UNIVERSITA' VITA-SALUTE SAN RAFFAELE

CORSO DI DOTTORATO DI RICERCA IN NEUROSCIENZE COGNITIVE

"At-home extension of computerised cognitive rehabilitation in People with Progressive Multiple Sclerosis: A Feasibility and Efficacy Pilot Randomised Controlled Trial"

DoS: Prof., Letizia Leocani

Tesi di DOTTORATO di RICERCA di Angela Boschetti

matr. 020257

Ciclo di dottorato XXXVII°

SSD MEDS-12/A

Anno Accademico 2021/2022

UNIVERSITA' VITA-SALUTE SAN RAFFAELE

CORSO DI DOTTORATO DI RICERCA IN NEUROSCIENZE COGNITIVE

"At-home extension of computerised cognitive rehabilitation in People with Progressive Multiple Sclerosis: A Feasibility and Efficacy Pilot Randomised Controlled Trial"

DoS: Prof., Letizia Leocani

Tesi di DOTTORATO di RICERCA di Angela Boschetti

matr. 020257

Ciclo di dottorato XXXVII°

SSD MEDS-12/A

Anno Accademico 2021/2022



CONSULTAZIONE TESI DI DOTTORATO DI RICERCA

Il/la sottoscritto/*I Angela Boschetti*
Matricola / *registration number 020257*
nat_a/ *born at Brescia*
il/*on 11/04/1995*
autore della tesi di Dottorato di ricerca dal titolo / *author of the PhD Thesis titled*

"At-home extension of computerised cognitive rehabilitation in People with Progressive Multiple Sclerosis: A Feasibility and Efficacy Pilot Randomised Controlled Trial"

□ AUTORIZZA la Consultazione della tesi / AUTHORIZES *the public release of the thesis*
X□ NON AUTORIZZA la Consultazione della tesi per 12 mesi /DOES NOT AUTHORIZE *the public release of the thesis for …… months*

a partire dalla data di conseguimento del titolo e precisamente */ from the PhD thesis date, specifically*
Dal / *from* 14/03/2025 Al / *to* 13/03/2026

Poiché /*because*:

□ l'intera ricerca o parti di essa sono potenzialmente soggette a brevettabilità/ *The whole project or part of it might be subject to patentability;*

X□ ci sono parti di tesi che sono già state sottoposte a un editore o sono in attesa di pubblicazione/ *Parts of the thesis have been or are being submitted to a publisher or arein press;*

□ la tesi è finanziata da enti esterni che vantano dei diritti su di esse e sulla loro pubblicazione/ *the thesis project is financed by external bodies that have rights over it and on its publication.*

E' fatto divieto di riprodurre, in tutto o in parte, quanto in essa contenuto / *Copyright the contents of the thesis in whole or in part is forbidden*

Data /Date 05/02/2025 Firma /Signature Angela Boschetti

DECLARATION

This thesis has been:

- composed by myself and has not been used in any previous application for a degree. Throughout the text I use both 'I' and 'We' interchangeably.
- has been written according to the editing guidelines approved by the University.

Permission to use images and other material covered by copyright has been sought and obtained. For the following image/s (specify), it was not possible to obtain permission and is/are therefore included in thesis under the "fair use" exception (Italian legislative Decree no. 68/2003).

All the results presented here were obtained by myself.

Parts of this thesis have been reprinted from a published research article where I am first author:
"Boschetti, A., Maida, E., Dini, M., Tacchini, M., Gamberini, G., Comi, G., & Leocani, L. (2024). A Review on the Feasibility and Efficacy of Home-Based Cognitive Remediation in People with Multiple Sclerosis. Journal of Clinical Medicine, 13(7), Article 7. https://doi.org/10.3390/jcm13071916"
Specifically:
- "Table 2. Efficacy of telerehabilitation for CI in MS." Is an identical reprint of the original table included in the published study.
-In text content from the study has been re-elaborated and appropriately referenced throughout the introduction and discussion sections

All sources of information are acknowledged by means of reference.

Acknowledgments

I would like to express my deepest gratitude to everyone who contributed to the completion of this thesis. A heartfelt thank to my supervisor, Prof. Letizia Leocani, for her guidance and encouragement throughout this research journey, and to Prof. Giancarlo Comi, who with his dedication to research and his tireless commitment has been an incredibly inspirational figure. I am also immensely grateful to my close colleagues Marta Tacchini and Michelangelo Dini for their support, as well as to Dr. Giulia Gamberini and Dr. Alessandra Caporali for their contribution in the current research project. I extend my appreciation to all those who, directly or indirectly, have played a role in helping me reach this milestone, particularly all the participants in the study, as well as the staff and management of the Casa di Cura Igea SpA in Milan.

Abstract

A great proportion of People with Multiple Sclerosis (PwMS) suffers from Cognitive Impairment (CI), which greatly diminishes the quality of life of those affected. Pharmacological treatments for CI in PwMS showed limited efficacy, and behaviourally-based interventions still remain the preferred care option. These typically involve in-clinic repeated one-on-one sessions with a therapist for a set period of time. This has been seen to be both costly and unfeasible for some PwMS. Telerehabilitation may provide a solution to some limitations of in-person cognitive remediation, specifically being a great resource to implement in the long-term assistance of PwMS, and, as add-on to standard rehabilitation in the continuity of care of these individuals. Nonetheless, evidence regarding its feasibility and efficacy is still scarce.

To address this gap, 25 PwMS were included in the current study. 15 individuals in the intervention group continued training at home with a computer software already used in the context of a routine in-patient stay, aimed at the training of memory, attention, processing speed and executive functions. 10 individuals in the control group discontinued training with the software and began computerised sham activities. Performance on selected neuropsychological tests and Patient Reported Outcome Measures (PROMs) was assessed before the beginning of the telerehabilitation vs. sham, immediately after, and at a 6-months follow-up appointment. Feasibility, measured as adherence to planned training hours, was the primary outcome, while Linear Mixed Models (LMM) were used to explore any performance gains in the intervention group compared to the control group.

The results suggest the feasibility of telerehabilitation is medium-to-high, and usability scores are generally high. However, no significant performance gains on any of the neuropsychological tests or PROMs were seen for the intervention group compared to the control group. All participants displayed improvements on processing speed, attention and visuo-motor speed at the 6-months follow-up, with the control group unexpectedly outperforming the intervention group. Benefits of training at the individual level were seen in some participants in both groups.

Overall, the current results are unsupportive of the superiority of telerehabilitation in treating CI in PwMS in this context. As it stands, gold standard treatments for CI in PwMS are still lacking. Exploring new frontiers in rehabilitation will be essential.

Table of contents

Acronyms and abbreviations 4

List of figures and tables 6

1 Introduction 7

1.1 Introduction to Multiple Sclerosis (MS) 7

1.1.1 MS epidemiology 8
1.1.2 MS aetiology 8
1.1.3 MS pathophysiology 10
1.1.4 MS symptoms and management 10

1.2 Cognition in MS 11

1.2.1 MS specific cognitive deficits 12
1.2.2 Neuropsychological assessment in MS 14
1.2.3 Treatment for CI in MS: evidence from pharmacological trials 15
1.2.4 Treatment for CI in MS: evidence from non-pharmacological trials 16

1.3 Limitations to in-person cognitive rehabilitation and introduction to telerehabilitation 21

1.4 Telerehabilitation for CI in MS: the state of the art 23

2 Study aims 30

2.1 Primary aim: feasibility of telerehabilitation 30

2.2 Secondary aim 1: immediate efficacy of telerehabilitation 30

2.3 Secondary aim 2: long-term efficacy of telerehabilitation 30

2.4 Secondary aim 3: transfer effects of telerehabilitation 30

3 Results 31

3.1 Baseline characteristics 31

3.2 Feasibility 34

3.3 Usability of telerehabilitation: SUS scores 35

3.4 Efficacy: neuropsychological outcome measures 36

3.5 Transfer effects: PROMs 42

3.6 Individual-level improvements 43

3.7 Post-hoc analysis 44
3.7.1 Rationale 44
3.7.2 Results from ANOVA 44
4 Discussion 48
4.1 Summary of main findings 49
4.2 Feasibility of telerehabilitation and system usability 50
4.3 Efficacy of telerehabilitation 52
4.3.1 Possible reasons for the lack of evidence for the efficacy of telerehabilitation 53
4.3.2 SDMT gains in the control group 57
4.3.3 In-clinic cognitive improvements 58
4.4 Strengths and limitations 59
4.5 Conclusive remarks 60
5 Methods 62
5.1 Study Design 62
5.2 Participants 62
5.3 Procedure 64
5.3.1 Participant screening and recruitment 64
5.3.2 Block randomisation 65
5.3.3 Telerehabilitation procedure 65
5.4 Variables and outcome measures 67
5.4.1 Variable measures 67
5.4.2 Primary outcome measure 67
5.4.3 Secondary outcome measures 68
5.5 Telerehabilitation intervention 70
5.5.1 Attention and processing speed modules 71
5.5.2 Memory modules 71
5.5.3 Executive modules 71
5.5.4 Training schedule 72
5.6 Sham activities 73
5.7 Data analysis 73
5.7.1 Main analysis 73
5.7.2 Post-hoc analysis 75

5.8 Ethical considerations.....75

6 References.....75

7. Appendices.....95

7.1 Appendix 1.....95

7.2 Appendix 2.....98

Acronyms and abbreviations

(1) Advanced Progressive Matrices (APM); (2) Attention Test (TEA); (3) Auditory Verbal Learning Test (AVLT); (4) BDI-II, Beck Depression Inventory-II; (5) BICAMS, Brief International Cognitive Assessment for Multiple Sclerosis; (6) Brief Repeatable Battery of Neuropsychological Tests (BRBNT); (7) Brief Visuospatial Memory Test-Revised (BVMT-R); (8) California Verbal Learning Test-II (CVLT-II); (9) Centre for Epidemiologic Studies Depression Scale (CES-D); (10) Central Nervous System (CNS); (11) Chicago Mood Depression Inventory (CMDI); (12) Clinically Isolated Syndrome (CIS); (13) Cognitive Failures Questionnaire (CFQ); (14) Cognitive Impairment (CI); (15) Cognitive Reserve Index questionnaire (CRIq); (16) Cognitive Functioning Tests (CFT); (17) Conners' Continuous Performance Test (CPT); (18) Controlled Oral Word Association Test (COWAT); (19) Computer-aided card-sorting procedure (CKV); (20) Delis-Kaplan Executive Function System (D-KEFS); (21) Diagnostic and Statistical Manual V (DSM-V); (22) Disease Modifying Therapies (DMTs); (23) Dysexecutive Questionnaire (DEX); (24) Epstein-Barr Virus (EBV); (25) Environmental Status Scale (ESS); (26) Expanded Disability Status Scale (EDSS); (27) EuroQOL five-dimension questionnaire (EQ-5D); (28) Everyday cognition scale (Ecog); (29) Fatigue Scale for Motor and Cognitive Functions (FSMC); (30) Fatigue Severity Scale (FSS); (31) Functional Assessment of Multiple Sclerosis (FAMS); (32) Hamburg-Wechsler Intelligence Test - Revised (HAWIE-R); (33) Hospital Anxiety Scale (HADS-A); (34) Human Leukocyte Antigen (HLA); (35) Integrated Auditory Visual 2 (IVA-2); (36) Judgment of Line Orientation (JLO); (37) Letter-Number Sequencing (LNS); (38) Major Histocompatibility Complex (MHC); (39) Minimal Assessment of Cognitive Function In Multiple Sclerosis (MACFIMS); (40) Mini-Mental State Examination (MMSE); (41) Modified Fatigue Impact Scale (MFIS); (42) Montreal Cognitive Assessment (MoCA); (43) Multiple Choice Vocabulary Test B (MWT-B); (44) Multiple Sclerosis (MS); (45) Multiple Sclerosis Quality of Life-29 (MSQoL-29); (46) Multiple Sclerosis Neuropsychological Questionnaire (MSNQ); (47) Nonverbal Learning Test (NVLT); (48) Neurocognitive Disorders (NCDs); (49) Neuropsychological Examination – CogniFit Personal Coach (NCP-C); (50) Numeric Pain Rating Scale (NPRS); (51) Paced Auditory Serial Addition Test (PASAT); (52) Patient Determined Disease Steps (PDDS); (53) Patient-Reported Outcome Measures (PROMs); (54) Perceived Deficits Questionnaire (PDQ); (55) Primary Progressive Multiple Sclerosis (PPMS); (56) Prominent Cognitive Function Tests (PCF); (57) Quality of Life (QoL); (58) Randomised Controlled Trials (RCTs); (59) Reliable Change

Index analysis (RCI); (60) Radiologically Isolated Syndrome (RIS); (61) Reaction Times (RTs); (62) Relapsing Remitting Multiple Sclerosis (RRMS); (63) Selective Reminding Test (SRT); (64) Spatial Recall Test (SPART); (65) Short Form Health Survey (SF-36); (66) Short form of the SF 36 health questionnaire (SF-12); (67) State-Trait Anxiety Inventory (STAI); (68) Stroop Test (ST); (69) Symbol Digit Modalities Test (SDMT); (70) Sustained Attention Test (DAUF); (71) Trail Making Test (TMT); (72) Unidimensional Self-Efficacy scale for Multiple Sclerosis (USE-MS); (73) Victoria Symptom Validity Test (VSVT); (74) Visual Analog Scale (VAS); (75) Wechsler Adult Intelligence Scale (WAIS); (76) Wisconsin Card Sorting Test (WCST); (77) Word List Generation (WLG); (78) Nine Hole Peg Test (NHPT).

List of figures and tables

Introduction section

- Table 1. **Efficacy of the RehaCom software for cognitive deficits in MS**
- Table 2. **Efficacy of digital telerehabilitation for CI in MS**

Results section

- Table 3. **Baseline characteristics of participants**
- *Figure 1*. **Baseline cognitive impairment on neuropsychological tests**
- Table 4. **Group comparisons on neuropsychological tests and PROMs at re-baseline assessment**
- Table 5. **Feasibility of telerehabilitation vs. sham activities**
- *Figure 2.* **Distribution of SUS scores**
- Table 6. **Mean scores (± SD) at the neuropsychological tests**
- *Figure 3.* **SDMT interaction plot**
- Table 7. **"Group" x "Time" r-T1 interaction**
- Table 8. **"Group" x "Time" r-T2 interaction**
- *Figure 4.* **CVLT-II interaction plot**
- *Figure 5*. **BVMT-R interaction plot**
- Table 9. **Mean scores (± SD) at the PROMS**
- Table 10. **Individual performance improvements at the neuropsychological evaluation**

Post-hoc analysis results section

- *Figure 6*. **In-clinic improvements on SDMT**
- *Figure 7*. **In-clinic improvements on BVMT-R**
- *Figure 8*. **In-clinic improvements on Stroop Test Word-Reading**
- *Figure 9*. **In-clinic improvements on Stroop Test Colour-Naming**

Materials and method section

- *Figure 10.* **Flow diagram of recruitment process**
- *Figure 11.* **Flowchart of the main experimental procedures**
- Table 11. **RehaCom training schedule**

Appendices section

- Table 12. **Full LMM results for neuropsychological outcome measures**
- Table 13. **Full LMM results for PROMs**

1 Introduction

1.1 Introduction to Multiple Sclerosis (MS)

Multiple Sclerosis (MS) is a chronic autoimmune disease of the Central Nervous System (CNS), characterised by focal areas of inflammation, demyelination, gliosis and axonal severing, as well as grey matter and cortical lesions (McGinley et al., 2021). It is the most common cause of non-traumatic disability in younger adults (Inglese & Bester, 2010), as People with Multiple Sclerosis (PwMS) are typically diagnosed between the ages of 20 and 40 (Ghasemi et al., 2017). Thus, MS likely affects individuals during their prime years, leading to profound implications for both the affected person and the immediate social circle.

Approximately 85% of MS cases begin with an episode of Clinically Isolated Syndrome (CIS), an initial acute attack of inflammation and demyelination, typically occurring in the optic nerves, brainstem, cerebellum, spinal cord or the cerebrum (Efendi, 2015). Radiologically Isolated Syndrome (RIS) has also been witnessed through Magnetic Resonance Imaging (MRI), and it is defined by incidental white matter lesions in the CNS that suggest a demyelinating disease, without previous history of demyelination or neurological disability typical of MS (Hosseiny et al., 2020). Importantly, patients with RIS are at higher risk of later experiencing other radiological events or clinical symptoms related to MS (Okuda et al., 2009).

Eventually, around 80% of PwMS are diagnosed with Relapsing Remitting Multiple Sclerosis (RRMS), a condition where symptoms typically develop over hours to days, often improving within weeks to months. Early in the disease, symptoms usually fully resolve or leave only partial repercussions. However, over time, any residual damage tends to accumulate, leading to varying degrees of disability (Vargas & Tyor, 2017). Among individuals with RRMS, approximately 60% will shift to Secondary Progressive Multiple Sclerosis (SPMS) within 10–15 years (Rodrigues et al., 2023), with disability steadily increasing. Instead, Primary Progressive Multiple Sclerosis (PPMS) affects around 15% of individuals, and it is characterised by gradual progression from onset, making it the most disabling form of the disease.

1.1.1 MS epidemiology

Between September 2019 and March 2020, the MS International Federation collected prevalence data from 115 countries, representing 87% of the global population. Results suggest 2.8 million people worldwide live with MS. Prevalence rates are particularly high (ranging from 101 to over 200 PwMS per 100,000 individuals) in most European countries, with Italy, Germany, Norway, Sweden, Finland and Iceland reporting the highest rates. Similarly, MS prevalence is highest in the United States of America and Canada, compared to Mexico and countries in Central and South America, where rates are lower (ranging from 25 to 50 PwMS per 100,000 individuals). Lower prevalence is also observed in Asia and Africa (excluding Egypt), although there is significant lack of data for many African regions. Countries like Turkey and the Russian Federation report a prevalence of 51-100 PwMS per 100,000 individuals, while Australia and New Zealand record 51 to 200 PwMS per 100,000 individuals (Walton et al., 2020).

A 30% increase in MS prevalence was registered since 2013 in most countries, with a more pronounced rise in incidence rates for RRMS (Koch-Henriksen & Magyari, 2021). Furthermore, females are twice as likely to have MS, with the ratio of females to males even being 4:1 in some regions, and with incidence rates that have increased even more in women in the last decade. The increase in MS is likely due to improved public knowledge regarding the disease, more access to neurological services, improved diagnosis, better care, and more advanced proficiency in quantifying the number of individuals affected by it. However, it has also been hypothesised that the heightened exposure to certain lifestyle factors may have played a role, including childhood obesity, infectious agents, and urbanisation (Koch-Henriksen & Magyari, 2021; Walton et al., 2020).

1.1.2 MS aetiology

The trigger for MS remains largely unknown, however, the disease is most likely elucidated by a multifactorial model, which involves an interaction between genetic and environmental factors. Concordance rates in monozygotic twins are higher compared to dizygotic twins and non-twin siblings, respectively 25.3% compared to 5.4% and 2.9% (Willer et al., 2003), arguing for, at least in part, a genetic susceptibility to the disease. Genome wide association studies found that genes situated within the Human Leukocyte Antigen (HLA) complex on chromosome 6

represent the most potent genetic risk factors, particularly the presence of class II variant HLA-DRB1*15:01 (Olsson et al., 2017). Additionally, 200 autosomal susceptibility variants located outside the Major Histocompatibility Complex (MHC) region, as well as one variant on chromosome X, along with 32 independent associations within the extended MHC, have been linked to MS (Baranzini & Oksenberg, 2017).

In addition, specific environmental influences also play a critical role. Smoking (Hedström et al., 2009), as well as mere exposure to passive smoke in non-smokers (Hedström et al., 2011) increase MS risk. Interestingly, oral consumption of tobacco through snuff decreases the probability of developing the disease (Hedström et al., 2009), suggesting that the association between smoke and MS could be more closely related to lung inflammation resulting from active and passive inhalation of smoke, rather than nicotine consumption itself, which may instead be a protective factor (Olsson et al., 2017). This notion also gains support from the correlation between MS and elements such as long-term exposure to air pollution and organic solvents. Furthermore, the infectious agent Epstein-Barr Virus (EBV) is also strongly associated to MS (Bjornevik et al., 2022), so that researchers have speculated that the EBV may even be a pre-requisite for the disease. Since the virus is extremely common within the population, and clearly not all people infected develop MS, it is surely fundamental to gain more insights into mechanisms or eventual abnormalities in the contracted infection, as MS may be influenced by the initial immune response to the virus (Soldan & Lieberman, 2023). Studies also provide compelling evidence for decreased sun exposure as a risk factor. Increased exposure to ultraviolet B radiation showed a significant correlation with reduced prevalence rates of MS (Orton et al., 2011), and elevated levels of circulating vitamin D were linked to reduced risk of developing the disease (Munger et al., 2006). Correspondingly, reduced sun exposure and lower levels of vitamin D have been associated with more severe MS, characterized by increased frequency of relapses and faster progression to disability (Lucas et al., 2015). Finally, obesity is an additional risk factor (Schreiner & Genes, 2021).

Importantly, there is a notable interplay between environmental risk factors and genetic predisposition. For instance, smoking influences MS-associated HLA risk alleles. Similarly, EBV interacts with HLA MS risk genetic variants, while polymorphisms near the central vitamin D metabolism enzyme gene are linked to heightened MS risk. Elements interacting with genetic risk variants possibly share

underlying pathways in the disease's development, emphasising their impact on the immune system (Olsson et al., 2017).

1.1.3 MS pathophysiology

Immune mechanisms, particularly abnormal lymphocyte activity, are thought to be primarily responsible for neuronal damage. Disease pathogenesis involves an autoimmune attack on myelin proteins, leading to structural defects in the CNS. Indeed, abnormal immune responses play a critical role in the development of MS (Liu et al., 2022). The principal factors contributing to the destruction of the myelin sheath are multifocal areas of inflammation, characterized by infiltrations of T-lymphocytes and macrophages, along with the death of oligodendrocytes (Ghasemi et al., 2017). Consequently, this leads to CNS plaques, which are visible with MRI. Of relevance, the latter technique can help uncover both multiple focal lesions within the brain and spinal cord at a single time point, as well as multiple lesions occurring at different time courses in the disease (Brisset et al., 2021).

