# UNIVERSITÀ DEGLI STUDI DI PADOVA

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# Telerehabilitation for cognitive disorders: randomized controlled trial in patients with stroke outcomes

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**Abstract**

The internship at the Department of Neurosciences, Biomedicine, and Movement of the University of Verona gave me the opportunity to closely observe the reality of acquired cognitive deficits and the management of patients affected by them. In this paper, I will focus specifically on patients with cognitive outcomes following a stroke. The study I will present explores the use of tele-rehabilitation through computerized tools as an alternative to traditional rehabilitation sessions with a neuropsychologist. The two groups involved use the same computerized tool (Neurotablet®) in different settings: the Experimental Group at home, following a weekly program provided by neuropsychologists, and the Control Group in a hospital setting. The aim of this study is to assess whether a computer-based restorative cognitive treatment administered through tele-rehabilitation can lead to cognitive improvements comparable to those achieved with the same treatment conducted in person. This approach paves the way for new perspectives and broader opportunities for a future in which cognitive treatment can be provided to anyone in need, despite the limited resources available in dedicated services.

# Chapter 1. Introduction

## 1.1 Stroke

The Italian Society of Neurology (SIN) defines stroke as: "a clinical syndrome characterized by the sudden onset of a focal (rarely global) neurological deficit that persists for more than 24 hours or leads to death and is caused by the closure (ischemic stroke) or rupture (hemorrhagic stroke) of a cerebral artery”. Globally, approximately 15 million people are affected by stroke each year. This cerebrovascular disease can have ischemic or hemorrhagic origin. An ischemic stroke is due to the closure of an artery, which prevents blood from reaching a specific area of the brain. Conversely, a hemorrhagic stroke results from the rupture of an artery, causing blood to leak into the brain. Consequently, brain tissue is damaged by both the reduction in blood flow and the pressure of accumulated blood outside the arteries. Ischemic stroke is the most common, accounting for about 62% of cases, while hemorrhagic stroke accounts for about 28% (Feigin et al., 2022). The primary risk factor for stroke appears to be high systolic blood pressure. Other risk factors include high body mass index, high fasting plasma glucose levels, environmental particulate pollution, and smoking (Feigin et al., 2022). Recent estimates of the stroke burden from the Global Burden of Disease (GBD, 2019) show that stroke remains the second leading cause of death and the third leading cause of combined death and disability. The GBD uses the Disability Adjusted Life Years (DALY) measure to quantify the impact of a particular disease, representing the sum of years of life lost due to premature mortality. From 1990 to 2019, there was a 143.0% increase in this measure. These alarming data allow us to estimate that globally, one in four people over the age of 25 will suffer a stroke during their lifetime (Feigin et al., 2022).

### 1.2 Stroke Clinical Manifestations

Subsequently to the acute event, various disorders may arise that affect the patient's level of functioning and hinder their return to work and the performance of daily life activities. These can include physical disabilities, such as paralysis or weakness on one side of the body (hemiparesis), difficulty walking or performing daily activities, and problems with balance and coordination. Many stroke survivors also experience swallowing problems (dysphagia), which can lead to malnutrition or aspiration pneumonia. Stroke can cause emotional and psychological issues, including anxiety, depression, and personality changes. Among the disorders that have the greatest impact on the patient's disability are cognitive ones. In fact, approximately half of all young stroke patients experience cognitive impairment, and about a quarter develop aphasia. These conditions. Recently, the American Heart Association/American Stroke Association Journals summarized in an article the main cognitive deficits affecting patients after a stroke (2022). Many patients experience aphasia, often associated with difficulties in global cognitive functions, including attention, learning, and memory. Attention is of central importance and serves as the critical foundation for any more complex cognitive operation. Memory impairment occurs in about half of patients with symptomatic stroke. Memory is crucial for functioning and survival, and its impairment due to stroke impacts the quality of life and the risk of post-stroke dementia. Another common deficit is unilateral spatial neglect, which is an impairment in perceiving and responding to stimuli on the side opposite to the brain lesion. This condition presents in various forms and is observed in up to half of the patients suffering from a stroke in the right hemisphere. Finally, there are deficits related to executive functions, which are important for adapting behavior and responding to new, changing, and challenging environmental conditions. The presence of cognitive deficits following stroke is associated with the worsening of the long-term prognosis of stroke. This deterioration can lead to dependence on others, depression, institutionalization, and mortality (Obaid, Douiri, et al., 2020). Additionally, cognitive decline can occur within 6 months of the event and may worsen into dementia within 5 years (Rohde et al., 2019). Cognitive decline not only affects the quality of life of stroke patients but can also impose a significant medical burden on the patient's family and society (Gerstl et al., 2023; Rochmah et al., 2021). Given the lack of successful pharmacological treatments for cognitive decline, identifying alternative therapeutic strategies to reduce cognitive deterioration after stroke remains a significant public health issue.

