilitation tools developed within this Ph.D. project are being used in different healthcare institutions, with other clinical groups for both research and clinical intervention purposes:

- The Reh@Task study (Chapter 3) took place in Centro Médico da Murtosa (Aveiro, Portugal) where it continues to be used by the rehabilitation professionals, not only with stroke but also with traumatic brain injury and other neurological pathologies.
- Casa de Saúde São João de Deus (Funchal, Portugal) is running an RCT using the Reh@City v2.0 and the Task Generator within an alcoholism rehabilitation program: *"Cognitive rehabilitation through virtual reality and paper-and-pencil interventions as complementary tools in addictive behaviors treatment: an RCT with alcohol use disorder participants"*.
- Casa de Saúde Câmara Pestana (Funchal, Portugal) included cognitive training with the Reh@City v2.0 and the Task Generator, in their Psychosocial Rehabilitation program for psychiatric patients.
- The Physical Medicine and Rehabilitation department from the Hospital Nélio Mendonça (Funchal, Portugal) is using the Reh@Task, Reh@City v2.0, and Task Generator in their recently created Cognitive Rehabilitation unit, which targets brain injury patients.
- The Santa Casa da Misericórdia (Mirandela, Portugal) is running an RCT using the Reh@City v2.0 and the Task Generator for the rehabilitation of traumatic brain injury patients. Additionally, they will use these tools for intervention with their stroke patients.

These practical applications go far beyond our initial expectations and encourage us to disseminate their use and improve them with further research and field studies.

Future work

Many healthcare providers are unfamiliar with ICTs and, as a consequence, a very small percentage of people with disabilities have access to technological devices that can assist them in the rehabilitation process (WHO, 2011). To mitigate this issue, it would be valuable to improve the acceptance and usability of the Task Generator, the Reh@Task, and the Reh@City v2.0 by interviewing the healthcare providers after using them as complementary tools for their work.

Moreover, as future work, we are also planning to upgrade the Task Generator by creating a tablet version that allows remote monitoring by the healthcare providers and automatic personalization through artificial intelligence and machine learning algorithms.

Finally, our results contribute with new evidence and provide a further understanding of the impact of using personalization and adaptation in VR simulations of ADL's and paper-and-pencil tasks in the rehabilitation of cognitive deficits, nonetheless, there is still a need for further research considering other clinical populations, as well as the implementation of a wider variety of cognitive tasks in all three tools.

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