1.1.4 MS symptoms and management

Depending on which regions of the CNS are affected, symptomatology can vary, with the most common symptoms being sensory disturbances, motor issues, visual deficits, gastrointestinal and urinary dysfunction, dizziness and vertigo, sexual dysfunction, Cognitive Impairment (CI) and affective disorder (Ghasemi et al., 2017). Comorbidities are also common and most often include depression and anxiety, vascular conditions and sleep disorders (McGinley et al., 2021).

Treatment in MS involves both targeting the disease with Disease-Modifying Therapies (DMTs) and managing symptoms and comorbidities with both pharmacological and non-pharmacological interventions. DMTs can modulate the immune system through diverse mechanisms, such as lymphocyte sequestration, shifting the balance between T helper cells, interfering with DNA synthesis in lymphocytes, depleting immune cells, and altering cytokine secretion patterns. While mechanisms of action are clear for some medications, but not for others, DMTs remain a great resource to help lower the frequency of relapses and diminish short-term disability (McGinley et al., 2021). Treatment of symptoms, instead, involves a large number of interventions, such that the need for a multidisciplinary MS care unit has been emphasised, where the MS neurologist and nurses work in synergy with a number of equally important additional services, such as psychological support,

occupational therapy, management of pain, continence and spasticity, social care, speech therapy, physical rehabilitation and cognitive remediation (Soelberg Sorensen et al., 2019). Notably, the latter has emerged as a focal point of interest in recent years, driven by its potential to address cognitive deficits and significantly enhance the quality of life of PwMS.

1.2 Cognition in MS

Cognition refers to the set of mental processes necessary to navigate the world, through sensation, perception, experience and thought. Major cognitive domains involve perception, attention, executive functions, learning and memory, language, motor abilities, and social cognition (American Psychiatric Association, 2013). When cognition is affected, a person may experience a disturbance in one or more cognitive domains. In clinical practice, CI is identified when an individual's performance on specific cognitive domains falls below an established threshold or cut-off, as measured by means of neuropsychological testing (Macías Islas & Ciampi, 2019; Fischer et al., 2014). On the other hand, according to the fifth edition of the Diagnostic and Statistical Manual (DSM-V), a Neurocognitive Disorder (NCD) manifests when there is significant cognitive decline compared to baseline performance in one or more cognitive domains, which is not better explained by delirium or another mental disorder or condition. Furthermore, the DMS-V reports the need to specify the condition underlying the NCD, including medical conditions such as MS, which can lead to cognitive deficits that progress along with the disease (American Psychiatric Association, 2013). Naturally, since baseline cognitive performance of a person is often not available, and estimating it can be quite challenging, the comparison of individual performance to that of a normative sample remains the most commonly used method in routine clinical practice to detect CI.

Estimates suggest that around 30-90% of PwMS experience cognitive deficits (Amato et al., 2014; Rao et al., 1991; Ruano et al., 2017). Specifically, CI affects 34.5% of individuals with CIS, 44.5% with RRMS, 79.4% with SPMS, and 91.3% with PPMS (Ruano et al., 2017). Moreover, it is associated with higher scores on the Expanded Disability Status Scale (EDSS), a scale measuring patient's disability, as well as older age (Ruano et al., 2017). Furthermore, CI has been seen to impact the quality of life of PwMS, affecting their personal, social and professional spheres (Amato et al., 2008; Mitchell et al., 2005; Ozakbas et al., 2004). Indeed, PwMS with CI report lower likelihood of employment, more reliance on personal assistance, less

participation in social activities, more challenges with parenting, and greater difficulties in certain instrumental tasks, such as driving (Rao et al., 1991; Schultheis et al., 2001, Schultheis et al., 2002; Shevil & Finlayson, 2006). Given its profound implications on the life of those affected, it becomes a critical symptom in MS, warranting thorough investigation.

1.2.1 MS specific cognitive deficits

Researchers have found that the most affected cognitive domains in MS are verbal and visuospatial learning and memory, attention, information processing, and executive functions (Macías Islas & Ciampi, 2019).

1.2.1.1 Learning and memory

Learning entails the acquiring of new information, while memory involves recalling this information at a later date. Importantly, for a piece of information to be remembered, it must undergo encoding, storage, and retrieval. There is also a difference between recall, which involves retrieval of information that has been encoded and stored in the past, and recognition, which entails recognising that a stimulus has been encountered before (Zucchella et al., 2018). Specific to MS, three hypotheses have been suggested to potentially account for memory and learning impairments (Gich et al., 2024).

First, memory deficits may be related to impaired retrieval of learned information, as evidenced by the fact that PwMS struggle in free recall but not in recognition tasks (Coolidge et al., 1996). On the other hand, it has also been witnessed that PwMS have deficits in encoding, impacting the learning of new material (Deluca et al., 1994; Demaree et al., 2001). Lastly, deficits in memory may be better explained by disruptions in other cognitive domains, namely processing speed and/or working memory, since differences in learning abilities in PwMS are correlated to both of these cognitive functions (Chiaravalloti et al., 2013).

Recent evidence also suggests that a decline in memory in MS may advance and shift as the disease progresses. In fact, patients with RIS and CIS had comparable performance to that of healthy controls in both encoding and retrieval of information, while patients with RRMS exhibited issues with delayed free recall, but they had similar performance to healthy controls in recognition tasks. On the other hand, patients with progressive forms of the disease showed worse performance both at

recalling information during the learning phases, and in immediate and delayed free recall. Moreover, in the recognition test, they also identified more words that were not actually presented in the initial learning list (Gich et al., 2024). Thus, it would appear that, at later stages of the disease, information is not even acquired and/or consolidated and/or stored properly.

1.2.1.2 Attention

Attention encompasses different processes such as directing focus to a specific stimuli while filtering out unnecessary information (selective attention), maintaining the focus for an extended time period (sustained attention), and splitting the focus to keep concentration on multiple information (divided attention) (Chiaravalloti et al., 2013; Sachdev et al., 2014; Zucchella et al., 2018). PwMS with low disability already have some mild deficits on phasic alertness and divided attention. In addition, these deficits are even more prominent in PwMS with higher disability status (Tinnefeld et al., 2005). Furthermore, PwMS were seen to perform poorly in a Posner cueing paradigm, a task which investigates speed and accuracy in orienting attention to a cued location in order to detect target stimuli (Gonzalez-Rosa et al., 2006).

1.2.1.3 Information processing

Closely tied to attention, is the domain of information processing, which can be divided into two major subcomponents: working memory and processing speed. Working memory permits the temporary retention and manipulation of information during cognitive tasks, and it is better understood as a complex multidimensional construct that falls within the neurocognitive domain of executive functions (Sachdev et al., 2014). Baddeley and colleagues proposed a foundational working memory model to define different components of this complex construct: the phonological loop, concerned with verbal and auditory stimuli; the visuospatial sketchpad, concerned with visual stimuli; the central executive, providing an attentionally-limited control system over the two previously described components; and the episodic buffer, responsible for limited-capacity storage of information (Baddeley, 2003). PwMS have deficits that concern both the phonological loop and the visuospatial sketchpad, but also the central executive (D'Esposito et al., 1996; Litvan et al., 1988; Rao et al., 1993).

Processing speed, instead, is the velocity at which information is processed, and, it is consistently impaired in PwMS, likely being the first cognitive deficit to emerge

(Van Schependom et al., 2015). Naturally, researchers have attempted to disentangle whether deficits in information processing in MS are more related to disruptions in working memory or processing speed. In this regard, evidence indicates that disturbances in processing speed are more frequent among PwMS than working memory deficits. Specifically, SPMS patients are predominantly affected by processing speed deficits compared to RRMS patients, and working memory deficits are present only in SPMS (Deluca et al., 2004). This suggests that processing speed is the primary information processing deficit in PwMS. Possibly, as the disease progresses, the decline in processing speed may start to also impact working memory abilities.

1.2.1.4 Executive functions

Lastly, executive functions are higher-level cognitive processes that enable a widespread assortment of actions (Gilbert & Burgess, 2008), such as planning, reasoning, problem solving, inhibiting of automatic responses, and switching between tasks. (Zucchella et al., 2018). Studies report that PwMS have deficits in response inhibition, abstract reasoning, phonemic fluency, semantic fluency, planning, and problem solving (Borkowska et al., 2021; Chiaravalloti & DeLuca, 2008; Pennington et al., 2023). Deficits in executive functions may also be influenced by other cognitive domains, namely information processing speed (Leavitt et al., 2014), but more research is needed on this topic. Furthermore, PwMS are also impaired in social cognition, particularly in skills of theory of mind and emotion recognition (Cotter et al., 2016; Dulau et al., 2017). However, once more, it is unclear whether deficits in these domains may be influenced by disruptions in other executive functions (Pennington et al., 2023).

As mental processes can be related to and mediated by each other, patients' cognitive profiles may be complex, with patterns of impairment possibly being entangled, and necessitating comprehensive assessments and targeted interventions.

1.2.2 Neuropsychological assessment in MS

Neuropsychological assessment is fundamental to provide quantitative and qualitative data regarding the cognitive status of a person, thus, it becomes a potent tool in both aiding the diagnosis of cognitive deficits and informing towards the best course of treatment. Different tools have been developed to assess CI in MS. Rao's

Brief Repeatable Battery of Neuropsychological tests (BRBNT), for instance, is a test battery assessing verbal memory and learning (selective reminding test), visuospatial learning and memory (10/36 spatial recall test), sustained attention, concentration, and processing speed (Symbol Digit Modalities Test -SDMT-; Paced Auditory Serial Addition Test -PASAT-) and semantic verbal fluency (word list generation test) (Boringa et al., 2001). Similarly, another available battery is the Minimal Assessment of Cognitive Function In Multiple Sclerosis (MACFIMS), which allows to assess language functioning (controlled oral word association test), spatial processing (judgment of line orientation test), verbal learning and memory (California Verbal Learning Test Second Edition -CVLT-II), visuospatial learning and memory (Brief Visuospatial Memory Test—Revised -BVMT-R), sustained attention, concentration, processing speed (SDMT and PASAT), and executive functions (Delis-Kaplan executive function system sorting test) (Benedict et al., 2006).

Since the MACFIMS takes around 90 minutes to administer, while the BRBNT takes 25-30 minutes, researchers have highlighted the need for a faster screening tool. As a result, Benedict and colleagues, developed the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS), a battery which can be used to screen patients efficiently, as it includes three subtests measuring the most affected cognitive functions in MS: the SDMT, the CVLT-II and the BVMT-R (Benedict et al., 2012). The BICAMS has good test-retest reliability and discriminant validity across a number of validation studies from different countries (Darwish et al., 2022; O'Connell et al., 2015; Polychroniadou et al., 2016; Walker et al., 2016), and, it is an excellent international cognitive battery which can provide a common language among researchers and clinicians.

Although the results from the neuropsychological assessment, alongside the latest evidence, should inform treatment choices, the modality in which testing can best guide treatment for CI in MS remains unclear and still lacks specific guidelines.

1.2.3 Treatment for CI in MS: evidence from pharmacological trials

Management of cognitive deficits in MS can include a wide range of interventions, such as, pharmacotherapy, cognitive rehabilitation, lifestyle modifications, psychological support, or a combination of different methods. Evidence from pharmacological studies is limited.

A recent systematic review included eighty-seven articles, published in the last three decades, which investigated the use of pharmacotherapy on cognitive outcomes, classifying evidence according to the 2017 American Academy of Neurology available guidelines for clinical trials. Looking into Class II and III Randomised Controlled Trials (RCTs), there was lack of evidence regarding the efficacy of DMTs on cognition. Interferon Beta 1-a yielded some positive results, there was contrasting evidence regarding Fingolimod, while some improvements were registered also for Daclizumab Beta. However, the magnitude of positive effects was minimal to insignificant, and no Class I studies were found looking into DMTs for cognition. Non-RCTs and observational studies also found some positive results, mostly in relation to Natalizumab, but with methodological issues which greatly hinder the findings. Regarding symptomatic pharmacological therapies, there was one Class I RCT favouring Dalfampridine, a drug used to improve walking in MS, yielding a modest effect size, contrasting evidence related to stimulants normally used in MS to treat fatigue, and solid evidence regarding the fact that drugs normally used to enhance cognition in dementia- and Gingko biloba- do not work in MS (Chen et al., 2020). Thus, overall, there does not seem to be enough evidence to establish a course of pharmacological treatment for CI in MS, as high quality research on the topic is still scarce.

1.2.4 Treatment for CI in MS: evidence from non-pharmacological trials

Behaviourally-based cognitive rehabilitation still remains the most widely used technique to address CI in clinical practice. It can aim at directly addressing present cognitive deficits with the goal of restoration of a lost function, or it can focus on providing patients with specific strategies and skills to manage cognitive dysfunction. However, to this day, there is no consensus on the optimal remediation path for CI in MS. While researchers have focused on a variety of interventions, including non-computerised rehabilitation, computerised tools, use of video games and virtual reality (Abdulhadi et al., 2020), recommendation guidelines have yet to be established.

1.2.4.1 Non-computerised interventions

Research on non-computerised interventions generally shows contrasting results (Aguirre et al., 2019; Hanssen et al., 2016; Lamargue et al., 2020; Mani et al., 2018; Martin et al., 2014; Rilo et al., 2018). For example, a recent RCT investigated cognitive rehabilitation by means of the "*Program Cognitif pour Sclérose En Plaques",*

delivered in group sessions, aimed at providing facilitation and reorganisation strategies, and found that, compared to a control condition, this kind of rehabilitation led to improvements in learning and working memory, but not in other cognitive domains measured (Brissart et al., 2020). Another RCT, part of the Rehabilitation of Memory in Neurological Disabilities trial, comparing group-based interventions in which one group of patients received compensatory rehabilitation and the other received restitutive rehabilitation, found that neither group showed improvements in memory (Martin et al., 2014). Another RCT looking at individual rehabilitation sessions using the protocol "REACTIV", aimed at training information processing speed, attention, executive functions, and working memory, found improvements in cued recall. Furthermore, this trial showed that PwMS also improved on some measures of phasic alertness, attention, visuospatial constructional ability and visual memory, compared to a control group. Nonetheless, other cognitive measures administered did not yield significant results (Lamargue et al., 2020). Rillo and colleagues found that training with "REHACOP", a programme integrating restoration, compensation and optimisation techniques, led to improvements in processing speed, working memory, verbal memory and executive functions. A group-based approach also showed that after rehabilitation, PwMS improved in the memory domain. Some improvements in executive functions were also registered, but not in attention (Mani et al., 2018).

1.2.4.2 Computerised interventions

Studies on computerised-cognitive training also yield contrasting results (Arsoy et al., 2018; De Luca et al., 2021; Pusswald et al., 2014). A RCT found that PwMS improved on simple and cued alertness and divided attention after computerised training with "Fresh Minder 2" software focused on dived attention, paired with counselling sessions (Pusswald et al., 2014). Another RCT investigating multimodal computerised training of attention, memory, reasoning, visual and verbal skills with "NOROSOFT Mental Exercise Program", found improvement after training relative to the control group on measures of processing speed, sustained attention, verbal fluency, categorical reasoning and executive functions, however, not on verbal or visuospatial memory and learning (Arsoy et al., 2018). De Luca and colleagues, instead, compared traditional "paper and pencil" cognitive remediation to the computerised cognitive rehabilitation software "ERICA" and, they found that the latter was superior in improving global cognition, verbal memory and learning, sustained

attention and processing speed, but not other cognitive domains measured (De Luca et al., 2021).

1.2.4.3 Systematic reviews

Systematic reviews on the topic similarly report mixed evidence. A relatively recent Cochrane review on memory rehabilitation included 44 RCTs or quasi-RCTs and found that cognitive rehabilitation was able to improve memory functioning, quality of life and depressive symptoms, however, no positive effects were found on anxiety symptoms and activities of daily living (Taylor et al., 2021). Another Cochrane review on cognitive rehabilitation included 22 studies on the topic and concluded that there was low-level evidence for positive results after cognitive remediation in MS (Rosti-Otajärvi & Hämäläinen, 2014). In contrast, two systematic reviews came across high quality evidence favouring a training protocol called "modified-story memory technique" (Brochet, 2022; Goverover et al., 2018). Goverover and colleagues also found good evidence in relation to an attention training programme and on multi-domain computerised training (Goverover et al., 2018), while another systematic review, which included 33 studies, concluded that even though most of these research papers showed some positive improvements in cognitive skills, the evidence presented in the literature remains inconclusive (Mitolo et al., 2015). Importantly, all reviews emphasised the presence of methodological issues within the studies investigated, which significantly limit the reliability of the findings.

1.2.4.4 Addressing heterogeneity in cognitive rehabilitation studies

The heterogeneity of techniques employed for cognitive remediation across various studies has often been reported as a possible reason for the contrasting findings. To address this issue, one could examine studies that consistently utilised the same tool for rehabilitation. For example, within the literature, a number of research papers focused on the use of the commercially available software RehaCom for cognitive rehabilitation (see Table 1).

Table 1. **Efficacy of the RehaCom software for cognitive deficits in MS**. The table summarises findings from 11 studies evaluating the efficacy of cognitive rehabilitation using the RehaCom software in People with Multiple Sclerosis (PwMS). Each row presents details from a different study, including information regarding participants and experimental groups, neuropsychological (NPS) outcome measures and Patient Reported Outcome Measures (PROMs), main results, and key cognitive improvements. Studies are ordered chronologically by publication year for ease of reference.

Study	Experimental Groups	NPS & PROMs	Main results	Cognitive gains
(Solari et al., 2004)	**IG**: 40 PwMS (2-weekly 45-minute sessions for 8 weeks) **CG**: 37 PwMS (visuo-motor training)	**NPS:** *BRBNT* (PASAT, SDMT, SRT, SPART, WLG) **PROMs:** CMDI; MSQoL	IG showed significant improvement on WLG at both 8 and 16 weeks after training	Phonemic retrieval
(Tesar et al., 2005)	**IG**: 10 PwMS (12 1-hour sessions for 4 weeks + compensatory strategies+ out-patient rehabilitation) **CG**: 9 PwMS (out-patient rehabilitation)	**NPS:** MWT-B; VLT; NVLT; DAUF; CKV; HAWIE-R (mosaic test) **PROMs:** BDI-II; MFIS	IG showed significant improvement on CKV and HAWIE-R	Executive functions; Spatial-construction abilities
(Mattioli et al., 2010)	**IG**: 10 PwMS (3-weekly 1-hour sessions for 12 weeks) **CG**: 10 PwMS (no treatment)	**NPS:** *BRBNT* (SRT, SDMT, PASAT); WCST; COWAT; TEA; **PROMs:** MADRS; MSQoL	IG showed significant improvement on PASAT, WCST and MADRS	Attention, processing speed; Executive functions; Depressive symptoms
(Filippi et al., 2012)	**IG**:10 PwMS (3-weekly 1-hour sessions for 12 weeks) **CG**: 10 PwMS (no treatment)	**NPS:** PASAT; WCST; COWAT	IG showed significant improvement on PASAT, WCST and COWAT	Attention, processing speed; Executive functions
(Cerasa et al., 2013)	**IG**: 12 PwMS (2-weekly 1-hour sessions for 6 weeks) **CG**: 11 PwMS (sham)	**NPS:** *BRBNT (*SRT, SPART, SDMT, PASAT, WLG); ST; TMT A & B; MMSE **PROMs:** BDI-II; STAI Y1; STAI Y2	IG showed significant improvement on ST	Executive functions

(Mattioli et al., 2012)	**IG**: 13 PwMS (3-weekly 1-hour sessions for 12 weeks) **CG**:11 PwMS (no treatment)	**NPS:** PASAT; WCST; COWAT/P; COWAT/S; TEA; SRT; SPART **PROMs:** MADRS; MSQoL	IG showed significant improvement on PASAT, WCST, COWAT/P & MADRS; At 9 months IG showed significant improvement on PASAT, WCST, COWAT/S, MADRS, MSQoL	Attention; Executive functions; Depressive symptoms; Quality of life
(Bonavita et al., 2015)	**IG**: 18 PwMS (2-weekly 50-minutes sessions for 8 weeks) **CG**: 14 PwMS (sham)	**NPS:** *BRBNT* (SRT, SPART, SDMT, PASAT, WLG); ST	IG showed significant improvement on SDMT, PASAT, SRT-delayed, SPART-delayed	Attention, processing speed; Verbal and visuospatial memory (delayed recall)
(Mattioli et al., 2016)	**IG**:22 PwMS patients (2-weekly 1-hour sessions for 15 weeks) **CG**: 19 PwMS (psychological intervention)	**NPS:** *BRBNT* (SRT, SPART, PASAT, SDMT); COWAT; ST **PROMs:** MFIS; MADRS; MSQoL	IG had significantly less cognitively impaired patients at a 1-year follow up appointment (20% vs. 94% respectively) and at a 2-years follow up appointment (33% vs. 76%) compared to CG	
(Messinis et al., 2017)	**IG**:32 PwMS (2-weekly 1-hour sessions for 10 weeks) **CG**: 26 PwMS (standard clinical care)	**NPS:** SRT; BVMT-R; Phonemic & semantic fluency; SDMT; TMT A & B; ST **PROMs:** BDI-Fast screen, FSS	IG showed significant improvement on all measures (except on phonemic fluency); Improvements lasted at a 6-month follow up (except for SDMT and semantic fluency). NOTE: no direct comparison to the CG	Verbal, visuospatial memory and learning; Executive functions; Attention, processing speed
(Arian Darestani et al., 2020)	**IG**: 30 PwMS (two-weekly 1-hour sessions for 5 weeks) **CG**: 30 PwMS (no treatment)	**NPS:** COWAT; CVLT-II	IG showed significant improvement on COWAT and CVLT-II, which lasted at	Verbal fluency; Verbal learning and memory

			a follow up assessment	
(Naeeni Davarani et al., 2020)	**IG**:30 PwMS (two-weekly 1-hour sessions for 5 weeks) **CG**: 30 PwMS (no treatment)	**NPS:** IVA-2; PASAT; SDMT; D-KEFS; JLO	IG showed significant improvement on all measures; Significant improvement remained at a 10-week follow up for JLO, D-KEFS, SDMT, PASAT	Attention, processing speed; Executive functions; Visuo-spatial skills

**Abbreviations:* BDI-II, Beck Depression Inventory-II; BDI-Fast screen, Beck Depression Inventory-Fast Screen; BRBNT, Brief Repeatable Battery of Neuropsychological Tests; BVMT-R, Brief Visuospatial Memory Test Revised; CKV, Computer-aided card-sorting procedure; CMDI, Chicago Mood Depression Inventory; CG, Control Group; COWAT, Controlled Oral Word Association Test; COWAT/P, Controlled Oral Word Association Test - Phonemic; COWAT/S, Controlled Oral Word Association Test - Semantic; CVLT-II, California Verbal Learning Test-II; DAUF, Sustained Attention Test; D-KEFS, Delis-Kaplan Executive Function System; FSS, Fatigue Severity Scale; HAWIE-R, Hamburg-Wechsler Intelligence Test Revised; IG, Intervention Group; IVA-2, Integrated Auditory Visual 2; JLO, Judgment of Line Orientation; MADRS, Montgomery–Åsberg Depression Rating Scale; MFIS, Modified Fatigue Impact Scale; MMSE, Mini-Mental State Examination; MSQoL, Multiple Sclerosis Quality of Life; MWT-B, Multiple Choice Vocabulary Test B; NVLT, Nonverbal Learning Test; PASAT, Paced Auditory Serial Addition Test; SDMT, Symbol Digit Modalities Test; SPART, Spatial Recall Test; SRT, Selective Reminding Test; ST, Stroop Test; STAI Y1, State-Trait Anxiety Inventory, Form Y1 (State Anxiety); STAI Y2, State-Trait Anxiety Inventory, Form Y2 (Trait Anxiety); TEA, Attention Test; TMT A & B, Trail Making Test, Parts A and B; VLT, Verbal Learning Test; WLG, Word List Generation; WCST, Wisconsin Card Sorting Test.