### 1.3 Cognitive Rehabilitation After Stroke

Cognitive rehabilitation is a non-pharmacological treatment aimed at individuals who have developed cognitive deficits after stroke. This program includes individualized interventions targeting specific cognitive domains like attention, memory, language, and executive functions, using activities to improve impaired functions and promote compensatory strategies. Post-stroke cognitive rehabilitation includes both restorative and compensatory non-pharmacological treatments. Restorative interventions directly address the impaired function and are specific to the damaged cognitive domains. Examples of restorative methods include training patients with episodic memory deficits to improve the encoding of information to be remembered. Compensatory interventions adapt to the external environment and enhance patients' ability to use their remaining cognitive skills, fully or partially spared, or environmental resources to reduce the impact of the deficit on the patient's daily life. An example is treating prospective memory deficits using a diary to remember and manage appointments. These types of interventions are not mutually exclusive and are often combined in a rehabilitation path to promote functional recovery at multiple levels. Cognitive rehabilitation relies on the principle of brain plasticity, the central nervous system's ability to adapt structurally and functionally in response to experience and injury (Ismail et al., 2017). After a stroke, brain plasticity enables the reorganization of neural circuits to take over tasks previously managed by damaged areas. This plasticity includes structural changes, such as increased synaptic connections, and functional changes, such as the formation of new neural pathways through learning. Brain plasticity is crucial not only for stroke recovery but also for continuous learning and adaptation throughout life. Factors such as age, stroke severity, and rehabilitation efforts affect neuroplasticity, with physical exercise and cognitive training playing significant roles in enhancing recovery outcomes (Hötting et al., 2013). According to current research, cognitive rehabilitation interventions seem effective in improving cognitive function after a stroke (das Nair et al., 2016). In a review by Rogers and colleagues (2018), the effects of cognitive remediation on individual cognitive domains were examined. Notably, an effect was observed for outcomes related to information processing speed. Other effects were observed in the attentional, memory, and executive domains. Moderate effects were found in the areas of language and visuospatial functioning. Additionally, the study also provides evidence of transfer effects to untrained cognitive domains. Cognitive rehabilitation is not only about restoring lost functions but also about enhancing the overall quality of life and psychological well-being of stroke survivors. In a study, Norlander and colleagues (2021) suggest that people's ability to accept their stroke-related issues and adapt their behavior and attitude are central factors for social participation after stroke. Family members and caregivers play a crucial role in the rehabilitation process, and their involvement can positively impact the patient's recovery journey (Maggio et al, 2024).

## 1.4 Computer-Assisted Cognitive Rehabilitation

In recent years, studies on computer-assisted cognitive rehabilitation (CACR) have shown positive effects regarding the use of computer-based programs to improve the cognitive functioning of stroke patients. Generally, it is considered a good choice for patients with mild cognitive impairment or dementia (Nie et al., 2022). CACR is a cognitive training regimen based on computer programs that include specific multimedia activities to improve various cognitive domains. The adoption of this practice has been facilitated by the needs that emerged during the last four years, marked by the SARS-COV-2 pandemic, which led to a significant reduction in rehabilitative assistance. The development of tele-rehabilitation tools, despite arising from challenging circumstances, offers significant benefits. These include reduced management costs, improved accessibility for patients in remote areas or with physical limitations, and the ability to continue treatment post-hospital discharge, thus extending the recovery process. The clinical use of CACR has been recognized as a good substitute or supplement to traditional cognitive rehabilitation. A recent study investigated the effect of the RehaCom rehabilitation software on reaction speed and the maintenance of attention and concentration in patients with chronic ischemic stroke. After several weeks of treatment, the results showed significant improvements in working memory and information processing speed in the experimental group compared to the control group (Amiri et al., 2023). The study by Cho and colleagues (2015) showed that, after computerized rehabilitation treatment of attention and memory skills, the experimental group differed significantly from the control group in tasks involving short-term memory, working memory, attention, and activation of the frontal and parietal lobes. Another study found that compared to conventional rehabilitation alone, the combination of CACR and virtual reality can effectively improve cognitive function and the management of daily activities in patients with post-stroke cognitive impairment (Shi et al., 2023). The integration of emerging technologies such as virtual reality (VR) and augmented reality (AR) into CACR presents exciting possibilities for improving rehabilitation outcomes. VR and AR can create immersive and interactive environments that engage patients in a more stimulating and motivating way, simulating real scenarios that provide practical experiences useful in recovering cognitive functions and daily living skills. Furthermore, the use of artificial intelligence (AI) in CACR systems can offer personalized rehabilitation plans that adapt to the patient's progress and specific needs, ensuring a more efficient and effective rehabilitation process (Naqvi et al, 2024). With the continued advancement of research in these areas, the potential to improve the quality of life and recovery outcomes for stroke survivors through innovative technological interventions becomes increasingly promising.

Based on the information provided, the aim of this study is to evaluate whether computer-based restorative cognitive treatment delivered via tele-rehabilitation produces an improvement in cognitive function comparable to that achieved through the same treatment conducted in-person, in patients with stroke outcomes. Investigating this approach is particularly relevant given the limitations and constraints of dedicated rehabilitation services, exacerbated during the pandemic period.

# Chapter 2. Materials and methods

## 2.1 Participants

Patients with ischemic or hemorrhagic stroke referred to the Neurorehabilitation Unit of the University Hospital of Verona were included in the study. They were recruited upon discharge from the Neurorehabilitation Unit.

The eligibility criteria were:

- Diagnosis of ischemic or hemorrhagic stroke;
- Age between 18 and 90 years;
- First stroke event;
- Stroke occurred more than 30 days prior;
- Adequate level of comprehension;
- Presence of one or more of the following cognitive impairments assessed through a screening evaluation using the Oxford Cognitive Screen (OCS, Mancuso et al., 2016):
    - Attention impairments
    - Memory impairments
    - Executive function impairments
- Availability of internet access at the patient's home, necessary for telemedicine procedures.

Patients were excluded if they had:

- Other neurological disorders;
- Pre-morbid cognitive decline;
- History of psychiatric disorders;
- Alcohol and/or drug abuse;
- Severe uncorrected visual deficits.

All participants provided informed written consent to participate in the study. This study was approved by the local Ethics Committee (approval number 3623CESC) and was conducted in accordance with the Declaration of Helsinki.

**2.2 Randomization, allocation and blinding**

Participants who met the inclusion criteria were randomly assigned in a 1:1 ratio to one of the two treatment groups: Experimental Group (EG) and Control Group (CG). The participants were allocated to one of the two intervention arms according to a balanced software-generated randomization scheme (www.randomizer.org). The examiner was blinded to group assignment.

**2.3 Treatment procedure**

Both groups underwent cognitive treatment for three hours per week, over a total of eight weeks, using the computerized tool Neurotablet®.

• The Experimental Group carried out the rehabilitative treatment independently and remotely. Each patient received the device and the necessary login credentials to access their account. They engaged in different cognitive exercises remotely programmed by the neuropsychologist based on rehabilitation goals. Patients were instructed to use the device for one hour per session, three times a week. The expert sets the training weekly based on the patient's progress, modifying the intensity or type of exercises.

• The Control Group underwent rehabilitative treatment in person with Neurotablet®. Patients performed cognitive exercises on the electronic device under the supervision of a neuropsychologist at the Neurorehabilitation department. The therapist selected exercises during each session, determining the activities and difficulty levels.

In addition to the rehabilitative activities, participants of SG also participated in 4 online individual meetings, each lasting 1 hour every 2 weeks. The tele-consultations were conducted using the telemedicine platform "Virtual Care-POHEMA," employed for remote care management. It was provided by the Brain Research Foundation Verona (BRFVr) and developed by the Gpi group (Gruppo per l'Informatica) (https://www.gpi.it/). These meetings, led by the neuropsychologist, allowed the patient to discuss any issues related to the use of the device at home.

### 2.4 The Neurotablet

Neurotablet® is a multi-platform neurocognitive rehabilitation software distributed by Neurab S.R.L., preinstalled on a Samsung Tab A® tablet. The device includes exercises divided into different cognitive domains: attention, memory, perception, language, neglect, and executive functions. The software features a clear and easy-to-understand interface. The main menu lists the cognitive domains mentioned above. For example, clicking on 'attention' displays a series of activities aimed at evaluating abilities in the different sub-domains of the selected cognitive area. Each exercise allows adjustments in stimulus characteristics such as type (letters, numbers, images), presentation mode (visual, auditory, or both), speed, number of trials, presence of distractors, and task timing. Therefore, the therapist can adjust the level of exercises based on the patient's performance, either increasing or decreasing their difficulty. The device also supports remote use, enabling therapist to monitor patient's work at home in real-time, including the time spent and progress made, using a dedicated tablet. Finally, it is possible to exchange messages with the patient, intervening in case any issues arise during the use of device. In neuroscience, such tools provide immediate feedback, with data from neuropsychological sessions being stored and made accessible to both operators and patients (Lee et al., 2014). This enables experts to remotely customize cognitive training based on each patient's neuropsychological profile, enhancing the stimulation of damaged brain areas by adjusting exercise parameters like difficulty and response times. The methods used in cognitive rehabilitation vary depending on the clinical population and specific goals, generally involving flexible tasks that adapt to the needs and capacities of patients. These activities, often resembling video games, range from attention-targeting tasks to memory exercises and problem-solving tasks for executive functions. Simple, engaging, and intuitive, these tasks create interactive protocols that engage patients of all ages (Carelli et al., 2017).