Results from these studies still highlight inconsistencies, showing both improvements in cognition after RehaCom and lack of significant changes. Indeed, while some studies report significant improvements in areas such as attention, executive functions, and memory, others show limited or no improvements in the same specific cognitive domains. Although the positive findings could be seen as promising and, perhaps, encouraging, the methodological issues within the studies continue to make it difficult to offer definitive recommendations. Better well-designed studies are needed at this stage.

1.3 Limitations to in-person cognitive rehabilitation and introduction to telerehabilitation

In addition to concerns related to the lack of gold standard treatments for CI in MS, researchers have highlighted a range of issues related to traditional cognitive remediation. Of interest, conventionally, behaviourally based cognitive rehabilitation is administered in-person by an expert neuropsychologist within appropriate healthcare settings. This usually consists of repeated one-on-one sessions, which can

last a prolonged period of time. This approach has been deemed as resource-intensive and not entirely feasible for all PwMS (Chiaravalloti et al., 2013; Filippi et al., 2012). Individuals living with the disease, indeed, reported a variety of issues related to accessing health care services (Chiu et al., 2017). Common complaints included: (1) Significant distance from health care facilities; (2) Living in rural areas; (3) Increased burden of travel due to fatigue; (4) Unreliability, insufficiency and often inadequacy (e.g. no lifting equipment) of transportation services; (5) Reliance on others for transportation when transit services are unavailable, requiring schedule adjustments based on others' availability; (6) Difficulty fitting appointments into working hours; (7) Issues with health-care facilities, such as scarcity of accessible parking, lack of ramps, heavy doors and limited space for wheelchairs to move around (Buchanan et al., 2006; Kroll et al., 2006; McDoom et al., 2014; Minden et al., 2007; Morrison et al., 2008; Scheer et al., 2003).

Telerehabilitation, defined as the delivery of rehabilitation where distance is a critical factor (Rogante et al., 2010), could help overcome some of the issues highlighted above, by providing rehabilitation services which could be implemented when patients are unable to reach a designated facility, with the advantage of providing a cost-effective solution (Peretti et al., 2017). Indeed, telerehabilitation has been seen to lead to a saving of 258 km in travel distance and a 17% reduction in lodging costs (Hatcher-Martin et al., 2020). Of relevance, telerehabilitation could become a fundamental tool in the continuous care of PwMS, aiding the management of symptoms throughout the individual's lifespan, as MS is a progressive disease which requires prolonged treatment and monitoring of outpatients.

A problem related to this is that of variable results also regarding the persistence of the effects of cognitive rehabilitation several months after the end of a therapeutic intervention. Some studies suggest that eventual benefits of cognitive training are maintained for several months after it ends (Fink et al., 2010; Mattioli et al., 2012, 2016; Parisi et al., 2014), while others highlight how cognitive improvements obtained after training interventions do not always persist (Campbell et al., 2016; Fink et al., 2010; Mattioli et al., 2016). One possibility is that maintaining cognitive improvements, following intensive cognitive rehabilitation, requires some kind of long-term ongoing intervention. The optimal frequency and duration of cognitive rehabilitation, therefore, remain unclear (Campbell et al., 2016). The possibility to resort to "maintenance" interventions, in this context, further raises doubts about

the feasibility of face-to-face cognitive rehabilitation. Providing home-based care to PwMS at this stage could become essential.

Moreover, telehealth could provide enough flexibility to allow patients to schedule rehabilitation sessions around work commitments with more ease. To this point, evidence suggests telerehabilitation helped reducing missed workdays of around 65% (Hatcher-Martin et al., 2020). In addition, PwMS seem to be favourable towards the use of telerehabilitation, with most of them being able to access the necessary technology, such as stable internet connection, computers, smartphones, etc. (Remy et al., 2020). Both patients and providers across various specialties have reported high levels of satisfaction with telehealth, indicating that home-based digital rehabilitation could be a valuable solution to overcome in-person accessibility challenges (Xiang & Bernard, 2021). In the context of cognitive remediation, users have also deemed telerehabilitation both acceptable and feasible (Cagnin et al., 2014; Lawson et al., 2022).

1.4 Telerehabilitation for CI in MS: the state of the art

Given the potential of telerehabilitation, it remains to be established whether it is a feasible tool in the context of treatment of CI in MS, and, also, whether it is efficient in achieving its purpose. Targeted research is key because telerehabilitation interventions may be fundamentally different from in-person rehabilitation. To begin with, many telerehabilitation tools allow for asynchronous training, meaning sessions can be self-administered, and they do not require the presence of a therapist. Although this allows for greater flexibility, it also raises doubts regarding the effects of limited interaction with the expert neuropsychologist, who usually guides in-person rehabilitation. A related issue is that of limited supervision from the therapist, thus reliance on patients and caregivers to maintain motivation throughout the training, ensure adherence to treatment and that instructions are thoroughly understood and followed. Furthermore, the home setting is likely to be less structured compared to that of the clinic/hospital, leading, perhaps, to more distractions, such as noises, interruptions from family members, etc. Reliance on appropriate technology without in-person supervision from the therapist may also constitute a difference compared to traditional rehabilitation, as patients with CI may struggle to use designated devices by themselves. For these reasons, it is important to discern research solely on home-based rehabilitation.

To this purpose, findings on the feasibility and efficacy of telerehabilitation for CI in PwMS were evaluated in a recent narrative review, which investigated articles published between January 2005 and September 2023. The results showed that the feasibility of digital telerehabilitation for CI in MS was generally good. While not all studies reported the feasibility of their target interventions, those that did found high adherence rates to planned treatment hours. In contrast, findings on efficacy were very much inconsistent, with only one single article reporting solely positive results (Boschetti et al., 2024). Table 2 reprinted from original published paper (Boschetti et al., 2024) shows a summary of the main findings from the research papers included in the review.

Table 2. **Efficacy of digital telerehabilitation for CI in MS**. The table (reprinted from Boschetti et al., 2024) shows the efficacy of digital training for each study. The table shows positive results on neuropsychological (NPS) measures in terms of improved performance after the training intervention compared to baseline. Improvements in performance from pre to post intervention on measures other than NPS, such as motor tests or Patient Reported Outcome Measures (PROMs) are also shown. Whether improvements were also seen in the control group is specified in brackets. Negative results on NPS measures and other measures are also reported. The table also shows eventual lasting performance improvements at follow-up assessment. Effect sizes for positive results on NPS measures are also displayed. Entries are organised from the earliest to the most recent study for easy reference.

Study	Positive results on NPS measures	Positive results on other measures	Negative results on NPS measures	Negative results on other measures	Positive results maintained at follow-up	Effect sizes for (immediate) positive results
(Hildebrandt et al., 2007)	CVLT-II (learning trials & long delay free recall); PASAT	NHPT	CVLT-II (short delay free recall, cued recall & long delay cued recall); Object alternation RTs & errors; Alertness with & without cueing	EDSS; Timed walked test; SF-12 bodily & mental scores; BDI; FSS	No follow up assessment performed	Not reported

(Vogt et al., 2009)	Corsi blocks backward (only in the distributed training group); Digit span backward; 2-back task omissions; PASAT; FST	FSMC; MFIS	Corsi blocks forward; Digit span forward; SDMT	CES-D; FAMS	No follow up assessment performed	Corsi block backward: $\eta_p^2 = 0.08$; Digit span backward: $\eta_p^2 = 0.11$; 2-back task omissions: $\eta_p^2 = 0.06$; PASAT: $\eta_p^2 = 0.10$; FST: $\eta_p^2 = 0.14$ (distributed training group). Digit span backward: $\eta_p^2 = 0.11$; 2-back task omissions: $\eta_p^2 = 0.06$; PASAT: $\eta_p^2 = 0.10$; FST: $\eta_p^2 = 0.11$ (high intensity training group)

(Shatil et al., 2010)	General memory; Visual working memory; Verbal auditory working memory (N-CPC)		Auditory (non-linguistic) working memory; Awareness divided attention Avoiding distractions; Hand – eye coordination; Inhibition Naming; Planning response time; Shifting attention Spatial perception; Time estimation; Visual perception; Visual scanning (N-CPC)	Zung depression scale; EDSS; FSS	No follow up assessment performed	General memory: η_p^2 = 0.207; Visual working memory: η_p^2 = 0.196; Verbal auditory working memory: η_p^2 = 0.191.
(Amato et al., 2014)	PASAT; SDMT (improvement also in the control group)	ESS (improvement also in the control group); MADRS (improvement also in the control group); VAS (improvement also in the control group)	Visual search; TMT A & B; SRT; SPART; WLG	FSS	PASAT; SDMT (improvement sustained also in the control group)	Not reported
(Charvet et al., 2015)	General composite cognitive score	Ecog	WAIS-IV letter number sequence; Corsi block; PASAT; SRT; BVMT-R		No follow up assessment performed	General composite cognitive score: d = 1.11

(De Giglio et al., 2015)	Stroop test; SDMT	MSQoL-54 mental health composite, role limitations-emotional, emotional well-being, cognitive function, health distress	PASAT 3	MFIS; MSQoL-54 physical health composite, physical function, role limitations-physical, pain, energy, health perceptions, social function, sexual function, overall QoL, sexual function	No follow up assessment performed	Stoop test: F^2 = 0.210; SDMT: F^2 = 0.177
(Hancock et al., 2015)	PASAT		SDMT; Stroop test; LNS; Digit backward; Raven's APM; BVMT-R; COWAT; CPT-II; AVLT	BDI; STAI; MFIS; MSQOL-54	No follow up assessment performed	PASAT: d= 0.90
(Campbell et al., 2016)	SDMT		CVLT-II; BVMT-R	EQ-5D; FAMS; PAM-13; USE-MS; HADS; MSNQ; FSS	not significant	Not reported
(Pedullà et al., 2016)	SRT consistent long-term retrieval & delayed recall; SDMT; PASAT; WLG		SRT long term storage; SPART; WCST		PASAT; SDMT	Not reported

(Charvet et al., 2017)	General composite cognitive score		SRT; BVMT-R; PASAT; TMT; WAIS-IV letter number sequence; WAIS-IV digit span backward; DKEFS		No follow up assessment performed	General composite cognitive score: d = 0.38
(Messinis et al., 2020)	SDMT, GVLT, BVMT-R	MFIS; BDI-FS; EQ-5D			No follow up assessment performed	SDMT: g = 2.980; GVLT: g = 2.898; BVMT-R: g = 1.699
(Vilou et al., 2020)	GVLT; BVMT-R; TMT-A; Stroop test		SDMT; TMT-B		No follow up assessment performed	GVLT: d = 0.6; BVMT-R: d = 0.38; TMT-A: d = 0.15; Stroop test: d = 0.32
(Blair et al., 2021)	DKEFS colour-word interference test; WAIS-III digit span backward	HADS-D	SDMT; PASAT; CVLT-II; BVMT-R; VSVT; WAIS-III spatial span forward and backward, WAIS-III arithmetic ; WAIS-III digit span forward; WAIS-III letter-number sequence	BDI-FS; FSS, MSNQ, HADS-A; SF-36; DEX; CFQ; Brief COPE; PDQ; NPRS	HADS-D	DKEFS colour-word interference test: d = 0.27; WAIS-III digit span backward: d = 0.69

**Abbreviations:* APM, Advanced Progressive Matrices; AVLT, Auditory Verbal Learning Test BDI, Beck's Depression Inventory; BDI-FS, Beck's Depression Inventory- fast screening; BVMT-R, Brief Visuospatial Memory Test-Revised; CES-D, Centre for Epidemiologic Studies Depression Scale; CFQ, Cognitive Failures Questionnaire; COWAT, Controlled Oral Word Associations Test; CPT, Conners' Continuous Performance Test; CVLT, California Verbal Learning Test; DEX, Dysexecutive Questionnaire; DKEFS, Delis-Kaplan Executive Function System; Ecog, Everyday cognition scale; EDSS, Expanded Disability Status Scale; EQ-5D, EuroQOL five-dimension questionnaire; ESS, Environmental Status Scale; FAMS, Functional Assessment of Multiple Sclerosis; FSS, Fatigue Severity Scale; FSMC, Fatigue Scale for Motor and Cognitive Functions; FST, Face Symbol Test; GVLT, Greek Verbal Learning Test; HADS-A, Hospital Anxiety Scale; HADS-D, Hospital Depression Scale; LNS, Letter–Number Sequencing; MADRS,

Montgomery and Asberg Depression Rating Scale; MFIS, Modified Fatigue Impact Scale; MSNQ, Multiple Sclerosis Neuropsychological Questionnaire; MSQoL-54, 54-item Multiple Sclerosis Quality of Life Questionnaire; NCP-C, Neuropsychological Examination – CogniFit Personal Coach; NHPT, Nine Hole Peg Test; NPRS, Numeric Pain Rating Scale; PAM-13, Patient Activation Measure; PASAT, Paced Auditory Serial Addition Test; PDQ, Perceived Deficits Questionnaire; QoL, Quality of Life; RTs, Reaction Times; SDMT, Symbol Digit Modalities Test; SF-12, short form of the SF 36 health questionnaire; SF-36, Short Form Health Survey; SPART, 10/36 Spatial Recall Test; SRT, Selective Reminding Test; STAI, State–Trait Anxiety Inventory; TMT, Trail Making Test; USE-MS, Unidimensional Self-Efficacy scale for Multiple Sclerosis; VAS, visual analog scale; VSVT, Victoria Symptom Validity Test; WAIS, Wechsler Adult Intelligence Scale; WCST, Wisconsin Card Sorting Test; WLG, Word List Generation.

Thirteen studies were identified in the review, as they investigated digital telerehabilitation tools for the treatment of cognitive deficits in MS. Studies looking at combined telerehabilitation and in-person interventions were not included in the research paper, nor were studies looking at the combined effects of telerehabilitation and home-based neuromodulation. Results provided a mixture of both positive and negative findings across studies. Some reported improvements on certain cognitive measures, while others showed no significant effects or even negative results.

As a result, a similar picture to that of in-person cognitive remediation in MS emerges, for which inconsistencies within the literature do not allow to draw firm conclusions regarding the efficacy of telerehabilitation tools for CI in MS. Once more, a number of methodological limitations within the studies were identified as possible confounds leading to variable results. Major shortcomings included: (1) Failure to report the feasibility of an intervention and lack of details on adherence to a certain treatment protocol; (2) Lack of double blinding, adequate control groups and controlled randomisation; (3) No follow up assessments to explore the long-term effects of rehabilitation; (4) Lack of blinded assessments and failure to properly control and account for practice effects; (5) Small sample sizes and heterogeneity among patients with varying cognitive deficits; (6) Heterogeneity of interventions and variability in treatment intensity parameters; (7) Inadequate inclusion criteria (e.g. including participants based on subjective complaints of cognitive impairment rather than objectively measured cognitive deficits); (8) Outcome measures not sensitive enough to detect changes after rehabilitation (Boschetti et al., 2024). The need for further research on the topic is evident. What is even more crucial, however, is the need for more rigorous studies and better-designed protocols. As it stands, the feasibility and the efficacy of home-based rehabilitation for CI in MS have yet to be established.

2 Study aims

The current pilot study wants to investigate a telerehabilitation intervention as part of the continuity of care of a group of PwMS, who previously received cognitive rehabilitation as in-patients. The study will compare an intervention group that will continue cognitive training at home after discharge from the clinic and a control group that will discontinue the training and begin sham activities. By doing so, this study aims to address the identified gaps, while contributing to the need for more methodologically sound research. The specific objectives are the following.

2.1 Primary aim: feasibility of telerehabilitation

Investigate the feasibility of a 12-week software-based telerehabilitation intervention for cognitive deficits in PwMS, measured by participants' actual adherence to the prescribed training schedule. This is the primary goal of the study as the efficacy of the chosen intervention will rely heavily on whether it is successfully implemented.

2.2 Secondary aim 1: immediate efficacy of telerehabilitation

Investigate the efficacy of a telerehabilitation intervention for cognitive deficits in PwMS in improving performance on selected neuropsychological measures administered immediately after the end of the telerehabilitation vs. home-based control (sham) activities.

2.3 Secondary aim 2: long-term efficacy of telerehabilitation

Investigate the long-term efficacy of a telerehabilitation intervention for cognitive deficits in PwMS in improving performance on selected neuropsychological outcome measures administered 6-months after the end of the telerehabilitation vs. home-based sham activities.

2.4 Secondary aim 3: transfer effects of telerehabilitation

Investigate both immediate and long-term transfer effects of a telerehabilitation intervention for cognitive deficits in PwMS in improving performance on selected PROMs, both immediately and 6-months after the end of the telerehabilitation vs. home-based sham activities.

3 Results

3.1 Baseline characteristics

25 PwMS were included in the study, 20 females and 5 males (mean age 56.48 ± 9.12). All participants in both groups were Caucasians. Before the beginning of the telerehabilitation (vs. sham), participants were hospitalised for an average of 54.8 (± 18.30) days and underwent on average 8.32 (± 3.84) cognitive rehabilitation sessions within the clinic. 14 participants were treated with DMTs during the course of the study: 6 received Fingolimod; 4 Teriflunomide; 1 Ozanimod; 2 Siponimod; 1 Glatiramer Acetate. Participants also used additional medications to manage secondary symptoms, such as Baclofen (11), Fampridine (9), Oxybutynin (6), antiepileptic drugs (7), benzodiazepines (4), selective serotonin reuptake inhibitors (4), and cannabinoids (2). Additionally, 6 PwMS had a comorbid cardiovascular condition, either hypertension or cardiopathy, 2 had a metabolic condition (hypothyroidism or type 2 diabetes), and 1 had osteoporosis. Regarding employment status, 10 PwMS were employed during the course of the study, 12 were retired, while 3 were unemployed. Regarding education level, 6 people had a middle school diploma, 10 had a high school diploma, 1 had a post-secondary vocational diploma, 1 had a bachelor's degree, while 8 had a master's degree, a single-cycle degree, or a PhD. Key demographic, clinical and treatment-related baseline characteristics for intervention and control groups are displayed in Table 3. Importantly, no significant baseline differences were observed between the two groups on any of these variables (all $p > 0.05$).

Table 3. **Baseline characteristics of participants**. The table shows key baseline characteristics of participants in intervention and control groups. The table includes demographic, clinical, and treatment-related information. Data is presented as mean ± SD for continuous variables, and as frequencies (n) for categorical variables. The table also displays the *t* or X^2 statistic, degrees of freedom, and *p-values*. Values marked with (a) indicate the use of independent samples t-test for continuous variables, while values marked with (b) indicate the use of a chi-squared test for categorical variables.

	Intervention Group (15)	**Control Group (10)**	**Statistic**	***P-value***
Demographics				
Age (years)	56.53 ± 10.06	56.4 ± 8.01	$t(23) = -0.035$	*0.972* (a)
Gender:			$X^2(1) = 0$	*1* (b)
Female	12	8		

Male	3	2		
Education (years)	14.6 ± 3.56	14 ± 5. 35	*t*(23)= -0.337	*0.738* (a)
Clinical Characteristics				
CRIq total score	110.9 ± 14.87	106 ±21.75	*t*(23)= -0.666	*0.511* (a)
Disease duration (years)	21.4 ± 13.36	21.5 ± 9.27	*t*(23)= 0.020	*0.983* (a)
EDSS	6.06 ± 0.88	6.35 ± 0.62	*t*(23)= 0.875	*0.39* (a)
Diagnosis:			$X^2(1)$= 0.074	*0.785* (b)
SPMS	10	8		
PPMS	5	2		
Hospitalisation (days)	54.87 ± 16.97	54.7 ± 21.10	*t*(23)= -0.021	*0.982* (a)
In-person cognitive rehabilitation sessions	8.06 ± 4.04	8.70 ± 3.71	*t*(23)= 0.395	*0.695* (a)
Treatment-related				
DMTs	8	6	$X^2(1)$= 0	*1* (b)

**Abbreviations*: CRIq, Cognitive Reserve Index questionnaire; DMTs, Disease Modifying Therapies; EDSS, Expanded Disability Status Scale; SD, Standard Deviation.

Upon participant recruitment, the neuropsychological evaluation conducted in-clinic (c-T0) revealed 14 participants had a score 1.282 Standard Deviation (SD) below the normative range on the SDMT, 5 on the CVLT-II and 12 on the BVMT-R. Similarly, 2 PwMS had an equivalent score of 0 at the MoCA, 3 at the Stroop test word-reading (item component), 1 at the Stroop test word-reading (time component), 10 at the Stroop test colour-naming (item component), 1 at the Stroop test colour-naming (time component), 10 at the Stroop test colour-word interference (item component) and 5 at the Stroop test colour-word interference (time component). *Figure 1* displays the percentage of impairment across intervention and control groups.