### 2.5 Evaluation protocol

Upon discharge from the Neurorehabilitation department, patients underwent a neuropsychological screening assessment with the Oxford Cognitive Screen (OCS Mancuso et al., 2016) a tool used to determine the inclusion/exclusion of subjects from the study. The OCS assesses cognitive impairments in linguistic, attentional, memory, numerical, and praxic domains. The screening is not specific for differentiating impaired functional areas but is sensitive to global cognitive impairments. Subjects included in the study, underwent subsequently a specially designed evaluation protocol.

The evaluation protocol was administered before treatment (T0), after completing 8 weeks of treatment (T1), and two months after the end of the treatment (T2).

*Evaluation protocol tests:*

- *Trail Making Test A (Siciliano et al., 2019)*

  This test assesses attention ability, selective attention in particular, psychomotor speed and sequencing skills. Numbers from 1 to 25 are scattered on a sheet. The goal is to connect the numbers in ascending order with a single line. The score is determined by the time taken, where longer time reflect poorer performance.

- *Trail Making Test B (Siciliano et al., 2019)*

  This test evaluates the ability to switch attention between two rules or tasks. Numbers from 1 to 13 and letters from A to M are randomly arranged on a sheet. The goal is to connect them with a single line in ascending order, alternating between numbers and letters (1-A-2-B-3-C, etc). The score is based on the time taken by the subject to complete the task; longer time indicate poorer performance.

- *Rey's 15 Words Test (Carlesimo et al., 1996)*

This test evaluates learning and long-term delayed recall of verbal information. A list of 15 words is presented five times, and after each presentation, the subject verbally recalls as many words as possible. The sum of the words recalled in each repetition respectively corresponds to the learning and long-term retention score. After a 15-minute interval, delayed recall is tested without presenting the list again. For both tests, higher scores indicate better performance.

- *Rey-Osterrieth Complex Figure Test (Caffarra et al., 2002)*

This test assesses visuospatial abilities. The subject first copies a complex geometric figure and, after a delay of 10 minutes, draws it from memory without seeing the original. Scores for both copying and delayed recall are based on the accuracy of reproduced features. Higher scores indicate better performance.

- *Dual Task (Baddeley et al.,1997)*

This test assesses the divided attention. The test consists of three 2-min trials. The first trial "Span", the patient repeats strings of numbers of the span length in the same order of presentation. In the second trial "Tracking", the subject must trace the outlines of squares as quickly as possible without lifting the pen. The final trial "Span and Tracking", involves performing both previous tasks in parallel, allowing the measurement of divided attention. An index score (mu) is calculated based on the comparison between single task performance on these two tasks and performance on the tasks under the dual task-condition. Higher scores indicate better performance.

In addition, questionnaires were administered to explore disability, quality of life and mood:

- *Hospital Anxiety and Depression Scale – HADS (Zigmond and Snaith, 1983)*

  This questionnaire measures the presence and severity of depression and anxiety through 14 items. Higher scores indicate higher levels of depression and anxiety.

- *Short Form Health Survey 36 – SF-36 (RAND, 1992)*

  This questionnaire evaluates health-related quality of life across 8 domains through 36. Higher scores indicate better health-related quality of life.

A specific questionnaire was also administered at T1 to assess the treatment feasibility, patient satisfaction, and costs incurred.

**2.6 Statistical Analysis**

The data were examined using SPSS 26.0, employing a non-parametric statistical analysis. The Mann-Whitney test was used to assess the homogeneity of the samples and for group comparisons. The variables included in the calculation of homogeneity are age, education, time from onset (time elapsed between injury and T0), and performance on part B of the TMT. The choice to use the TMT B as a variable in the calculation of homogeneity stems from the fact that attention is a foundational cognitive skill that provides the necessary cognitive infrastructure for both academic and everyday tasks, influencing the priority of cognitive processes for access to consciousness or response (Mackie et al. 2013).

The within-group analysis of patients' performance on the evaluation protocol tests (comparison T0-T1 and T0-T2) was conducted using the Wilcoxon test. Comparisons were corrected using the Least Significant Difference (LSD) method, which provides an overview of the significant differences.

# Chapter 3. Results

### 3.1 Sample

From July 2021 to April 2024, 294 subjects who experienced a stroke event were assessed, of which 40 were deemed eligible for participation in the study. These individuals exhibited attentional, memory, and/or executive disorders, as observed in the OCS (Mancuso et al., 2016), and were under 85 years of age. Out of the 40 patients, 21 were assigned to the Experimental Group and 19 to the Control Group. Among the 21 patients in the Experimental Group, 16 were evaluated at T0 and completed the rehabilitation cycle (T1). Ten were evaluated at T2. Among the 19 patients in the Control Group, 16 were evaluated at T0 and completed the rehabilitation cycle (T1), with 8 evaluated at T2. Of the selected patients, 2 participated in a cross-over study, receiving both treatments. Nineteen patients are considered drop-outs. The lesion site was located in the right hemisphere for 9 patients, in the left hemisphere for 11 patients, and bilaterally in 1 patient. The stroke was ischemic in origin for 18 patients and hemorrhagic for the remaining 3. The subjects' ages ranged from 45 to 82 years (mean age 62.99 years); education levels ranged from 5 to 18 years (mean education 8.82 years); 17 subjects were male and 6 were female. For further demographic details of the sample, see Table 1.

*Figura 1. Flowchart*

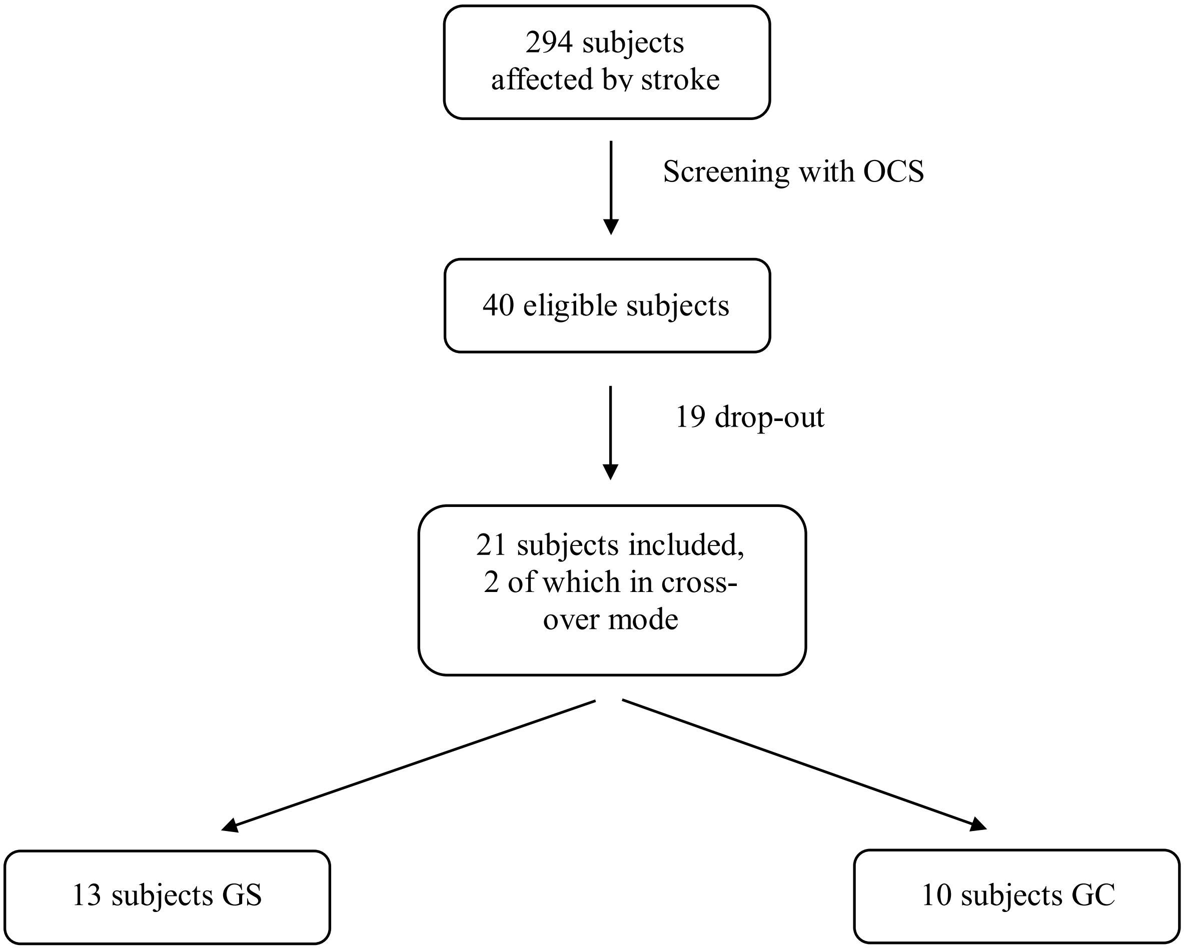


*Table 1. Sample Data*

| | *EG* *Mean (±sd)* | *CG* *Mean (±sd)* |
|---|---|---|
| *Participants* | 13 | 10 |
| *Age* | 63,46 (±8,33) | 62,40 (±14,14) |
| *Gender (M/F)* | 9M / 4F | 8M / 2F |
| *Lesion site* | 53,84% dx, 38,46% sx, 7,7% bilateral | 40% dx, 60% sx |
| *Education* | 8,08(±3,22) | 9,80 (±4,98) |