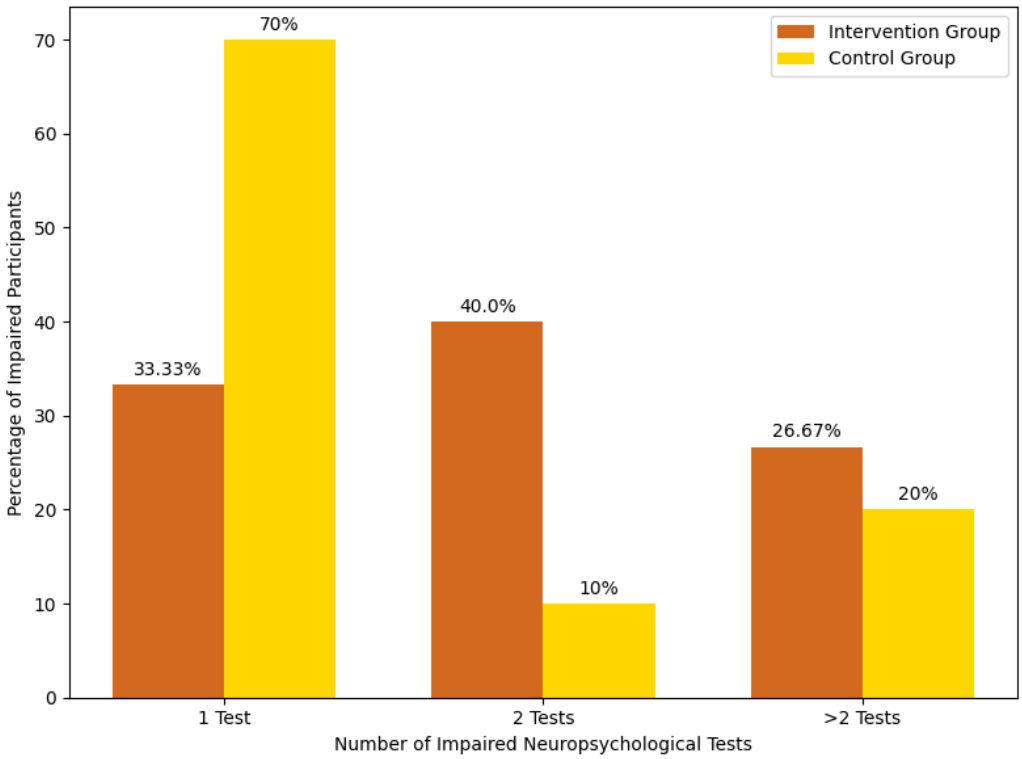


Figure 1. **Baseline cognitive impairment on neuropsychological tests.** The bar graph shows percentage of participants with impairment on the neuropsychological tests administered at c-T0 for intervention and control group. The x-axis displays number of impaired tests (1, 2, or >2), while the y-axis the percentage of impaired participants.

Most importantly, participants did not significantly differ at any of the neuropsychological tests or PROMs administered during the re-baseline remote assessment conducted before the beginning of the telerehabilitation (r-T0), as summarised in Table 4.

Table 4. **Group comparisons on neuropsychological tests and PROMs at re-baseline assessment**. The table reports the comparison between intervention and control groups across neuropsychological (NPS) tests and Patient Reported Outcome Measures (PROMs) at r-T0 re-baseline assessment. Each row displays the *t* statistic, degrees of freedom, and False Discovery Rate (FDR)- adjusted *p-values*. Welch's t-test was computed for Stroop Test Colour-Word Interference (Time component) and Multiple Sclerosis Quality of Life-29 (MSQOL-29) Mental Composite Score, while all other analyses were independent samples t-test.

NPS tests	***t statistic***	$P_{adjusted}$
MoCA	$t(23)= 0.790$	*0.834*
BICAMS		
SDMT	$t(23)= 0.683$	*0.834*
CVLT-II	$t(23)= 0.541$	*0.848*
BVMT-R	$t(23)= 1.160$	*0.834*

Stroop Test		
Word-reading (item)	*t*(22)= 1.758	*0.834*
Word-reading (time)	*t*(22)= -1.174	*0.834*
Colour-naming (item)	*t*(21)= 0.438	*0.851*
Colour-naming (time)	*t*(21)= -0.810	*0.834*
Colour-word interference (item)	*t*(21)= -0341	*0.851*
Colour-word interference (time)	*t*(11.44)= 1.086	*0.834*
PROMs		
MFIS		
MFIS-21 total	*t*(22)= -0.061	*0.966*
MFIS-21 (physical)	*t*(22)= 0.301	*0.851*
MFIS-21 (cognitive)	*t*(22)= -0.610	*0.842*
MFIS-21 (psycho-social)	*t*(22)= 0.721	*0.834*
FSS	*t*(23)= 0.042	*0.966*
BDI-II	*t*(23)= -0.936	*0.834*
MSQOL-29		
MSQOL-29 total	*t*(22)= -1.024	*0.834*
MSQOL-29 (physical composite)	*t*(22)= -1.341	*0.834*
MSQOL-29 (mental composite)	*t*(12.45)= -0.367	*0.851*
PDDS	*t*(22)= 0.931	*0.834*

**Abbreviations*: BDI-II, Beck Depression Inventory-II; BICAMS, Brief International Cognitive Assessment for Multiple Sclerosis; BVMT-R, Brief Visuospatial Memory Test-Revised; CVLT-II, California Verbal Learning Test-II; FSS, Fatigue Severity Scale; MFIS-21, Modified Fatigue Impact Scale (21 items); MoCA, Montreal Cognitive Assessment; MSQOL-29, Multiple Sclerosis Quality of Life-29; PDDS, Patient Determined Disease Steps; PROMs, Patient-Reported Outcome Measures; SDMT, Symbol Digit Modalities Test.

3.2 Feasibility

80% of participants in the intervention group completed at least half (13.5 hours) of the target training hours, while 66.7% completed at least two-thirds (18 hours). In the control group, adherence was even higher, with all participants (100%) completing at least half of the planned training hours, and 80% completing at least two-thirds. Table 5 shows detailed reports of adherence in both intervention and control groups.

An independent samples t-test showed no statistically significant difference in the actual hours of completed training between intervention and control group, *t*(23)= -1.758, *p= 0.092*. As job status may influence training compliance, a Welch's t-test

also showed that there was no statistically significant difference in training hours between PwMS who worked and those who did not, $t(12.76)= 0.894$, $p= 0.387$.

Table 5. **Feasibility of telerehabilitation vs. sham activities.** The table presents the compliance data for the intervention and control groups over the course of the study. The mean (± SD) total hours of training and the mean (± SD) hours of completed training during each of the three months (with corresponding percentages), are reported for each group. Additionally, percentages of participants who completed varying intervals of training are displayed.

	Intervention Group (n= 15)	**Control Group (n= 10)**
Hours of completed training		
Overall	18 (± 5.11)	22 (± 5)
	68%	81%
1st month	6 (± 1.50)	8 (± 2.17)
	66,67%	88.89%
2nd month	6 (± 2.15)	8 (± 2.17)
	66,67%	88.89%
3rd month	5 (± 2.55)	6 (± 3.19)
	55.66%	66,67%
% (n) of PwMS who completed X hours of training		
0-9 hours	6.66% (n= 1)	(n= 0)
10-18 hours	26.66% (n= 4)	40% (n= 4)
19-27 hours	66.66% (n= 10)	60% (n= 6)

*_Abbreviations_: SD, Standard Deviation

3.3 Usability of telerehabilitation: SUS scores

SUS scores were mostly clustered in the higher usability range (above 75), indicating generally favourable user satisfaction (see *Figure 2*).

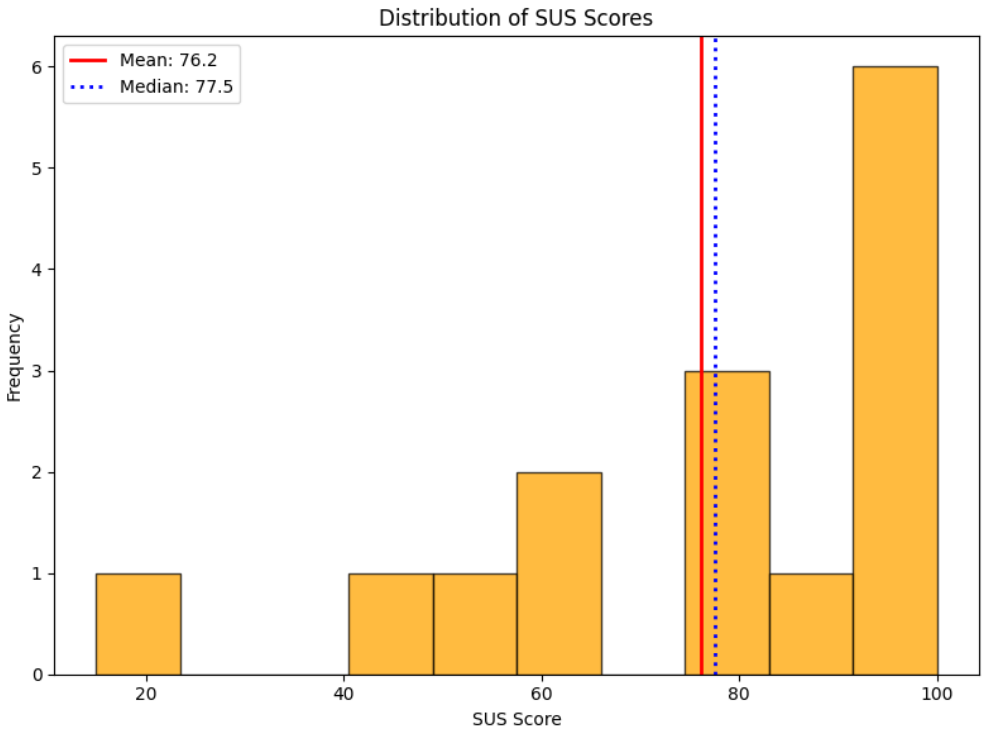


Figure 2. **Distribution of SUS scores.** The distribution graph shows the distribution of the System Usability Scale (SUS) scores for the 15 participants in the intervention group. The histogram displays the frequency of scores, the mean score (red solid line) and median score (blue dotted line).

3.4 Efficacy: neuropsychological outcome measures

Table 6 reports the mean test scores of participants in the intervention and control groups at the different assessments throughout the course of study.

Table 6. **Mean scores (± SD) at the neuropsychological tests.** The table shows the neuropsychological (NPS) test scores of participants in the Intervention Group (IG) and Control Group (CG) across three time points: re-baseline (r-T0), immediately post-intervention (r-T1), and 6-months follow-up (r-T2). The results are reported as mean (± SD) for each test.

	r-T0		**r-T1**		**r-T2**	
NPS Test	**IG**	**CG**	**IG**	**CG**	**IG**	**CG**
MoCA	25.40 ±1.88	26.20 ±3.19	25.20 ±1.97	26.40 ±2.50	26.73 ± 2.15	26.88 ±2.59
BICAMS						
SDMT	29.73 ±6.80	32.50 ±13.39	31.27 ±8.69	33.90 ±10.29	28.73 ±8.44	39.63 ±15.01

CVLT-II	53.13 ±9.70	55.70 ±14.10	53.13 ±12.39	57.30 ±11.34	58.82 ±1.78	61.38 ±11.53
BVMT-R	19.73 ±6.45	23.00 ±8.30	18.07 ±6.26	21.90 ±9.16	22.45 ±7.22	23.88 ±8.22
Stroop Test						
Word-Reading Item	48.07 ±10.40	56.80 ±13.97	49.85 ±9.86	57.90 ±11.52	47.00 ±16.03	54.88 ±12.38
Word-Reading Time	63.57 ±12.35	56.97 ±15.21	61.54 ±13.23	53.00 ±9.61	71.89 ±30.96	55.88 ±9.67
Colour-Naming Item	38.23 ±7.24	39.70 ±8.83	37.69 ±8.47	40.50 ±8.87	38.78 ±7.97	34.88 ±8.84
Colour-Naming Time	86.31 ±15.21	80.80 ±17.33	84.62 ±18.13	81.50 ±17.18	85.44 ±15.84	92.25 ±22.56
Colour-Word Interference Item	20.69 ±5.12	19.70 ±8.73	22.31 ±6.37	18.60 ± 0.55	20.56 ±7.65	18.13 ±5.08
Colour-Word Interference Time	157.62 ±40.00	192.50 ±95.30	159.23 ±54.31	176.10 ±54.69	179.56 ±67.31	190.75 ±46.47

*_Abbreviations_: BICAMS, Brief International Cognitive Assessment for Multiple Sclerosis; BVMT-R, Brief Visuospatial Memory Test-Revised; CVLT-II, California Verbal Learning Test-I; MoCA, Montreal Cognitive Assessment; SDMT, Symbol Digit Modalities Test.

A LMM analysis revealed no significant main effect of "Group" for any of the neuropsychological measures under investigation (all $p > 0.05$). Similarly, no main effect of "Time" r-T1 was found for any neuropsychological measure, indicating no changes in performance were registered from before to immediately after telerehabilitation or sham activities (all $p > 0.05$). No main effect of "Time" r-T2 was found for the MoCA, the CVLT-II, the BVMT-R and the Stroop test, suggesting no changes in performance were registered from before to 6 months after cognitive training or sham activities on these tests (all $p > 0.05$). On the other hand, a main effect of "Time" r-T2 was observed for the SDMT (b= 5.942, SE= 2.021, t=2.940, $p_{adjusted}$= 0.04, 95% CI= [0.18, 0.97], $b_{standardised}$= 0.57), showing score improvements at the 6-months follow-up assessment compared to baseline. Interaction term "Group" x "Time" r-T1 was not significant for any of the neuropsychological measures (all $p > 0.05$), while interaction term "Group" x "Time" r-T2 was not significant for MoCA, CVLT-II, BVMT-R and Stroop test (all $p > 0.05$),

while a significant "Group" x "Time" r-T2 interaction was observed for the SDMT (b= -6.697, SE=2.646, t= -2.532**,** $p_{adjusted}$= *0.04*, 95% CI= [-1.16, -0.14], $b_{standardised}$= -0.65). This suggests that the control group showed greater improvements on SDMT scores at the 6-months follow-up, respective to re-baseline, compared to the intervention group (see *Figure 3*). Full results of the LMM are available in Appendix 1.

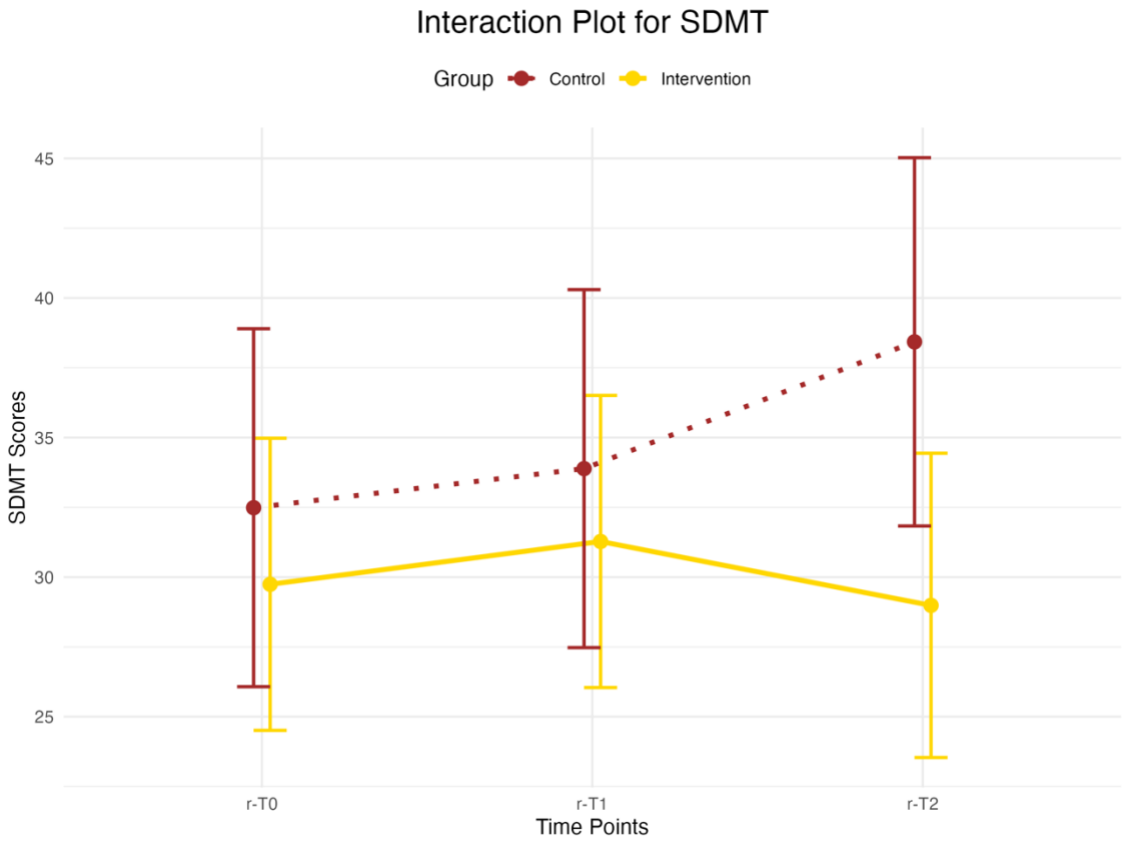


Figure 3. **SDMT interaction plot.** The interaction plot shows the SDMT scores for control and intervention groups at three time points: before telerehabilitation (r-T0), immediately after (r-T1) and at the 6-months follow-up (r-T2). The plot includes error bars displaying 95% Confidence Intervals (CI).

Tables 7-8 summarise key findings of interest for the current study, namely the interaction terms "Group" x "Time" r-T1, to examine how intervention vs. control groups performed after the training compared to before the training or sham, and the interaction between "Group" x "Time" r-T2, to examine how intervention vs. control groups performed 6 months after compared to before the training or sham. *Figures 4* and *5*, instead, display the interaction plots for the other two BICAMS subtests, where null results were observed.

Table 7. **"Group" x "Time" r-T1 interaction.** The table shows the "Group" x "Time" r-T1 interaction results from the LMM for each neuropsychological (NPS) test. The table displays beta coefficients (b), Standard Errors (SE), *t-values*, False Discovery Rate (FDR)-adjusted *p-values*, 95% Confidence Intervals (CIs), and standardised beta coefficients.

NPS test	***b***	**SE**	***t***	$p_{adjusted}$	**95% CIs**	$b_{standardised}$
MoCA	-0.400	0.997	-0.401	*0.789*	[-1.02, 0.68]	-0.17
BICAMS						
SDMT	0.133	2.400	0.056	*0.956*	[-0.45, 0.48]	0.01
CVLT-II	-1.600	4.063	-0.394	*0.788*	[-0.83, 0.56]	-0.14
BVMT-R	-0.567	2.716	-0.209	*0.835*	[-0.80, 0.65]	-0.08
Stroop Test						
Word-Reading Item	0.644	3.680	0.175	*0.862*	[-0.54, 0.64]	0.05
Word-Reading Time	1.939	8.004	0.242	*0.810*	[-0.85, 1.08]	0.12
Colour-Naming Item	0.800	1.506	0.531	*0.730*	[-0.27, 0.47]	0.10
Colour-Naming Time	-2.392	4.226	-0.566	*0.766*	[-0.63, 0.35]	-0.14
Colour-Word Interference Item	2.715	1.538	1.766	*0.229*	[-0.06, 0.87]	0.41
Colour-Word	18.015	17.562	1.026	*0.416*	[-0.28, 0.88]	0.30

Interference Time						

**Abbreviations*: BICAMS, Brief International Cognitive Assessment for Multiple Sclerosis; BVMT-R, Brief Visuospatial Memory Test-Revised; CVLT-II, California Verbal Learning Test-I; MoCA, Montreal Cognitive Assessment; SDMT, Symbol Digit Modalities Test.

Table 8. **"Group" x "Time" r-T2 interaction.** The table shows the "Group" x "Time" r-T2 interaction results from the LMM for each neuropsychological (NPS) test. The table displays beta coefficients (b), Standard Errors (SE), *t-values*, False Discovery Rate (FDR)-adjusted *p-values*, 95% Confidence Intervals (CIs), and standardised beta coefficients.

NPS test	***b***	**SE**	***t***	$p_{adjusted}$	**95% CIs**	$b_{standardised}$
MoCA	0.749	1.087	0.689	*0.659*	[-0.61, 1.25]	0.32
BICAMS						
SDMT	-6.697	2.646	-2.532	***0.047****	[-1.16, -0.14]	-0.65
CVLT-II	1.206	4.462	0.270	*0.788*	[-0.66, 0.87]	0.10
BVMT-R	2.632	2.980	0.883	*0.768*	[-0.45, 1.15]	0.35
Stroop Test						
Word-Reading Item	-3.566	4.098	-0.870	*0.779*	[-0.94, 0.37]	-0.29
Word-Reading Time	12.470	8.813	1.415	*0.660*	[-0.31, 1.81]	0.75
Colour-Naming Item	2.281	2.003	1.021	*0.730*	[-0.27, 0.83]	0.28
Colour-Naming Time	-5.227	4.714	-1.109	*0.733*	[-0.85, 0.25]	-0.30
Colour-Word	-0.992	1.715	-0.579	*0.755*	[-0.66, 0.37]	-0.15

Interference Item						
Colour-Word Interference Time	36.068	19.554	1.845	*0.312*	[-0.05, 1.24]	0.60

**Abbreviations*: BICAMS, Brief International Cognitive Assessment for Multiple Sclerosis; BVMT-R, Brief Visuospatial Memory Test-Revised; CVLT-II, California Verbal Learning Test-I; MoCA, Montreal Cognitive Assessment; SDMT, Symbol Digit Modalities Test.