## 3.2 Data Analysis

### 3.2.1 Homogeneity between Experimental Group (EG) and Control Group (CG)

The Mann-Whitney test was conducted to analyze the homogeneity between the two groups at T0. The groups were homogeneous in terms of age, education, time from onset (time elapsed between injury and T0), and performance on part B of the TMT ($p=.116$; $z= -1.572$).

### 3.2.2 Between-Groups Analysis

The non-parametric Mann-Whitney test was employed to compare the Experimental Group (EG) and the Control Group (CG). This analysis identified only one statistically significant difference between the data collected at T0 (pre-treatment) and T1 (post-treatment), specifically in the test measuring selective visual attention and visuo-spatial search speed (Trail Making Test-A, TMT-A, $p = .028$; $z = -2.203$). This finding suggests an improvement in selective attention and processing speed at the end of the intervention in one of the groups. However, no other statistically significant differences emerged across the evaluation protocol tests. The lack of significant differences across most measures reinforces the hypothesis that the two treatment modalities are comparable in effectiveness. These findings highlight that, despite the single significant result, the overall impact of both treatment approaches appears to be equivalent across the studied dimensions of cognitive function.

### 3.2.3 Within-Groups Analysis

The Wilcoxon test was utilized to conduct the within-group analysis, comparing performances on different tests between T0-T1 and T0-T2 in the Experimental Group and separately in the Control Group.

### 3.2.4 Experimental Group

Within the EG, a statistically significant difference was observed in the TMT-A test ($p=.039$; $z= -2.062$) when comparing pre- and post-treatment performances. There was an average improvement of 15.31 seconds in visuo-spatial exploration speed. A significant improvement was also noted in the learning and delayed recall tasks of the Rey 15 Words Test (Immediate: $p=.049$; $z= -1.966$; Delayed: $p=.025$; $z= -2.235$), with patients improving their performance by an average of 3.53 points and 1.62 points, respectively. The improvement in the learning task of the Rey 15 Words Test was also evident when comparing performances at T0-T2, indicating maintenance of performance two months later ($p=.017$; $z= -2.379$). A statistically significant improvement was also found in the delayed recall of the Rey Complex Figure Test ($p=.015$; $z= -2.433$) from T0 to T2, with an average improvement of 5.5 points. For further details, see Table 2.

*Table 2. Performance of EG in assessments at T0, T1, and T2, and within-group analysis*

| *Test* | *Mean T0* | *Mean T1* | *Mean T2* | *P value (z score) T0-T1* | *P value (z score) T0-T2* |
|---|---|---|---|---|---|
| *TMT-A* | 70,69(±36,69) | 55,38 (±24,29) | 57,7 (± 34,28) | *p*=.039 (z= -2.062)* | *p*=.306 (z=-1.023) |
| *TMT-B* | 189,77(±113,75) | 183,53 (±113,11) | 162,70 (±104,46) | *p*=.386 (z=-0.866) | *p*=.61 (z=-0.510) |
| *Rey's 15 Words Test (immediate)* | 31,61 (±11,96) | 35,15 (±10,67) | 39,10 (± 12,40) | *p*=.049 (z=-1.966)* | *p*=.022 (z=-2.295)* |
| *Rey's 15 Words Test (delayed)* | 6 (±3,42) | 7,61 (±3,99) | 7,40 (± 3,44) | *p*=.025 (z=-2.235)* | *p*=.056 (z=-1.914) |
| *Rey-Osterrieth Complex Figure Test (immediate)* | 24,26 (±7,36) | 27,26 (±6,40) | 28,70 (± 6,50) | *p*=.071 (z=-1.807) | *p*=.262 (z=-1.122) |
| *Rey-Osterrieth Complex Figure Test (delayed)* | 12,34 (±6,76) | 14,73 (±7,56) | 17,85 (± 6,73) | *p*=.065 (z=-1.847) | *p*=.015 (z=-2.433)* |
| *Dual Task* | 85,73 (±25,73) | 85,75 (±24,32) | 88,47 (± 17,66) | *p*=.722 (z=-0.356) | *p*=.721 (z=-0.357) |

### 3.2.5 Control Group

From the statistical analysis of the performances of the CG subjects, comparing performance at T0 and T1, significant results were found for the TMT A test (p=.005; z=-2.803), with an average improvement of 41.6 seconds. Significance was also observed for both tasks of the Rey 15 Words Test (Immediate: p=.005; z=-2.807; Delayed: p=.028; z=-2.203), with an average improvement of 7.4 points for the learning task and 2.4 points for the delayed recall task. These improvements were maintained in both tasks when comparing performances at T0 and T2 (Immediate: p=.021; z=-2.313; Delayed: p=.017; z=-2.379), with an average improvement of 13.50 points in the learning task and 3.38 points in the delayed recall task. Finally, a significant score was noted in the TMT-B task in the T0-T2 comparison (p=.027; z=-2.207), with performances improving by an average of 27.07 seconds. For further details, please refer to Table 3.

*Table 3. Performance of CG in assessments at T0, T1, and T2, and within-group analysis*

| *Test* | *Mean T0* | *Mean T1* | *Mean T2* | *P value (z score) T0-T1* | *P value (z score) T0-T2* |
|---|---|---|---|---|---|
| *TMT-A* | 104,00 (±45,64) | 62,40 (±38,41) | 81,5 (±72,29) | *p*=.005 (z=-2,803)* | *p*=.161 (z=-1,400) |
| *TMT-B* | 271,80 (±96,27) | 214,90 (±109,29) | 179,37 (±122,85) | *p*=.063 (z=-1.859) | *p*=.027 (z=-2.207)* |
| *Rey's 15 Words Test (immediate)* | 22,00 (±9,47) | 29,40 (±9,08) | 35,5 (±15,10) | *p*=.005 (z=-2.807)* | *p*=.021 (z=-2.313)* |
| *Rey's 15 Words Test (delayed)* | 3,00 (±2,70) | 5,40 (±2,87) | 6,37 (±2,97) | *p*=.028 (z=-2.203)* | *p*=.017 (z=-2.379)* |
| *Rey-Osterrieth Complex Figure Test (immediate)* | 26,00 (±8,97) | 27,30 (±7,16) | 29,37 (±7,05) | *p*=.678 (z=-0.415) | *p*=.128 (z=-1.524) |
| *Rey-Osterrieth Complex Figure Test (delayed)* | 9,95 (±6,99) | 12,40 (±7,08) | 16,62 (±8,62) | *p*=.167 (z=-1.383) | *p*=.069 (z=-1.820) |
| *Dual Task* | 70,00 (±27,95) | 83,95 (±17,82) | 89,93 (±25,02) | *p*=.123 (z=-1.540) | *p*=.091 (z=-1.690) |

# Chapter 4. Discussion

## 4.1 Disclaimer

The study presented, involving a sample of 23 participants, should be regarded as a pilot study. The inferences and conclusions drawn from the data analysis are strictly related to this sample and cannot be generalized. The LSD method for post hoc comparisons offers a basic view of significant differences and is useful for preserving statistical power and avoid overly conservative corrections, especially in studies with few comparisons or small samples.