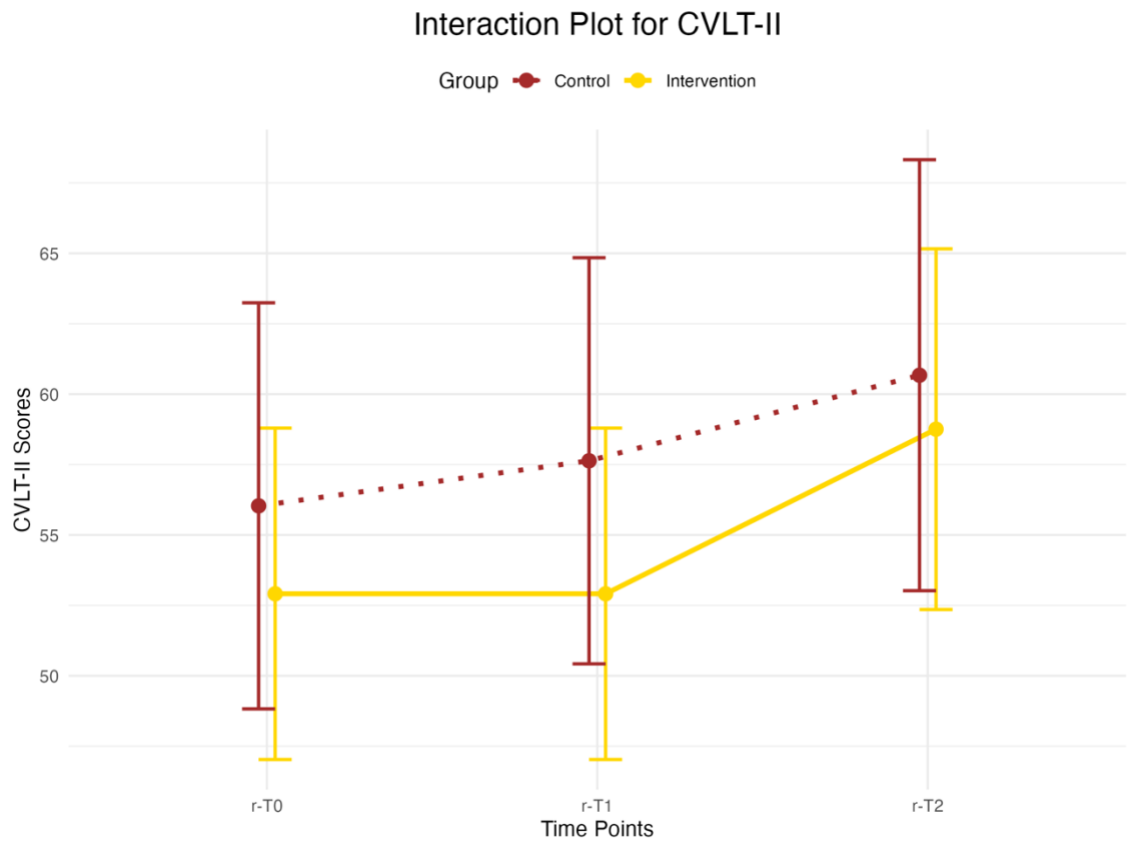


Figure 4. **CVLT-II interaction plot.** The interaction plot shows the CVLT-II scores for control and intervention groups at three time points: before telerehabilitation (r-T0), immediately after (r-T1) and at the 6-months follow-up (r-T2). The plot includes error bars displaying 95% Confidence Intervals (CI).

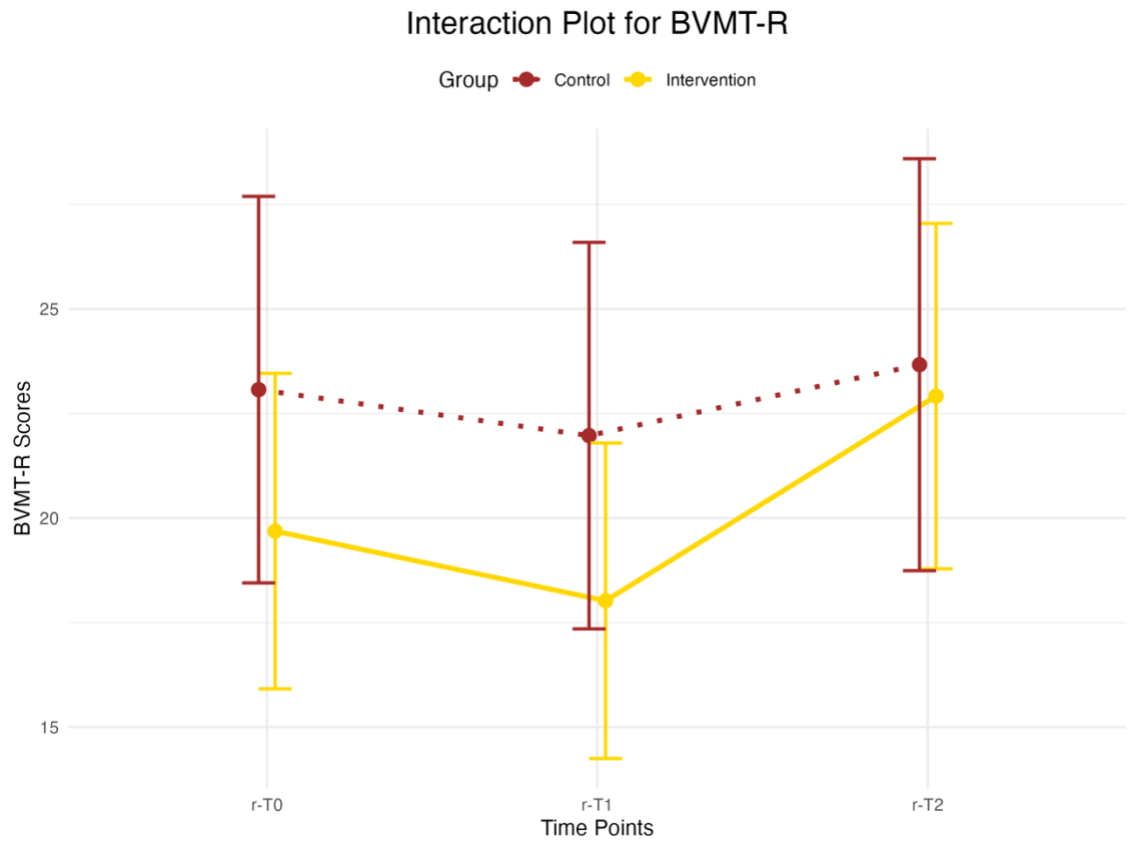


Figure 5. **BVMT-R interaction plot.** The interaction plot shows the BVMT-R scores for control and intervention groups at three time points: before telerehabilitation (r-T0), immediately after (r-T1) and at the 6-months follow-up (r-T2). The plot includes error bars displaying 95% Confidence Intervals (CI).

3.5 Transfer effects: PROMs

Table 9 reports the mean scores at PROMs of participants in the intervention and control groups at the different assessments throughout the course of the study.

Table 9. **Mean scores (± SD) at the PROMS.** The table shows the Patient Reported Outcome Measures (PROMs) scores of participants in the Intervention Group (IG) and Control Group (CG) across three time points: at re-baseline (r-T0), immediately post-intervention or sham (r-T1), at the six-month follow-up (r-T2). The results are reported as mean ± (SD) for each group.

	r-T0		**r-T1**		**r-T2**	
PROMs	**IG**	**CG**	**IG**	**CG**	**IG**	**CG**
MFIS-21						
MFIS-21 Total	37.86 ±16.49	37.40 ±19.93	37.33 ±18.06	40.80 ±19.49	36.20 ±14.75	35.63 ±22.16

MFIS-21 Physical Subscale	20.5 ± 8.28	21.6 ± 9.55	20.13 ± 9.23	23.6 ± 7.96	20.5 ± 8.81	20.13 ± 8.61
MFIS-21 Cognitive Subscale	13.14 ± 8.80	10.8 ± 9.90	13.2 ± 9.73	12.5 ± 12.09	10.5 ± 13.65	12.3 ± 7.07
MFIS-21 Psycho-social Subscale	4.21 ± 2.36	5.00 ± 2.98	4.00 ± 2.00	4.80 ± 2.78	4.60 ± 2.32	4.38 ± 2.83
FSS	43.87 ± 12.59	44.10 ± 14.58	44.87 ± 9.83	44.78 ± 13.14	44.90 ± 13.16	40.38 ± 17.01
BDI-II	4.21 ± 2.36	5.00 ± 2.98	4.00 ± 2.00	4.80 ± 2.78	4.60 ± 2.32	4.38 ± 2.83
MSQOL-29						
MSQOL-29 Total	46.54 ± 6.60	43.77 ± 6.44	41.19 ± 12.95	45.93 ± 4.36	44.13 ± 4.06	43.43 ± 10.10
MSQOL-29 Physical Composite Score	44.53 ± 8.56	40.09 ± 7.13	42.50 ± 9.08	43.05 ± 7.36	42.11 ± 4.99	41.11 ± 9.78
MSQOL-29 Mental Composite Score	52.12 ± 5.95	50.66 ± 11.49	48.28 ± 14.80	53.80 ± 5.48	51.82 ± 7.52	51.80 ± 13.60
PDDS	5.07 ± 1.54	5.60 ± 1.07	5.33 ± 1.54	5.50 ± 1.43	5.20 ± 1.81	5.63 ± 1.30

*Abbreviations: BDI-II, Beck's Depression Inventory; FSS, Fatigue Severity Scale; MFIS-21, Modified Fatigue Impact Scale 21; MSQOL-29, Multiple Sclerosis Quality of Life Questionnaire 29; PDDS, Patient Determined Disease Step.

A LMM analysis revealed no significant main effect of "Group", nor "Time" for any of the PROMs (all $p > 0.05$). Similarly, Interaction terms "Group" x "Time" were not significant (all $p > 0.05$) for any of the PROMs. Appendix 2 displays full results.

3.6 Individual-level improvements

Although the LMM assessing group-level differences over time did not reveal significant improvements in the intervention group after training, a secondary analysis to examine changes at the individual-level was conducted. Indeed, the Reliable Change Index (RCI) allowed to identify single participants who experienced meaningful improvements. This analysis highlighted potential individual benefits of training vs. sham across groups, summarised in Table 10.

Table 10. **Individual performance improvements at the neuropsychological evaluation.** The table shows the number of participants with significant improvement at a specific neuropsychological (NPS) test at two time points (r-T1 and r-T2), relative to r-T0, for both the Intervention Group (IG) and Control Group (CG). Significant improvements are determined by a Reliable Change Index (RCI) ≥ 1.96.

	N participants that improved at r-T1		**N participants that improved at r-T2**	
NPS test	**IG (15)**	**CG (10)**	**IG (15)**	**CG (10)**
MoCA	3	1	5	2
BICAMS				
SDMT	2	2	1	3
CVLT-II	3	2	5	2
BVMT-R	1	1	4	0

3.7 Post-hoc analysis

3.7.1 Rationale

Given the current null results on the efficacy of telerehabilitation when comparing groups, and the general lack of improvements in both groups, except for the SMDT at r-T2, a natural follow-up question arose. That is whether PwMS improved on the selected cognitive outcomes when treated for CI within the clinic, in the context of the in-patient stay. The current exploratory post-hoc analysis wanted to answer precisely this question formulated a posteriori. Although the exploratory nature of these analysis, investigating performance changes in-clinic may help shed some light into the current null results.

3.7.2 Results from ANOVA

For relevance, only statistically significant results are reported in this section.

3.7.2.1 SDMT

The results from the ANOVA revealed a main effect of "Group", $F(1,23)= 5.05$, $p= 0.035$, indicating that the control and intervention groups differed in their overall SDMT scores. Specifically, the controls had higher scores (mean= 38.25 ± 8.37) compared to individuals in the intervention group (mean= 31.60 ± 7.15). A significant main effect of "Time" was also observed, $F(1,23) = 8.35$, $p = 0.008$, with an overall slight increase in score of 2.92 points between c-T0 and c-T1. The interaction "Group

x Time" was not significant, F(1,23)= 0.12, *p= 0.737*. *Figure 6* helps visualise score changes from c-T0 to c-T1 across groups.

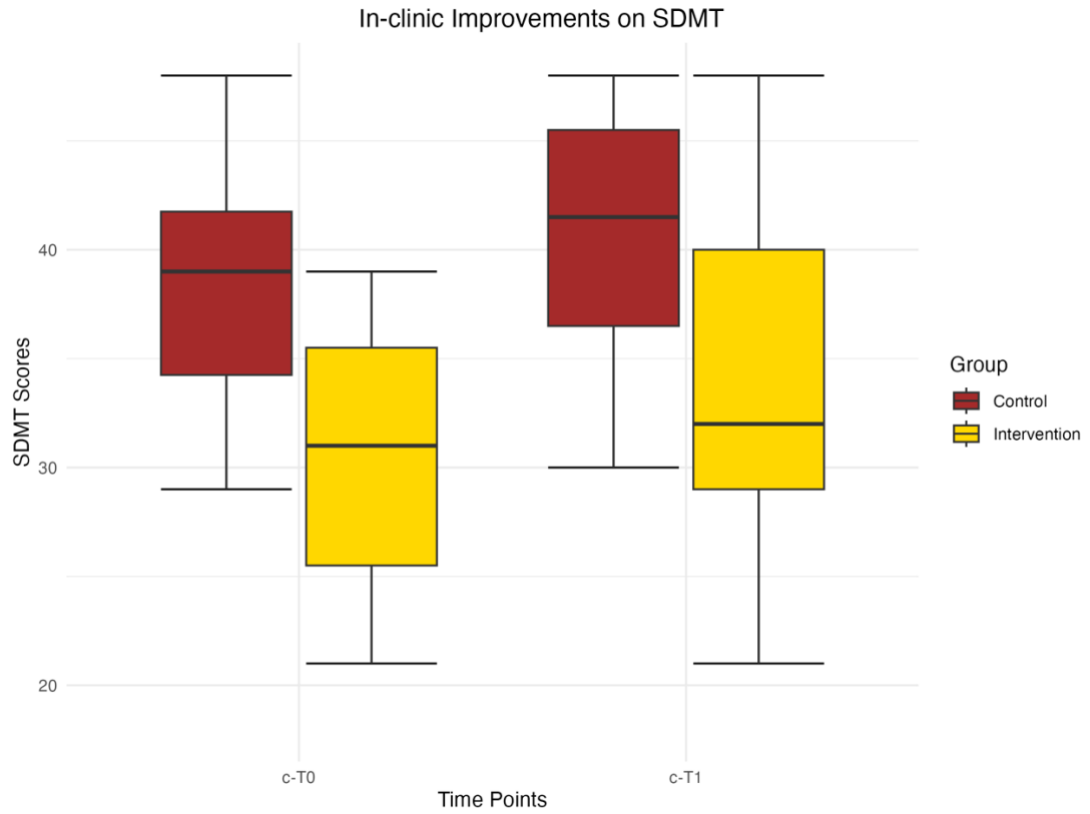


Figure 6. **In-clinic improvements on SDMT.** The boxplot shows the distribution of SDMT scores for both the intervention and control groups across two time points: before and after in-clinic cognitive rehabilitation.

3.7.2.2 BVMT-R

The results of the ANOVA also revealed a significant main effect of "Time", F(1,23)= 33.427, *p <0.001*, for the BVMT-R, indicating scores differed significantly between c-T0 and c-T1 across participants. Specifically, there was an overall consistent improvement of 8.72 points. There was no significant main effect of "Group", nor "Group × Time" interaction (all *p >0.05*). *Figure 7* helps visualise score changes from c-T0 to c-T1 across groups.

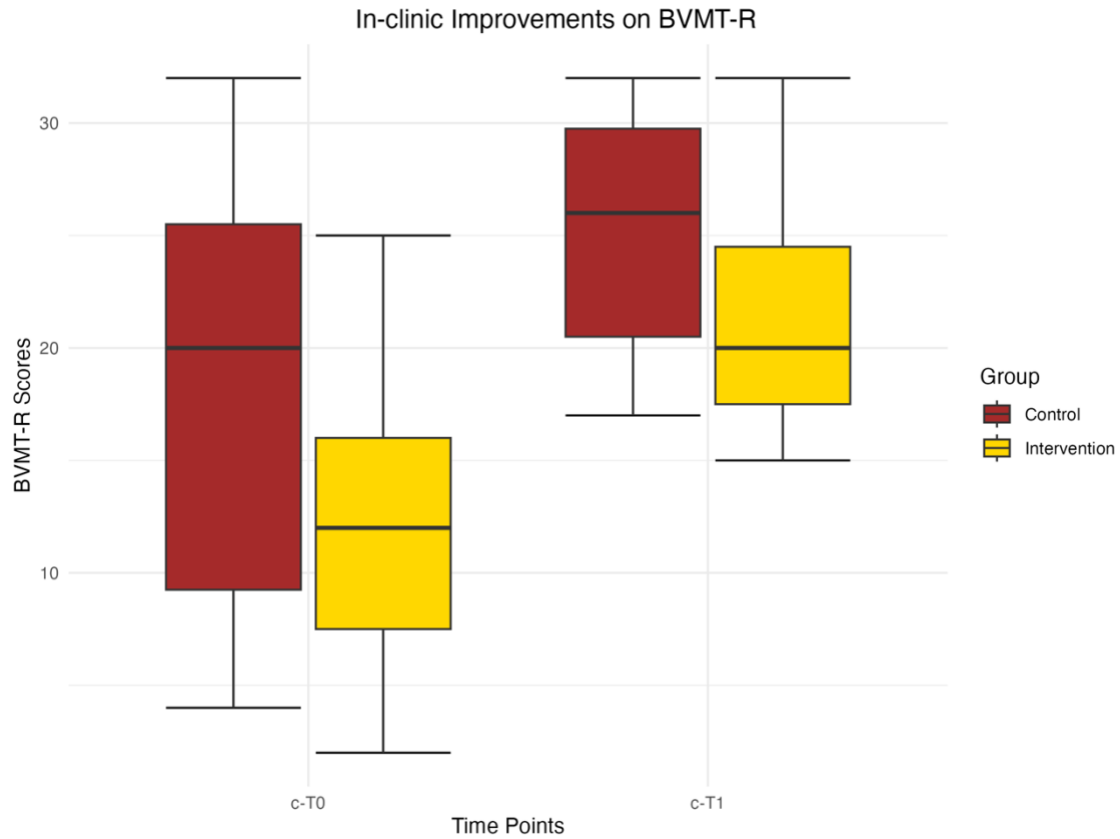


Figure 7. **In-clinic improvements on BVMT-R**. The boxplot shows the distribution of BVMT-R scores for both the intervention and control groups across two time points: before and after in-clinic cognitive rehabilitation.

3.7.2.3 Stroop test word-reading

The ANOVA showed a significant main effect of "Time", F(1,23)= 6.179, *p= 0.021*, for the Stroop Test word-reading (item component), indicating a change in scores from c-T0 to c-T1. Namely, there was a slight increase in scores of 3.32 points. There was no significant main effect of "Group", or "Group × Time" interaction (all *p >0.05*). *Figure 8* helps visualise score changes from c-T0 to c-T1 across groups.

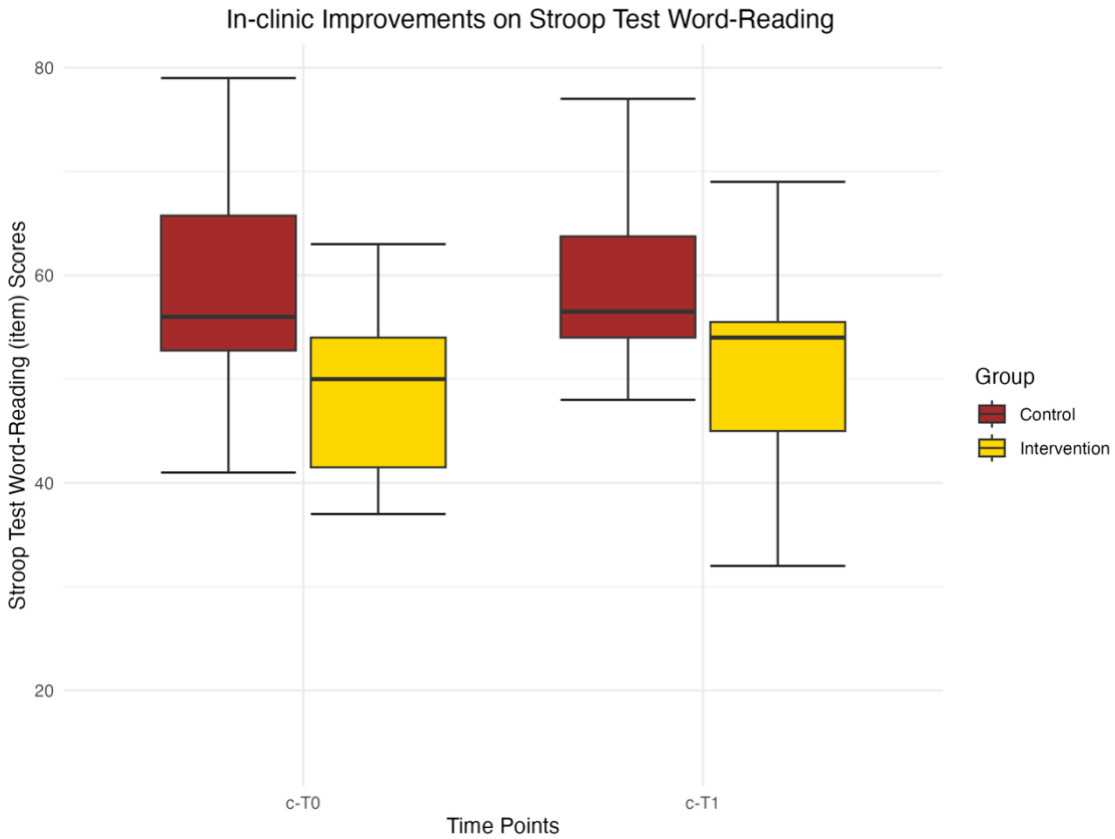


Figure 8. **In-clinic improvements on Stroop Test Word-Reading**. The boxplot shows the distribution of Stroop test (word-reading) scores for both the intervention and control groups across two time points: before and after in-clinic cognitive rehabilitation.

3.7.3.4 Stroop test colour-naming

The ANOVA showed a significant main effect of "Time", $F(1,23)= 8.716$, $p= 0.007$, indicating a change in scores on the Stroop test colour-naming (item component) from c-T0 to c-T1. There was a slight increase in scores of 3.76 points. There was no significant main effect of "Group", or "Group × Time" interaction (all $p > 0.05$). *Figure 9* helps visualise score changes from c-T0 to c-T1 across groups.