## 4.2 Discussion of results

The analysis of sample homogeneity confirmed that the Experimental Group (EG) and the Control Group (CG) are comparable in terms of demographic characteristics and performance on the TMT-B. Although the two groups differ in size, there were no statistically significant differences, which enhances the reliability of the results. Once the reliability of the data was established, the initial hypothesis was evaluated using the non-parametric Mann-Whitney test. The aim was to investigate whether there were differences between the two groups following the two rehabilitation approaches employed. If the groups had shown statistically significant differences post-treatment, the hypothesis would have been rejected, indicating that the rehabilitation modalities (in-person and remote) would not be comparable in terms of cognitive gain. Since no significant differences emerged in changes between T0, T1, and T2, the hypothesis was confirmed, demonstrating that some cognitive abilities remained stable even in the long term. Therefore, both treatments are considered equivalent in terms of their effectiveness in cognitive improvement. This conclusion represents a significant resource for the future of cognitive rehabilitation, suggesting that telerehabilitation tools could be integrated to expand treatment offerings. These tools reduce the direct commitment of professionals, allowing them to schedule exercises remotely one or more times a week, thereby enabling them to manage a larger number of patients. This approach reduces waiting times and allows a broader population to access timely interventions. By further examining the data regarding progress between T0 and T1 and between T0 and T2 within each group, conclusions could be drawn about the cognitive improvements associated with each type of rehabilitation. In the EG, the most significant improvements were observed in the areas of attention and memory. Specifically, the TMT-A test and the Rey 15 Words Test (both immediate and delayed recall) highlighted developments in cognitive abilities. For TMT-A, the progress involved selective visual attention and visuospatial search, while the Rey 15 Words Test indicated improvements in the learning and long-term recall of verbal material. The comparison between T0 and T2 confirmed the maintenance of verbal material learning abilities. Additionally, two months after the treatment's conclusion, an improvement was recorded in the ability to recall visuospatial material, evaluated through the Rey Complex Figure Test. These results align with existing literature. The study by Cho et al. (2015) demonstrated that cognitive rehabilitation using computerized tools produced benefits in sustained attention and short-term memory. The experimental group utilized the RehaCom software to train various cognitive functions, with specific exercises designed to stimulate attention, concentration, and memory. The control group, which followed a traditional paper-and-pencil treatment, did not achieve significant improvements. A more recent study, also based on the use of RehaCom software, showed that treatment improved activities of daily living (ADL), attention, and response control in patients with chronic stroke. Although the precise mechanism through which RehaCom affects cognitive dysfunctions remains unknown, it is hypothesized that its action on brain regions involved in executive and attentional functions enhances structural and functional connections, leading to improved cognitive performance (Veisi-Pirkoohi et al., 2020). The study by Amiri et al. (2023) confirmed that using RehaCom software in an experimental group, with 45-minute sessions over ten days, led to significant improvements in working memory and information processing speed. Improvements for the control group (CG) were also significant in the domains of attention and memory. The Rey 15 Words Test, both in the learning task and in the delayed recall, demonstrated a change in the subjects' mnemonic abilities, with the results remaining stable even two months after the end of treatment, as confirmed by the T2 data. In addition to mnemonic abilities, T2 showed improvements from patients in both groups on tests that did not exhibit enhancement following the T1 post-treatment evaluation. Notably, the TMT-B task for the control group, which measures attentional shifting, and the delayed recall of the Rey Complex Figure Test, which investigates long-term visuospatial material retention. Due to the multiple variables at play in this type of research (age, education, type of lesion, and its allocation), it is challenging to explain this kind of delayed effect improvement. A recent review by Rosenich and colleagues (2020) encourages future research to better consider the role of premorbid variables related to lifestyle, such as cognitive reserve. Cognitive reserve is a complex mechanism that strengthens pre-existing cognitive processing strategies to maximize performance when neural networks are compromised by injuries like stroke, recruiting alternative neural networks or pathways not typically used by healthy individuals to compensate for deficits. These functions highlight how complicated it can be to trace the cause of a lack of cognitive improvement and, conversely, to explain the prerequisites for spontaneous recovery. Elliot and Parente, through a meta-analysis in 2014, demonstrated that intervening on memory in cognitively compromised patients, especially post-stroke, proved effective in most cases. However, they noted that significant improvements in memory occurred spontaneously over time, suggesting the need for baseline assessments immediately after stroke or TBI, so that the rate of spontaneous improvement can be measured and documented once a therapeutic intervention begins. Furthermore, since shifted attention and long-term memorization of visuospatial material are complex skills requiring the simultaneous activation of multiple cognitive domains, they may take longer to change compared to other functions. What can be stated is that training cognitive functions even after the end of treatment would increase the likelihood of eventual recovery. Finally, regarding the present study, it should be noted that increasing the sample size could help to explore the issue further and obtain results that may assist in better interpreting this data , also enabling the use of more accurate and precise statistical methods for post hoc comparisons.

# Chapter 5. Conclusion

The literature thus appears to reflect a picture consistent with the results of the present study. Cognitive improvements vary based on the methods and specific objectives of each research study, but a common thread can be found: both long- and short-term memory, as well as sustained attention, seem to benefit from rehabilitation more than other cognitive abilities, both during the acute phase and the chronic phase of the illness. The data collected, along with the significance values (p-values) reported in Tables 2 and 3, and the evidence present in the literature, confirm that tele-rehabilitation treatments and in-person treatments may yield similar results in terms of effectiveness. This strengthens the initial hypothesis that the two intervention modalities can be considered comparable. No substantial differences were found in the improvements achieved between the two treatment modalities. Future research is hoped to further explore this issue, better identifying the strengths and weaknesses of distance cognitive rehabilitation. However, the clear advantage of tele-rehabilitation lies in resource savings, especially in terms of time. In this study, for instance, professionals dedicated three hours weekly for each patient in the Control Group, whereas in the Experimental Group, the time needed for tablet programming was reduced to just 15 minutes per week per patient. The introduction of an innovative treatment like tele-rehabilitation would allow for significant time savings for professionals, enabling them to manage a larger number of patients and thereby helping to reduce waiting lists for access to therapies.

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