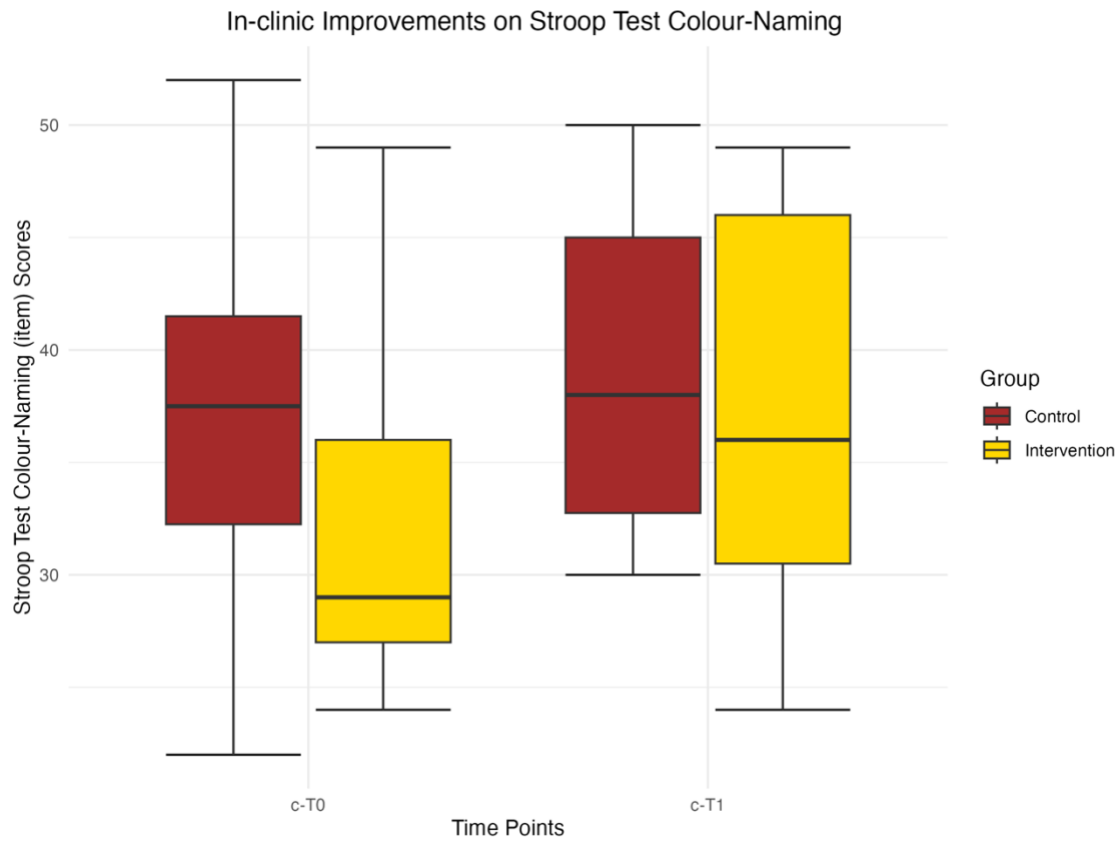


Figure 9. **In-clinic improvements on Stroop Test Colour-Naming**. The boxplot shows the distribution of Stroop test (colour-naming) scores for both the intervention and control groups across two time points: before and after in-clinic cognitive rehabilitation.

4 Discussion

Telerehabilitation has emerged as a possible approach for managing CI in PwMS, with the goal of offering broader accessibility to rehabilitation services, allowing the continuity of care of individuals unable to reach designated healthcare facilities, as well as providing support during the lifelong course of the disease. Some studies have shown evidence regarding adequate adherence to telerehabilitation tools for CI in PwMS, however, others have failed to report measures of compliance to specific study procedures. Moreover, there are inconsistent and variable findings regarding the efficacy of various telerehabilitation interventions (Boschetti et al., 2024). To address this gap, the current study first tried to investigate adherence to home-based cognitive training with the RehaCom software in PwMS. Establishing the feasibility of such an intervention was foundational to a subsequent exploration of its efficacy. Moreover, the current study also tried to investigate efficacy of telerehabilitation compared to control computerised sham activities. Both immediate efficacy (right

after the end of the training vs. sham), and efficacy at a follow-up assessment (6 months after the end of training vs. sham) were investigated. Efficacy was evaluated in terms of improved performance on neuropsychological measures across the cognitive domains mostly affected in MS -processing speed, attention, memory, and executive functions. Potential transfer effects to PROMs -including fatigue, depressive symptoms, quality of life, and perceived disability- were also explored.

4.1 Summary of main findings

First of all, the results showed no baseline differences in terms of demographic, clinical and treatment-related variables between intervention and control groups, indicating randomisation was successful and groups resulted to be well-matched in terms of the aforementioned characteristics. Similarly, no baseline differences between groups were found at the r-T0 re-baseline assessment, conducted before the beginning of the telerehabilitation or sham, on any of the neuropsychological tests or PROMs, indicating participants in both groups had comparable cognitive-affective profiles.

Second, participants in both groups exhibited a notable portion of cognitive deficits upon recruitment, with the most common impairments registered on the SDMT, which is perhaps not surprising, considering that the SDMT is vastly considered as the most recommended cognitive assessment tool in MS, not only because of its high sensitivity, strong test–retest reliability, and robust predictive validity, but also because it seems to be very effective at differentiating between PwMS with and without CI (Dini et al., 2025). In general, most participants had deficits in one or two cognitive tests administered, with a higher percentage of participants in the intervention group having impairment in more than one test.

Overall, the findings from the study support the feasibility and usability of the proposed telerehabilitation intervention, as evidenced by the medium-to-high adherence rates to the planned training sessions, as well as the SUS scores mostly clustering in the high usability range. On the other hand, group-level comparisons on both neuropsychological measures and PROMs did not show an advantage favouring telerehabilitation compared to sham activities, neither immediately post-training nor at the 6-months follow-up appointment. The only significant finding was that participants, on average, improved on the SDMT from re-baseline to 6-months follow-up, with the control group unexpectedly outperforming the intervention group. Individual-level analysis revealed a minor portion of participants achieved meaningful

improvements on neuropsychological tests, however, this was true for both intervention and control groups.

Post-hoc exploratory analysis showed significant improvements in cognition took place when participants were hospitalised and underwent in-clinic cognitive remediation. Specifically, both groups showed improvements on SDMT, BVMT-R and Stroop test subcomponents word-reading and colour naming.

4.2 Feasibility of telerehabilitation and system usability

The primary aim of the current pilot RCT was to assess the feasibility of a 12-week cognitive rehabilitation intervention delivered at home via software. The results indicated that both the telerehabilitation and the sham activities registered moderate-to-high adherence rates, evidenced by the fact that most participants completed at least half of the scheduled sessions. Furthermore, more than half of participants in both groups completed at least two-thirds of scheduled training or sham. These findings indicate a strong commitment to the program, with most PwMS in the intervention group completing a substantial portion of the planned training hours. The medium-to-high adherence rates suggest home-based training in this context was clearly feasible, with most patients being able to engage with it. These findings are in line with those from previous studies on cognitive telerehabilitation in MS, which also reported good feasibility to telerehabilitation tools (Campbell et al., 2016; De Giglio et al., 2015; Hancock et al., 2015; Pedullà et al., 2016) and even exceed the compliance rates found in other studies on the topic (Charvet et al., 2015; Charvet et al., 2017; Shatil et al., 2010; Vilou et al., 2020). Taken together these results are extremely important, as high adherence to telerehabilitation is fundamental to determine whether home-based interventions can realistically be employed in the continuity of care of PwMS.

In addition, since the current intervention was asynchronous, and training could be self-administered by the individual, with no supervision from the clinician, the positive feasibility results suggest this feature was not an obstacle to participation, and PwMS were well-able to implement and complete training, even if a therapist was not supervising them "online". Furthermore, the study found no significant differences in adherence rates between PwMS with or without employment, suggesting asynchronous interventions can be successfully incorporated into a variety of lifestyles.

Moreover, results on the consistency of session completion throughout the course of the three months, show that PwMS successfully exhibit high adherence from the beginning of the telerehabilitation, and they are able to maintain it until its end. This was also true for the sham activities. This is important as it shows that both the telerehabilitation intervention and the sham activities were engaging enough to sustain participation, allowing for a fair comparison. This was further supported by the fact that most PwMS who dropped out of the study, did so before starting either the telerehabilitation or sham activities. Notably, only one participant in the control group withdrew after the start of the sham training, but this was due to severe health reasons rather than boredom or lack of interest, further underscoring the overall acceptance and feasibility of the program by the participants.

When usability of telerehabilitation was investigated, participants in the intervention group generally reported good-to-excellent usability. The high satisfaction suggests that the software's interface and functionalities were sufficiently intuitive, reducing dropout risks and technological frustration. Since usability heavily influences adherence, these results are reassuring, as from a user-experience standpoint, telerehabilitation can be a viable add-on to standard care. This usability advantage possibly directly translated into the medium-to-high feasibility rates found in the current study.

Since most studies on telerehabilitation for CI in PwMS primarily reported solely the proportion of participants who adhered to a set percentage of scheduled training, or inferred feasibility of an intervention from the dropout rates (Boschetti et al., 2024), the strength of the current study comes from the fact that adherence was extracted precisely from the software, which was able to capture the minutes of actual completed training vs. the planned training minutes, allowing for detailed reports. On the other hand, this was not true for the sham activities, which relied on participants' self-reports, caregivers' self-reports, and completion of activities. This self-reporting method is inherently less precise and may have introduced bias. For example, participants or caregivers might have inaccurately reported the amount of time spent on sham activities due to memory limitations or misunderstanding of what counts as "completion". This could have resulted in overestimating or underestimating adherence. Similarly, social desirability bias cannot be ruled out, as participants might have over-reported adherence to sham to align with perceived expectations or to present themselves in a favourable light. Thus, future studies

should explore more objective and standardised methods to measure compliance to sham activities. For example, one study used a computer-based gaming program to deliver active sham training (Charvet et al., 2015), allowing for more precise recordings. This was unfortunately not possible in the current study. Nonetheless, as the primary interest was to investigate feasibility in the intervention group, this limitation relative to the control group can be overlooked.

Indeed, when exploring telerehabilitation for cognitive deficits in PwMS, the results show that it was feasible and well-received, with most participants engaging regularly and consistently with the intervention. The small portion of PwMS who completed significantly fewer sessions suggests there is still a need to identify and address specific barriers to telerehabilitation. These may include technological issues, cognitive challenges, or motivational obstacles that may impede session completion. Future studies should prioritise investigating and mitigating these factors to enhance participation.

4.3 Efficacy of telerehabilitation

Despite moderate-to-high adherence, no significant advantage of the proposed telerehabilitation intervention compared to the control activities was seen for any of the neuropsychological outcome measures or PROMs, across all time points. Immediately after training, neither group showed improvements on any of the cognitive outcomes or transfer effects to PROMs. Furthermore, the two groups also did not show improvements at the 6-months follow-up appointment at any of the neuropsychological tests investigated or PROMs, except for the SDMT. At the follow-up assessment, there was a general improvement in the SMDT scores, but performance of the control group unexpectedly exceeded that of the intervention group.

As a result, the current findings do not support the efficacy of telerehabilitation for ameliorating cognitive deficits in PwMS. When looking at studies within the literature which involved the use of the RehaCom software in-clinic, and considering the outcome measures of relevance for the current study, it is possible to argue that the current results are in line with research papers that also did not report positive findings on the efficacy of cognitive rehabilitation (Cerasa et al., 2013; Mattioli et al., 2010; Solari et al., 2004). One the other hand, they are in contrast with studies that instead found some benefits of training (Arian Darestani et al., 2020; Bonavita et al., 2015; Naeeni Davarani et al., 2022). Furthermore, previous studies, in the context

of telerehabilitation with this software, have reported positive outcomes, such that one study found improvements on the SDMT after cognitive training, but not on other BICAMS subtests (Campbell et al., 2016), while another found improvements in all BICAMS subtests (Messinis et al., 2020). However, the current findings do not align with these results. Specifically, the data did not show patterns of improvement, suggesting a potential discrepancy in results that needs to be further investigated.

4.3.1 Possible reasons for the lack of evidence for the efficacy of telerehabilitation

One possibility for the null results could be that the training intensity and duration were insufficient to allow for plasticity-related changes to occur, however, this is unlikely considering that the studies mentioned above also adopted similar training schedules (3-weekly 45-minute sessions) for even less than 12 weeks, and still demonstrated some benefits of treatment (Campbell et al., 2016; Messinis et al., 2020).

Several studies have shown that cognitive rehabilitation can induce plasticity-related changes in the brain (Bonavita et al., 2015; Campbell et al., 2016; Cerasa et al., 2013; Filippi et al., 2012). Filippi and colleagues found that PwMS exhibited increased activation in the posterior cingulate cortex and precuneus, as well as the dorsolateral Prefrontal Cortex (PFC) bilaterally, compared to a control group which received no rehabilitation. This suggests that cognitive training may enhance brain network efficiency, particularly in regions associated with self-referential thinking, attention, and executive control. At follow-up, the treatment group demonstrated increased recruitment of the dorsolateral PFC bilaterally. This suggests that cognitive rehabilitation may also promote long-term neuroplasticity, reinforcing prefrontal networks involved in executive functioning and working memory. Resting-state analyses also revealed an increase in activity over time in the treatment group compared to controls. Furthermore, correlations indicated that these functional changes were associated with improvements in tests measuring attention and executive functions (Filippi et al., 2012).

Similarly, Bonavita and colleagues reported increased functional connectivity in the default mode network, particularly in the posterior cingulate cortex and bilateral inferior parietal cortex. Since the default mode network is linked to self-awareness and memory consolidation, these changes suggest that cognitive training may induce

adaptive cortical reorganization, leading to better cognitive performance (Bonavita et al., 2015).

Interestingly, Cerasa and colleagues also found changes at the brain level, particularly, increased activity in the posterior cerebellar lobule and superior parietal lobule, after cognitive remediation, even in the absence of consistent performance improvements at the neuropsychological evaluation (Cerasa et al., 2013). This suggests that functional reorganisation can occur independently of measurable behavioral improvements, possibly because neural changes may take place even with no evident performance changes on cognitive tests. On this basis, it cannot be excluded that the neuropsychological outcome measures used in the current study were not sensitive enough to detect subtle benefits of cognitive rehabilitation, which may not have been evident at the behavioural level. Nonetheless, MRI was not employed here, making it impossible to know whether brain changes actually occurred following cognitive rehabilitation in this case. Further research using neuroimaging will be necessary to explore these mechanisms.

One the other hand, it should be said that PwMS in the current study were all individuals with progressive forms of MS, characterised by high disability status, and with a mean age in the mid-fifties. Perhaps, cognitive training was less effective in this cohort due to older age and greater disability. This is particularly relevant considering that individuals with the progressive forms of the disease, and greater disability, tend to have more severe cognitive deficits, specifically in memory and learning, attention, working memory and processing speed (Deluca et al., 2004; Gich et al., 2024; Tinnefeld et al., 2005). Indeed, previous studies, that came across some benefits of telerehabilitation, included younger participants, with lower levels of disability, some of whom had a different disease course, namely RRMS (Campbell et al., 2016; Messinis et al., 2020). Perhaps, participants in the current study may have had more severe disease progression, potentially reducing their capacity to benefit from cognitive training, possibly due to diminished brain plasticity.

Furthermore, PwMS in the current study had on average “medium” scores on the Cognitive Reserve Index (CRI). There is evidence to suggest that individuals with lower cognitive reserve often exhibit less neural compensation mechanisms, meaning their brains may struggle to reorganise and adapt to injury or cognitive decline (Stern, 2009). Research in stroke and traumatic brain injury has also shown that higher cognitive reserve is related to better recovery and greater responsiveness to

rehabilitation (Kesler et al., 2003). On this basis, it cannot be excluded that participants in this study did not benefit from telerehabilitation in this context due to limited capacity for brain reorganisation and plasticity due to "medium" - instead of "high"- cognitive reserve. Additionally, some participants in the current study had comorbid health conditions (e.g., cardiovascular issues, metabolic disorders) and were taking multiple medications. Such factors may have attenuated the effects of the intervention, as side effects, such as fatigue, could also interfere with cognitive training processes.

Another possibility is that since patients were heterogenous in terms of cognitive profiles, as they presented deficits in different domains in various combinations, standardised training may not have been the best option for treatment of cognitive dysfunctions in this context. However, it is common for studies to focus on either executive functions, attention and working memory, because they are known key contributors of performance across a wide range of neuropsychological components, or on the most commonly affected cognitive domains in PwMS (Boschetti et al., 2024). One telerehabilitation study, which was designed to implement a home-based protocol based on the specific cognitive deficits for each person with MS, found improvements after training on measures of general memory, visual working memory and verbal auditory working memory, but not in other domains tested (Shatil et al., 2010), suggesting personalised interventions may be beneficial to a certain extent. There is also evidence to suggest that studies focusing on the rehabilitation of one cognitive domain may have better outcomes, specifically, the rehabilitation of attention seems to produce evident beneficial effects (Cerasa et al., 2013; Filippi et al., 2012).

Naturally, both tailored and standardised approaches have their respective advantages and limitations. The more specific a treatment plan is for the individual deficits, the harder it gets to standardise treatment and outcome measures, and to generalise its results. Furthermore, this approach relies on the availability of a comprehensive neuropsychological baseline assessment, which may not always be feasible in everyday clinical practice. A standardised approach, instead, has the advantage of providing a tool for standard care that is easier to generalise, but it may lack sensitivity when the outcome measures are not specific for the cognitive functions affected in the clinical sample (Boschetti et al., 2024). This methodological aspect may have influenced the results of the current study and warrants further exploration, possibly directly comparing specific vs. standardised cognitive training.

Moreover, the lack of therapist involvement in a fully remote asynchronous cognitive rehabilitation protocol may have impacted the efficacy of the training itself. The clinician usually plays a crucial role in traditional in-clinic rehabilitation settings by providing strategies, real-time feedback, and immediate support during exercises, which can enhance both the challenge and engagement of the training. However, at home, the patient often lacks this level of supervision and involvement. Additionally, home-based rehabilitation is inevitably linked to less control over the training setting, and participants may face distractions. Factors such as fatigue, lack of supervision, reduced motivation or interruptions in the home environment may reduce the overall impact of the training. This may explain the lack of results in the telerehabilitation part of the study, while the very same participants were able to previously benefit from in-clinic cognitive remediation.

Also, it should be said that participants in the intervention group completed about 68% of their intended training hours, which is good in the context of telerehabilitation, however, by contrast, many in-clinic studies using RehaCom (Bonavita et al., 2015; Mattioli et al., 2010; Mattioli et al., 2012, Mattioli et al., 2016) typically ensure near-full adherence because sessions are normally supervised in a structured setting. Lower engagement at home may have led to a suboptimal "dose" of cognitive stimulation. Clearly, these aspects need further investigation, with a direct assessment of the benefits of the presence of clinicians in "real time" during cognitive training, and the costs of the lack of this support.

Surely, the scarcity of significant improvements in outcome measures do not support the clear superiority of telerehabilitation in improving cognitive deficits in PwMS. Similarly lack of significant changes in PROMs do not support any transfer effects to any domains other than cognition. On the other hand, even if group level changes were not significant, individual-level results suggest that a pool of participants, although small, actually experienced meaningful cognitive gains from the training. This was true for both groups, although more people in the intervention group seemed to improve at measures of general cognition, verbal and visuospatial learning and memory, but not processing speed, visuospatial skills and attention. This analysis is important as it shows that some PwMS respond positively to home-based training, even if the overall effects did not reach group-level significance. This is especially relevant in MS, where disease progression and symptom severity vary considerably across individuals and where there is much disease heterogeneity.

4.3.2 SDMT gains in the control group

The fact that participants in the control group improved more compared to those in the intervention group at the SDMT, at the 6-months follow-up assessment, is somewhat unexpected, particularly since no improvements were seen immediately after training. First off, it cannot be ruled out that some natural "recovery" mechanisms have emerged. Indeed, PwMS in the control group may have experienced spontaneous cognitive fluctuations (Dini et al., 2025). Another possibility is that controls may have accidentally engaged in cognitively stimulating activities outside the trial which perhaps acted as confounding variables.

As a related issue, it cannot be overruled that improved performance is due to practice effects and does not reflect a real improvement in processing speed, attention and visuo-motor abilities. Indeed, at least 11 of the 18 participants from whom the 6-month follow-up data is available, took part in another parallel ongoing trial at the Casa di Cura Igea SpA during the course of this study, which involved repeated assessments with a digital version of the SDMT. This overlap may have influenced the current results. Thus, although alternate versions of tests were used for the assessments in this study, practice effects rather than true cognitive improvements may be biasing the findings. However, it is important to note that both PwMS in the intervention and control groups equally participated in the other study. As such, any potential bias introduced by practice effects should have impacted both groups to a similar extent.

Another possibility is that the sham activities designed for the current study may have inadvertently served as relevant cognitive stimulation. Indeed, the sham activities included reading journal articles and answering related questions, describing pictures, completing sudokus and anagrams. These activities may have been sufficient to engage memory, attention and problem solving processes. Thus, PwMS in the control group may have been unintentionally challenged, leading to the improvements found. On the other hand, maybe these individuals had more energy or motivation or other intrinsic factors that influenced the results. Also, it is possible that engaging in any form of activity is preferable to remaining "inactive". Indeed, it may be that any form of home-based activity post-hospitalisation supported improvements over a longer timescale.

It is interesting to notice that there are several studies that failed to implement adequate control conditions and came across more positive results of telerehabilitation for CI in MS (Blair et al., 2021; Hildebrandt et al., 2007; Shatil et al., 2010; Vilou et al., 2020; Vogt et al., 2009) compared to studies that implemented active control conditions (Amato et al., 2014; Campbell et al., 2016; L. Charvet et al., 2015; L. E. Charvet et al., 2017; Hancock et al., 2015), with some exceptions (Messinis et al., 2020; Pedullà et al., 2016). This shows the importance of an active control group in finding a true effect rather than a "placebo" effect. Furthermore, although feasibility was good in both groups, it was higher in the control group. Admitting that the sham activities were challenging enough at a cognitive level, this difference in adherence may have biased the results in favour of the control group.

Nonetheless, the fact that PwMS in the control group improved more compared to individuals in the intervention group is further evidence for the lack of benefits of telerehabilitation for CI in this patient cohort. This conclusion is reinforced by the moderate-to-strong effect size, which indicates that being in the intervention group was associated with less improvements in SDMT performance over time.

4.3.3 In-clinic cognitive improvements

Since all participants were hospitalised and received cognitive rehabilitation in-clinic with the software RehaCom, under the supervision of a trained neuropsychologist, exploratory post-hoc analysis were conducted to investigate whether PwMS improved on the selected cognitive outcomes when they were treated for CI in the context of the hospitalisation.

The results revealed that SDMT scores were higher in the control group compared to the intervention group, and that, overall, there was an improvement in SDMT scores over time. Furthermore, all participants, improved after in-clinic cognitive training on the BVMT-R, the Stroop Test word-reading and the Stroop test colour-naming. Based on these results, one possible explanation for the lack of improvements observed during telerehabilitation is that participants had already achieved significant cognitive gains during the in-clinic rehabilitation phase, and there was no longer room for additional improvements. However, performance gains on both SDMT and Stroop test, although statistically significant, were minimal, and the only clinically relevant improvement was seen for the BVMT-R. Nonetheless, it cannot be excluded that telerehabilitation in the context of the continuity of care of PwMS, may not provide any additional benefits. Home-based tools for CI may be more

effective when used as primary interventions rather than as follow-up to prior in-clinic cognitive training. Nonetheless, this is highly speculative and needs to be systematically tested. Furthermore, the general inconsistent findings regarding their efficacy make it hard to embrace this conclusion at this stage. Further studies are needed to continue to explore this possibility and to identify the optimal context for telerehabilitation in PwMS.

4.4 Strengths and limitations

Surely, this study is not free of shortcomings, which may have potentially led to the negative findings on efficacy. First of all, this is a pilot study with the primary aim of assessing feasibility of telerehabilitation. As such, it included a small sample of participants. Although common in longitudinal clinical research, a sample of only 25 participants in total may not have allowed for enough statistical power to detect differences in outcomes. Furthermore, this cohort of participants with progressive MS and high disability status may not be representative of a larger MS population. Moreover, there was some variability among participants in terms of the number of days spent as in-patients and the number of cognitive rehabilitation sessions received within the clinic. This variability arose naturally from the hospitalisation context and could not be controlled by the study. However, it may have acted as a confounding variable, influencing the subsequent experimental procedures. Additionally, during their in-patient stay, participants received various other rehabilitation services, such as physiotherapy, occupational therapy, and neurostimulation. Since these interventions were not standardised across patients, it is unclear whether they introduced additional confounding effects. Moreover, although most assessments were conducted remotely, the neuropsychological evaluation of four participants at the follow-up appointment was administered in presence within the clinic, thus, even if assessments conducted remotely and in-presence were treated as the same, this may have been improper, and possibly the two modalities were not directly comparable. Another notable limitation is the absence of a control group receiving in-person cognitive rehabilitation. The inclusion of such a group would have provided a valuable benchmark for evaluating the relative effectiveness of the remote intervention. Human interaction with a therapist, particularly in a face-to-face setting, can play a critical role in enhancing patient motivation, engagement, and adherence to the rehabilitation programme. In-person therapy also allows for immediate, adaptive feedback and richer interpersonal communication, which may amplify therapeutic outcomes. Without this comparison, it remains uncertain whether

the lack of observed efficacy is attributable to the inherent limitations of telerehabilitation itself, or simply to its difference from traditional delivery modes.

On the other hand, the current study also has several strengths, as it tried to overcome some methodological limitations of previous research. First of all, it is a RCT which implemented double-blinding, used alternate versions of tests, same patient assessor, adequate active control condition, and included a follow-up assessment. Moreover, participants were recruited based on objectively measured cognitive deficits rather than subjective complaints, which has not always been the case for previous studies on the matter (Boschetti et al., 2024). Thus, despite some limitations highlighted above, the study is methodologically sound.

4.5 Conclusive remarks

Based on the current findings, it cannot be affirmed that, although the high feasibility and usability, the employed telerehabilitation intervention for CI in MS was beneficial in terms of improvements of cognitive deficits, nor affective symptoms, quality of life or perceived disability status. However, these negative findings should be interpreted with caution in light of the limitations that may have masked potential benefits.

First, it is possible that the outcome measures used in this study were not sufficiently sensitive to detect subtle cognitive or functional changes. Many standard neuropsychological tests may lack ecological validity or responsiveness to change. Second, participants in this study were individuals with progressive forms of MS and high levels of disability, which may imply reduced neuroplastic potential and thus lower responsiveness to cognitive rehabilitation interventions. Third, the absence of direct therapist involvement in the telerehabilitation setting may have influenced patient engagement, task adherence, and the overall effectiveness of the cognitive exercises. The lack of real-time guidance and motivational feedback, which are often critical in rehabilitation settings, could have limited the impact of the intervention.

These considerations underscore the urgent need for new therapeutic frontiers in the field of cognitive rehabilitation. Future studies should adopt multimodal assessment strategies to better capture intervention efficacy. This includes not only comprehensive neuropsychological batteries, but also functional and structural neuroimaging, neurophysiological techniques, and biomarkers known to be

associated with cognitive processes and synaptic plasticity (e.g. Brain-Derived Neurotrophic Factor).

In addition, it is imperative to explore the role of the therapist more systematically. Future designs should include control groups receiving in-person cognitive rehabilitation, as well as hybrid or synchronous remote models, where therapists can interact in real time with participants, for instance through video conferencing or screen-sharing tools that allow the therapist to dynamically support, guide, or adjust exercises.

Finally, cost-efficiency remains a critical factor for the sustainable implementation of telerehabilitation. To meet this challenge while preserving therapeutic quality, Artificial Intelligence (AI) may represent a key component of next-generation platforms. By leveraging real-time performance data, AI systems can dynamically tailor cognitive exercises, modifying task difficulty and content based on individual progress and error trends. Beyond adaptation, AI can emulate aspects of therapist interaction by delivering motivational prompts, corrective cues, and context-aware guidance, thereby fostering greater engagement and adherence. Machine learning techniques can analyse complex, multimodal datasets, including cognitive scores, neuroimaging data, and biomarkers, to identify response patterns and predict which patients are most likely to benefit from specific interventions. This paves the way for precision rehabilitation, aligning therapeutic strategies with each individual's neurobiological and cognitive profile. Moreover, AI could also actively support the session delivery process. Virtual assistants or avatars may provide real-time support, adjust the pace of activities, and respond adaptively to indicators such as engagement or fatigue. Natural language interfaces would enable users to interact conversationally with the system, while the integration of behavioral analytics, such as eye movements, voice inflection, or response latency, could help detect cognitive overload or emotional disengagement. In response, the system could offer breaks, encouragement, or changes in task flow, enhancing both usability and therapeutic impact. In this way, AI not only personalises the intervention but also transforms telerehabilitation into a more interactive, intuitive, and emotionally attuned experience.

On this basis, alternatives to the hereby explored intervention have to be considered, with the opportunity to explore more innovative therapeutic paradigms.

5 Methods

5.1 Study Design

The current study is a double-blind, sham-controlled, pilot RCT adopting a mixed-factorial design, incorporating both between- and within-subjects factors, to investigate the feasibility and efficacy of a telerehabilitation tool for CI in MS. The between-subjects factor labelled "Group" was based on the random allocation of participants to either the intervention or the control group. As a result, this factor had two levels: (1) Telerehabilitation; (2) Sham activities. The within-subjects factor labelled "Time" involved repeated assessments of the same participant at multiple time points. This factor had three levels: (1) Baseline assessment (r-T0), conducted before the start of telerehabilitation or sham; (2) Immediate post-intervention assessment (r-T1), conducted immediately after the completion of telerehabilitation or sham; (3) Follow-up assessment (r-T2), conducted six months after the end of the telerehabilitation or sham.

5.2 Participants

70 eligible PwMS were identified from the in-patient services of the Casa Di Cura Igea SpA in Milan. 12 of them explicitly did not want to participate in the study, while 1 wanted to participate but did not have the time due to work commitments. 6 people ultimately did not undergo cognitive rehabilitation in-clinic and were therefore deemed ineligible for the study. The reason for this choice was motivated by the purpose of the research to evaluate telerehabilitation within the context of continuity of care of patients who had previously received in-clinic cognitive rehabilitation. 4 individuals chose to leave the clinic earlier against medical advice, 1 could not participate due to motor deficits which did not allow for pc usage, while 2 did not have a pc.

As a result, 44 PwMS took part in the study, 21 of which were randomly allocated to the intervention group and 23 to the control group. 6 PwMS in the intervention group and 12 in the control group decided to drop out from the study before the beginning of the telerehabilitation (vs. sham training). Reported reasons for dropouts involved unreachability despite multiple attempts to contact participants (11), scheduling conflicts and time constraints (6), and inability to access laptop or computer when contacted again (1). 1 participant in the control group dropped out

after 5 weeks of sham activities due to serious health reasons which no longer allowed participation, thus, the study included 15 participants in the intervention group and 10 in the control group.

All participants completed both the assessments before and immediately after the telerehabilitation (or sham). Instead, assessments conducted 6 months from the end of the telerehabilitation (or sham) were available for 10 participants in the intervention group and 8 in the control group. Unfortunately, the remaining participants were lost to follow-up. *Figure 10* shows a summary of the recruitment procedure, which began in November 2022 and ended in March 2024.

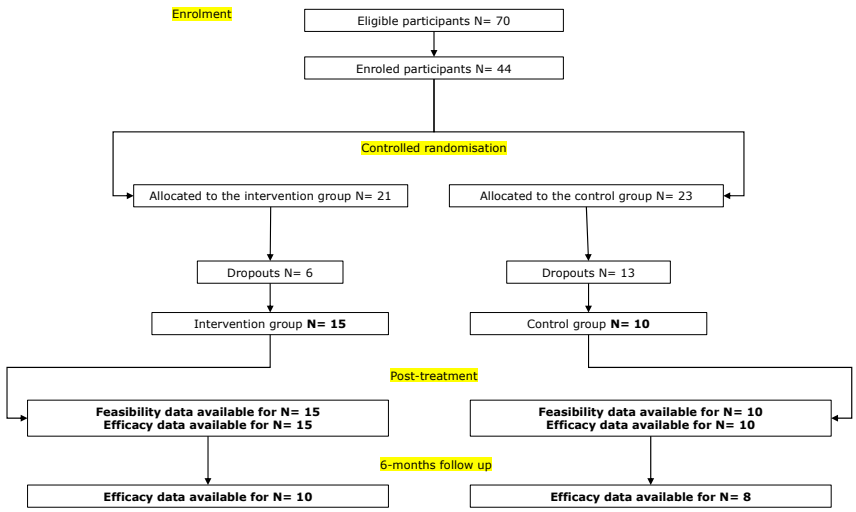


Figure 10. **Flow diagram of recruitment process.** The diagram shows the enrolment and retention of participants, randomisation into intervention and control groups, number of dropouts, and number of cases with available data for each time point throughout the study.

Inclusion criteria to participate in the study were the following: (1) Age between 18-80 years old; (2) MS diagnosis based on the revised McDonald's criteria (Thompson et al., 2018); (3) EDSS score of 0.0 - 7.5; (4) Absence of language comprehension deficits as evidenced by the normal performance on the Token Test (Mondini et al., 2003); (5) Ability to give informed consent and comply with any study-specific procedures; (6) Ability to read and write in Italian; (7) Schooling >3 years; (8) Objective cognitive deficits in at least one neuropsychological test, as indicated by performance 1.282 SD below the mean of the normative population of reference on any of the BICAMS subtests (Goretti et al., 2014) and/or an equivalent score of 0 (Italian system) at either the MoCA (Nasreddine et al., 2005) and/or Stroop

Test (Brugnolo et al., 2016); (9) Early availability for repeated study visits over a 12-month period; (10) Cognitive rehabilitation not carried out in the 6 months prior to consent; (11) Availability to access and ability to use normal Windows PCs or Mac PCs with "VMWare Fusion" virtual machine, suitable for installing computer software for cognitive rehabilitation; (12) Availability to access stable internet connection.

Instead, exclusion criteria were the following: (1) Sensory deficits (visual, auditory) that would significantly impair performance on cognitive tests; (2) Presence of additional neurological disorder/condition (e.g. dementia, epilepsy, severe head trauma); (3) Presence of major psychiatric disorders or severe psychiatric symptoms (e.g. acute psychosis) or ongoing substance abuse within 3 months prior to consent; (4) Presence of a relapse due to MS disease within 3 months prior to consent; (5) Current or recent use of corticosteroids (e.g., cortisone) within 3 months prior to consent.

5.3 Procedure

5.3.1 Participant screening and recruitment

PwMS were screened for inclusion and exclusion criteria upon arrival at the Casa di Cura Igea SpA in Milan, where they were admitted as part of a routine in-patient stay provided annually for PwMS by the Italian national healthcare system. A baseline assessment (c-T0) was carried out within the clinic by an expert neuropsychologist, who conducted the initial clinical interview and the neuropsychological evaluation, as part of standard clinical care. Additional inclusion criteria were verified in this occasion, such as the presence of objective cognitive deficits, as well as intact performance on the Token test (Mondini et al., 2003). Eligible individuals were then informed about the study procedures and invited to take part in it. Upon agreement to participate, they were asked to sign an informed consent. All participants provided informed consent in accordance with the Declaration of Helsinki, and they were all made aware of their right to withdraw from the study at any time, and that participation was completely voluntary.

After consent, information regarding patients' demographics, clinical history, and cognitive status was collected. Following c-T0 assessment, patients with clinical indication underwent cognitive rehabilitation as part of their in-patient stay with a trained neuropsychologist. Before discharge from the clinic, patients were assessed again (c-T1) through neuropsychological testing. In this context, both assessments

(c-T0 and c-T1) and cognitive rehabilitation were part of normal hospitalisation procedure, and the study did not interfere with the planned clinical activities at any stage, both for ethical reasons and to ensure the ecological validity of the study itself. Nonetheless, it is important to mention that all participants were initially hospitalised, assessed via neuropsychological testing twice, and underwent cognitive rehabilitation with the software RehaCom within the clinic, under the guidance and supervision of a trained neuropsychologist.

5.3.2 Block randomisation

Before the conclusion of the in-patient stay, participants were randomised into intervention or control group, through block randomisation, aimed at balancing the quantitative asymmetry of individuals assigned to either the intervention or control group (Doig & Simpson, 2005). An online program (https://www.sealedenvelope.com) was used to set up the randomisation process in advance. Each participant was associated with a unique code and each block was made up of ten unique codes, which were randomly placed in the intervention or control group with a ratio of 1:1. This meant that for each block there were 5 individuals randomly assigned to the intervention group, and 5 to the control group. Participants were informed that two months after discharge from the clinic, they would be contacted to continue to receive cognitive training at home with one among two possible interventions, maintaining patients blinding to the study conditions.

5.3.3 Telerehabilitation procedure

Two months after the conclusion of the in-patient stay, the actual study on telerehabilitation (vs. sham) began, as PwMS were contacted and assessed remotely (r-T0) by an experimenter who administered the neuropsychological tests of interest for the study. This allowed to acquire a new baseline (re-baseline) of participants' cognitive status (compared to c-T0) before the beginning of the telerehabilitation vs. sham. PROMs were also collected online as part of this re-baseline assessment. The decision to administer r-T0 remotely was made to facilitate the inclusion of participants residing in remote regions, who may have had difficulties in reaching the clinic’s premises for follow-up appointments. This approach was also consistent with the home-based nature of the study. The remote assessment was carried out via the videoconferencing software Zoom, which allowed for real-time audio-visual communication. Participants were instructed to use their PCs for the Zoom evaluation and not tablets or smartphones. The visual material was displayed on the

participant's screen through screen sharing, and the experimenter recorded participant's responses in real time using a paper version of the test material. At the beginning of each assessment, the examiner ensured that the participant was alone, and that environmental distractions were limited to a minimum. Validated alternative versions of neuropsychological tests that were repeated within a 6-months interval were used, to minimise practice effects due to repeated testing (Bartels et al., 2010). Permission to use test material was obtained from the respective publishers or authors (if required).

After the r-T0 re-baseline assessment, participants in the intervention group continued training at home with the computer software RehaCom, already used during in-clinic cognitive rehabilitation, following a schedule of 3 45-minute weekly sessions, for a total of 12 weeks of intervention. On the other hand, participants in the control group engaged in a series of computerised sham activities at home on the same schedule and for the same duration as the intervention group. At the end of the 12 weeks of telerehabilitation (or sham), all participants were remotely evaluated once more (r-T1), and PROMs were collected again online. An additional assessment (r-T2) was conducted six months after the end of the telerehabilitation (or sham).

Repeated assessments of a same participant were conducted by the same experimenter to eliminate inter-rater bias, and assessors were blind to study conditions. Indeed, during all remote assessments, participants were reminded to not disclose information received regarding their planned training to their assessors. An additional experimenter was designated to inform participants about their planned intervention and assist with any technical difficulties. All assessments were conducted remotely, except for 4 r-T2 assessments, which were collected from in-person evaluations within the clinic, as participants were due to be hospitalised again. This allowed to not miss follow up data from 4 participants. *Figure 11* provides a summary of the main experimental procedures.

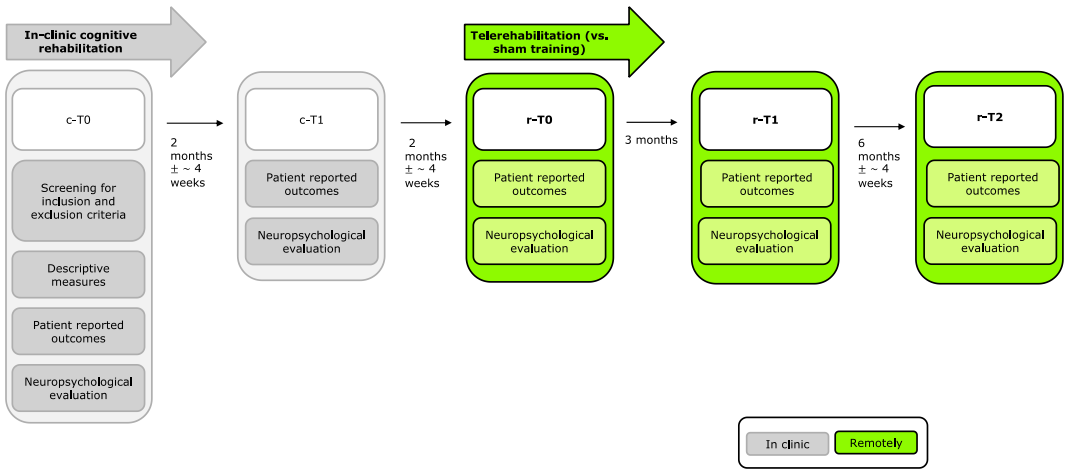


Figure 11. **Flowchart of the main experimental procedures**. This chart shows the procedure process from screening and recruitment to patient interactions in the clinic and the telerehabilitation component of the study. It details each appointment, including patient assessments and the types of data collected during these evaluations.

5.4 Variables and outcome measures

5.4.1 Variable measures

An initial screening involved the collection of general descriptive measures, such as date of birth, sex, gender, ethnic background, education, as well as clinical descriptive measures, such as MS specific diagnosis, disease duration and pharmacotherapy. Cognitive reserve was computed through the Cognitive Reserve Index questionnaire (CRIq) (Nucci et al., 2012), a tool which allows to estimate the cognitive reserve of a person by collecting information regarding one's adult life. It provides an estimate of total CRI, as well as school, work and free time CRIs. A score of ≤ 70 represents low CRI, a score of 70-84 a medium-low, a score of 85-114 medium, a score of 115-130 medium-high, while a score ≥ 130 high CRI. Disability status was scored from the EDSS (Kurtzke, 1983), a clinical rating scale used to quantify disability in MS (0 = normal neurological examination, 10 = death from MS).

5.4.2 Primary outcome measure

The primary outcome was the feasibility of home-based cognitive rehabilitation. The software used for telerehabilitation allowed to record precisely adherence to treatment in terms of minutes of actual completed training over planned minutes of

training for each participant in each session. Adherence to sham was also recorded in minutes based on participants' and caregivers' self-reports and the completion of planned activities.

5.4.3 Secondary outcome measures

5.4.3.1. Neuropsychological assessment

- MoCA (Conti et al., 2015; Nasreddine et al., 2005): A brief screening measure of global cognitive functioning, highly sensitive to mild cognitive impairment. It allows to quickly and accurately evaluate visuo-constructional abilities, executive functions, naming abilities, short term memory, attention, concentration, working memory, language and orientation to time and place. Scores are cumulative for each cognitive domain, with a total score of maximum 30. Higher scores indicate better cognitive performance.
- BICAMS (Benedict et al., 2012; Goretti et al., 2014): Short validated neuropsychological battery to measure most frequently affected cognitive domains in MS. It contains three neuropsychological tests: (1) the SDMT, a test measuring processing speed, attention and concentration and visuo-motor integration. It consists of a key legend of 9 different symbols paired with numbers from 1 to 9 and multiple rows of symbols paired with empty boxes. Participants are asked to complete the empty boxes as fast as possible by orally indicating the correct number paired with each symbol, in a given time (90 seconds). Scoring is based on the number of correct responses in 90 seconds, with higher scores indicating better cognitive performance; (2) the CVLT-II, measuring verbal learning and memory. It consists of a list of 16 words, belonging to 4 different semantic categories. The examiner reads the list of words multiple times (maximum 5), while participants are asked to remember and recall as many words as possible in each trial. Scoring is based on total number of correctly recalled words across trials, with higher scores indicating better cognitive performance; (3) the BVMT-R, measuring visuospatial learning and memory. It consists of six semi-geometric shapes, arranged in a 2x3 grid, presented to participants multiple times (3 maximum) for 10 seconds each time. At the end of each trial participants are asked to draw as many shapes as they can remember. Scoring is based on both accuracy and correct placement of shapes drawn, with highest scores indicating better cognitive performance.

- Stroop Test (Brugnolo et al., 2016; Stroop, 1935): A tool measuring selective attention, processing speed and executive functions, particularly a person's ability to inhibit cognitive interference and cognitive flexibility. It consists of three different trial conditions: (1) Word-reading, in which participants are simply asked to read a list of colour words (e.g., "red", "blue", "green") printed in black ink, allowing to record baseline reading speed; (2) Colour-naming, in which participants are asked to name the colour of a series of coloured squares (e.g., "red", "blue", "green"), allowing to record baseline colour naming; (3) Colour-word interference, in which participants view a list of colour words printed in colours that do not match the word (e.g. the word "red" written in "blue"), and have to name the colour of the ink in which the word is written, ignoring the meaning of the word itself (e.g. if the word "red" is written in "blue" participants will have to say "blue" to give the correct response). This allows to measure ability to inhibit automatic responses and block out cognitive interference. In each condition, participants are asked to respond as fast as possible, and scoring is based on both the number of correct responses (items) in a given time (30 seconds) and total time taken to complete each trail condition. A higher score on items and a lower score on time (faster execution of the test) indicate better cognitive performance.

5.4.3.2. PROMs

- Modified Fatigue Impact Scale (MFIS) (Fisk et al., 1994; Strober et al., 2020): A 21-item self-report scale measuring physical, cognitive, and psychosocial fatigue. Each item is rated on a 5-point Likert scale (0 = never to 4 = very often), indicating the frequency of the fatigue-related issue. Individual scores are summed to calculate overall score for each subscale, with higher scores indicating greater fatigue.
- Fatigue Severity Scale (FSS) (Krupp et al., 1989): A 9-item self-report scale measuring severity of fatigue and its impact on daily functioning. Each item is rated on a 7-point Likert scale (1 = strongly disagree to 7 = strongly agree). Higher scores indicate greater fatigue severity.
- Shortened version of the Multiple Sclerosis Quality of Life Scale (MSQOL-29) (Rosato et al., 2016): A 29-item self-report scale measuring health-related quality of life that considers several subdomains (body pain, emotional well-being, cognitive function, social function, energy, health distress, physical function, sexual function, health perceptions, overall quality of life, health

change). Each item is rated on a Likert scale, reflecting experiences over a specific time frame. Higher scores in each subcomponent (physical, mental, psychosocial) indicate better quality of life.

- Beck's Depression Inventory-II (BDI-II) (Beck et al., 1996): A widely used self-report inventory to measure the severity of depressive symptoms; contains items that assess both physical and affective/cognitive symptoms. Higher scoring indicates a greater presence of depressive symptoms.
- Patient Determined Disease Step (PDDS) (Learmonth et al., 2013; Rizzo et al., 2004): A self-reported disability scale to assess mobility level and functional impairment. Possible responses range from 0 (normal) to 8 (bedridden).
- System Usability Scale (SUS) (Bangor et al., 2008; Brooke, 1996): A 10-item rating scale to measure users' perceptions of usability across various domains, including software, applications, websites, and hardware devices. Items (e.g. "I found the system unnecessarily complex") are rated on a 5-point Likert scale (from 1 = Strongly Disagree to 5 = Strongly Agree). Higher scores indicate better usability of a tool. Administered only at r-T1 to participants in the intervention group to collect feedback about the use of the RehaCom software.

5.5 Telerehabilitation intervention

Remote cognitive rehabilitation was conducted using the RehaCom software (Hasomed GmbH, 2022), which has a license for home use. Rehacom is a cognitive rehabilitation software developed by HASOMED® GmbH certified with CE mark as a medical device. It can be installed on normal Windows PCs or Mac PCs with "VMWare Fusion" virtual machine, and it requires stable internet connection to be both downloaded and used. It includes more than 20 modules for the training of cognitive functions, it is easy to use, and the difficulty of the exercises is adaptive to the ongoing performance of participants to ensure optimal levels of training complexity, avoiding both boredom and frustration. Furthermore, the software allows for frequent and repetitive training, as well as the use of feedback, so that participants can better monitor their performance during cognitive exercises. The modules used in the study targeted the cognitive domains most frequently impaired in PwMS, namely attention, processing speed, memory and executive functions.

5.5.1 Attention and processing speed modules

- Attention and concentration: This module focuses on shape comparison. Participants are required to identify a figure from a series of options that exactly matches the displayed "comparison figure". This module trains selective attention, sustained attention and concentration.
- Divided Attention 2: Set in a driving simulator, participants must carefully monitor their surroundings, including the landscape and the car's dashboard, while also responding to various auditory cues. This module trains divided attention, but also strongly implies processing speed and executive components such as inhibition of irrelevant information, task-switching, planning and anticipation.

5.5.2 Memory modules

- Working Memory: Participants must retain in memory an increasing number of cards from a deck, which may contain visual or auditory content. They are then asked to recognise the memorised cards. This module trains the ability to memorise and manipulate information.
- Topological Memory: Participants are required to memorise the positions of cards displaying different images or geometric shapes. Once the cards are covered, they must recall the correct placement of each card based on their prior memorisation. This module trains visuospatial memory and learning.
- Physiognomic Memory: Participants must indicate whether they have previously seen the image of a face of a person and also match faces with names and professions. This module trains memory for faces.
- Verbal Memory: Participants view short stories on the screen, and they must memorise all the details presented, to correctly answer questions about the story's content later. This module trains learning and short-term verbal memory.

5.5.3 Executive modules

- Plan a Day: Participants must navigate a map to reach different locations according to a plan based on a list of activities. They have to arrange tasks in an optimal sequence and mark their appointments in a diary. This module trains planning, organisation skills and problem solving.

- Shopping: Participants receive a shopping list of items to find within a virtual supermarket and place in a shopping cart. This module trains working memory, practical organizational skills, problem solving, selective attention and impulse inhibition.

5.5.4 Training schedule

Sessions were organised so that training was repetitive, following the principles of cognitive rehabilitation to induce brain plasticity. Each month, participants engaged in 8 exercises focused on memory, 8 on attention, and 8 on executive functions, with the same exact schedule for each participant, following a specific calendar. Table 11 shows the monthly training schedule which was repeated for three months. Training was asynchronous and participants could decide autonomously the 3 days a week in which to perform it. However, for consistency, they were asked to maintain the same three days (e.g. Monday, Wednesday, Friday) throughout the whole course of the telerehabilitation. Occasional exceptions were allowed. Participants could also decide the time of day at which to perform the training to allow more flexibility.

Table 11. **RehaCom training schedule.** The table shows the weekly training schedule for RehaCom exercises, organised across four weeks. Each week includes three training days, featuring different cognitive tasks. Each session ranges from 20 to 25 minutes in duration. Tasks are rotated weekly to provide diverse cognitive challenges aimed at enhancing attention, memory, and planning skills. The four-week schedule is repeated three times, resulting in a total of 12 weeks of training. This structure allows for repetitive training.

Week number	**Day 1**	**Day 2**	**Day 3**	**Duration of exercises**
Week 1	Divided attention 2	Plan a day	Verbal memory	25 minutes
	Working memory	Attention and concentration	Shopping	20 minutes
Week 2	Divided attention 2	Shopping	Topological memory	25 minutes
	Physiognomic Memory	Attention and concentration	Plan a day	20 minutes
Week 3	Working memory	Attention and concentration	Shopping	25 minutes
	Divided attention 2	Plan a day	Verbal memory	20 minutes
Week 4	Physiognomic Memory	Attention and concentration	Plan a day	25 minutes

	Divided attention 2	Shopping	Topological memory	20 minutes

5.6 Sham activities

The sham treatment involved non-structured computerised activities using Microsoft Word, including reading and comprehension of journal articles, picture descriptions, easy sudokus and anagrams.

5.7 Data analysis

5.7.1 Main analysis

Comparisons between intervention and control group were conducted on baseline characteristics to ensure groups were comparable and no significant pre-existing differences would act as confounding variables. Descriptive statistics were reported as means ± SD for continuous variables, and as frequencies (n) for categorical variables. Group comparisons, instead, were performed using independent samples t-test or Welch's t-test (when assumption of equal variance was not met) for continuous variables, and Chi-square test for categorical variables.

Primary outcome feasibility was assessed in each group and throughout group comparison. Descriptive statistics, such as means, SD and percentages were computed for the actual hours of training, specifically examining the average of completed training hours for each group and the percentage of participants who completed a certain amount of scheduled training. An independent samples t-test was conducted to compare total training hours between intervention and control groups. To explore potential confounding effects of job status on training compliance, a secondary Welch's t-test was performed, comparing training hours between participants who were employed during the course of the study and those who were not. A complementary analysis looked at SUS scores distribution to determine usability of the RehaCom software.

Secondary outcome efficacy of training was assessed with Linear Mixed Models (LMM) analysis to account for the 2 ("Group") x 3 ("Time") mixed factorial design of the study. The LMM allowed to study the main effects of "Group" (Intervention Group; Control group) and "Time" (r-T0: assessment before training or sham; r-T1:

assessment immediately after training or sham; r-T2: assessment at the 6-months follow-up) on the neuropsychological variables of interest. Most importantly, LMM allowed to investigate main hypothesis regarding the interaction terms between "Group" and "Time". Specifically, LMM allowed to compare the intervention group to the control group, as well as the assessments r-T1 and r-T2 to the re-baseline assessment r-T0. Age and Education were added as covariates in the model. Random intercepts were also included to account for inter-individual variability. LMM was chosen over ANOVA due to its ability to provide an output of easier interpretation, handle better missing data, have greater statistical power and be less reliant on stringent assumptions (Hilbert et al., 2019). Effect sizes for the LMM were reported as standardised beta coefficients, alongside their corresponding 95% Confidence Intervals (CIs). This approach was also used to test any transfer effects to measures other than neuropsychological, namely the PROMs of interest.

When analysing baseline differences between groups on neuropsychological measures and PROMs, as well as when running LMM, control for Type I error, due to multiple comparisons, was done by employing the False Discovery Rate (FDR) adjustment method. This approach ensured balance between sensitivity and specificity when interpreting statistical significance across multiple tests. The significance level for all analyses was set at $p_{adjusted}<0.05$.

In addition to examining group-level differences, a RCI was conducted to assess the eventual presence of meaningful improvements at the level of the individual participants. This analysis was applied across both the intervention and control groups for most neuropsychological outcome measures. Necessary data for RCI analysis, including reliability coefficient (r) and SD values, were acquired from the appropriate normative data for MoCA (Pirani et al., 2022) and BICAMS subtests (Goretti et al., 2014). One the other hand, to the best of the author's knowledge, no recent r values from Italian validations were available for the Stroop test, which was therefore excluded from the RCI analysis. Significant improvements at the individual-level were determined by an RCI value ≥ 1.96.

Statistical analyses were performed using R Language statistical software (version 4.3.2), libraries "lme4" (Bates et al., 2015), "lmerTest" (Kuznetsova et al., 2017), "ggplot2" (Wickham, 2016) and "stats" (R Core Team, 2023), as well as Python programming language (version 3.13), library "matplotlib" (Hunter, 2007).

5.7.2 Post-hoc analysis

A 2x2 Analysis of Variance (ANOVA) was employed, accounting for the factor "Time" (before vs. after in-clinic cognitive rehabilitation) and "Group" (intervention vs. control groups) to see if PwMS improved from c-T0 to c-T1 on the neuropsychological tests of interest, as well as if any group differences were present, while accounting for the interaction terms. No correction for multiple comparisons was employed here given the exploratory a posteriori nature of these analysis, which were primarily targeted towards generating new hypotheses rather than confirming already existing ones. For this reason, the subsequent results should be interpreted with caution, and further confirmatory studies are required. The significance level for all analysis was set at $p<0.05$, and they were also performed using R Language statistical software.

5.8 Ethical considerations

The study was approved by the internal research committee of the Casa Cura Igea SpA in Milan (protocol number 928_2022).

6 References

Abdulhadi, E., Ireland, D., Simpson, R., Morrow, S. A., Le, E., Donkers, S., & Knox, K. B. (2020). *Cognitive Impairment: Non-pharmacological Rehabilitation Interventions*

Aguirre, N., Cruz-Gómez, Á. J., Miró-Padilla, A., Bueichekú, E., Broseta Torres, R., Ávila, C., Sanchis-Segura, C., & Forn, C. (2019). Repeated Working Memory Training Improves Task Performance and Neural Efficiency in Multiple Sclerosis Patients and Healthy Controls. *Multiple Sclerosis International*, *2019*(1), 2657902. https://doi.org/10.1155/2019/2657902

Amato, M., Goretti, B., Viterbo, R., Portaccio, E., Niccolai, C., Hakiki, B., Iaffaldano, P., & Trojano, M. (2014). Computer-assisted rehabilitation of attention in patients with multiple sclerosis: Results of a randomized, double-blind trial. *Multiple Sclerosis Journal*, *20*(1), 91–98. https://doi.org/10.1177/1352458513501571

Amato, M. P., Zipoli, V., & Portaccio, E. (2008). Cognitive changes in multiple sclerosis. *Expert Review of Neurotherapeutics*, *8*(10), 1585–1596. https://doi.org/10.1586/14737175.8.10.1585

American Psychiatric Association & American Psychiatric Association (Eds.). (2013). *Diagnostic and statistical manual of mental disorders: DSM-5* (5th ed). American Psychiatric Association

Arian Darestani, A., Naeeni Davarani, M., Hassani-Abharian, P., Zarrindast, M.-R., & Nasehi, M. (2020). The therapeutic effect of treatment with RehaCom software on verbal performance in patients with multiple sclerosis. *Journal of Clinical Neuroscience*, *72*, 93–97. https://doi.org/10.1016/j.jocn.2020.01.007

Arsoy, E., Tüzün, E., & Türkoğlu, R. (2018). Effects of computer-assisted cognitive rehabilitation in benign multiple sclerosis. *TURKISH JOURNAL OF MEDICAL SCIENCES*, *48*(5), 999–1005. https://doi.org/10.3906/sag-1803-53

Baddeley, A. (2003). Working memory and language: An overview. *Journal of Communication Disorders*, *36*(3), 189–208. https://doi.org/10.1016/S0021-9924(03)00019-4

Bangor, A., Kortum, P. T., & Miller, J. T. (2008). An Empirical Evaluation of the System Usability Scale. *International Journal of Human–Computer Interaction*, *24*(6), 574–594. https://doi.org/10.1080/10447310802205776

Baranzini, S. E., & Oksenberg, J. R. (2017). The Genetics of Multiple Sclerosis: From 0 to 200 in 50 Years. *Trends in Genetics*, *33*(12), 960–970. https://doi.org/10.1016/j.tig.2017.09.004

Bartels, C., Wegrzyn, M., Wiedl, A., Ackermann, V., & Ehrenreich, H. (2010). Practice effects in healthy adults: A longitudinal study on frequent repetitive cognitive testing. *BMC Neuroscience*, *11*, 1–12

Bates, D., Mächler, M., Bolker, B., & Walker, S. (2015). Fitting Linear Mixed-Effects Models Using lme4. *Journal of Statistical Software*, *67*(1), 1–48. https://doi.org/10.18637/jss.v067.i01

Beck, A. T., Steer, R. A., & Brown, G. (1996). Beck depression inventory–II. *Psychological Assessment*

Benedict, R. H., Amato, M. P., Boringa, J., Brochet, B., Foley, F., Fredrikson, S., Hamalainen, P., Hartung, H., Krupp, L., & Penner, I. (2012). Brief International Cognitive Assessment for MS (BICAMS): International standards for validation. *BMC Neurology*, *12*, 1–7

Benedict, R. H., Cookfair, D., Gavett, R., Gunther, M., Munschauer, F., Garg, N., & Weinstock-guttman, B. (2006). Validity of the minimal assessment of cognitive function in multiple sclerosis (MACFIMS). *Journal of the International Neuropsychological Society : JINS*, *12*(4), 549–558. https://www-proquest-com.sanraffaele.idm.oclc.org/docview/218862669/abstract/3FAD33C917354AF2PQ/1

Bjornevik, K., Cortese, M., Healy, B. C., Kuhle, J., Mina, M. J., Leng, Y., Elledge, S. J., Niebuhr, D. W., Scher, A. I., Munger, K. L., & Ascherio, A. (2022). Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis. *Science*, *375*(6578), 296–301. https://doi.org/10.1126/science.abj8222

Blair, M., Goveas, D., Safi, A., Marshall, C., Rosehart, H., Orenczuk, S., & Morrow, S. A. (2021). Does cognitive training improve attention/working memory in persons with MS? A pilot study using the Cogmed Working Memory Training program. *Multiple Sclerosis and Related Disorders*, *49*, 102770. https://doi.org/10.1016/j.msard.2021.102770

Bonavita, S., Sacco, R., Della Corte, M., Esposito, S., Sparaco, M., d'Ambrosio, A., Docimo, R., Bisecco, A., Lavorgna, L., Corbo, D., Cirillo, S., Gallo, A., Esposito, F., & Tedeschi, G. (2015). Computer-aided cognitive rehabilitation improves cognitive performances and induces brain functional connectivity changes in relapsing remitting multiple sclerosis patients: An exploratory study. *Journal of Neurology*, *262*(1), 91–100. https://doi.org/10.1007/s00415-014-7528-z

Boringa, J., Lazeron, R. H., Reuling, I. E., Ader, H., Pfennings, L. E., Lindeboom, J., De Sonneville, L. M., Kalkers, N., & Polman, C. (2001). The brief repeatable battery of neuropsychological tests: Normative values allow application in multiple sclerosis clinical practice. *Multiple Sclerosis Journal*, *7*(4), 263–267

Borkowska, A. R., Daniluk, B., & Adamczyk, K. (2021). Significance of the Diagnosis of Executive Functions in Patients with Relapsing-Remitting Multiple

Sclerosis. *International Journal of Environmental Research and Public Health*, *18*(19), Article 19. https://doi.org/10.3390/ijerph181910527

Boschetti, A., Maida, E., Dini, M., Tacchini, M., Gamberini, G., Comi, G., & Leocani, L. (2024). A Review on the Feasibility and Efficacy of Home-Based Cognitive Remediation in People with Multiple Sclerosis. *Journal of Clinical Medicine*, *13*(7), Article 7. https://doi.org/10.3390/jcm13071916

Brissart, H., Omorou, A. Y., Forthoffer, N., Berger, E., Moreau, T., De Seze, J., Morele, E., & Debouverie, M. (2020). Memory improvement in multiple sclerosis after an extensive cognitive rehabilitation program in groups with a multicenter double-blind randomized trial. *Clinical Rehabilitation*, *34*(6), 754–763. https://doi.org/10.1177/0269215520920333

Brisset, J.-C., Vukusic, S., & Cotton, F. (2021). Update on brain MRI for the diagnosis and follow-up of MS patients. *La Presse Médicale*, *50*(2), 104067. https://doi.org/10.1016/j.lpm.2021.104067

Brochet, B. (2022). Cognitive Rehabilitation in Multiple Sclerosis in the Period from 2013 and 2021: A Narrative Review. *Brain Sciences*, *12*(1), Article 1. https://doi.org/10.3390/brainsci12010055

Brooke, J. (1996). SUS-A quick and dirty usability scale. *Usability Evaluation in Industry*, *189*(194), 4–7

Brugnolo, A., De Carli, F., Accardo, J., Amore, M., Bosia, L. E., Bruzzaniti, C., Cappa, S. F., Cocito, L., Colazzo, G., Ferrara, M., Ghio, L., Magi, E., Mancardi, G. L., Nobili, F., Pardini, M., Rissotto, R., Serrati, C., & Girtler, N. (2016). An updated Italian normative dataset for the Stroop color word test (SCWT). *Neurological Sciences*, *37*(3), 365–372. https://doi.org/10.1007/s10072-015-2428-2

Buchanan, R. J., Stuifbergen, A., Chakravorty, B. J., Wang, S., Zhu, L., & Kim, M. (2006). Urban/Rural Differences in Access and Barriers to Health Carefor People with Multiple Sclerosis. *Journal of Health and Human Services Administration*, *29*(3), 360–375. https://www.jstor.org/stable/25790698

Cagnin, A., Jelcic, N., Agostini, M., Meneghello, F., Parise, S., Galano, A., Tonin, P., Dam, M., & Busse, C. (2014). Feasibility and efficacy of cognitive telerehabilitation in

early Alzheimer’s disease: A pilot study. *Clinical Interventions in Aging*, 1605. https://doi.org/10.2147/CIA.S68145

Campbell, J., Langdon, D., Cercignani, M., & Rashid, W. (2016a). A randomised controlled trial of efficacy of cognitive rehabilitation in multiple sclerosis: A cognitive, behavioural, and MRI study. *Neural Plasticity*, *2016*

Campbell, J., Langdon, D., Cercignani, M., & Rashid, W. (2016b). A Randomised Controlled Trial of Efficacy of Cognitive Rehabilitation in Multiple Sclerosis: A Cognitive, Behavioural, and MRI Study. *Neural Plasticity*, *2016*, 1–9. https://doi.org/10.1155/2016/4292585

Cerasa, A., Gioia, M. C., Valentino, P., Nisticò, R., Chiriaco, C., Pirritano, D., Tomaiuolo, F., Mangone, G., Trotta, M., Talarico, T., Bilotti, G., & Quattrone, A. (2013). Computer-Assisted Cognitive Rehabilitation of Attention Deficits for Multiple Sclerosis: A Randomized Trial With fMRI Correlates. *Neurorehabilitation and Neural Repair*, *27*(4), 284–295. https://doi.org/10.1177/1545968312465194

Charvet, L. E., Yang, J., Shaw, M. T., Sherman, K., Haider, L., Xu, J., & Krupp, L. B. (2017). Cognitive function in multiple sclerosis improves with telerehabilitation: Results from a randomized controlled trial. *PLOS ONE*, *12*(5), e0177177. https://doi.org/10.1371/journal.pone.0177177

Charvet, L., Shaw, M., Haider, L., Melville, P., & Krupp, L. (2015a). Remotely-delivered cognitive remediation in multiple sclerosis (MS): Protocol and results from a pilot study. *Multiple Sclerosis Journal - Experimental, Translational and Clinical*, *1*, 2055217315609629. https://doi.org/10.1177/2055217315609629

Charvet, L., Shaw, M., Haider, L., Melville, P., & Krupp, L. (2015b). Remotely-delivered cognitive remediation in multiple sclerosis (MS): Protocol and results from a pilot study. *Multiple Sclerosis Journal - Experimental, Translational and Clinical*, *1*, 2055217315609629. https://doi.org/10.1177/2055217315609629

Chen, M. H., Goverover, Y., Genova, H. M., & DeLuca, J. (2020). Cognitive Efficacy of Pharmacologic Treatments in Multiple Sclerosis: A Systematic Review. *CNS Drugs*, *34*(6), 599–628. https://doi.org/10.1007/s40263-020-00734-4

Chiaravalloti, N. D., & DeLuca, J. (2008). Cognitive impairment in multiple sclerosis. *The Lancet Neurology*, *7*(12), 1139–1151. https://doi.org/10.1016/S1474-4422(08)70259-X

Chiaravalloti, N. D., Moore, N. B., Nikelshpur, O. M., & DeLuca, J. (2013). An RCT to treat learning impairment in multiple sclerosis: The MEMREHAB trial. *Neurology*, *81*(24), 2066–2072. https://doi.org/10.1212/01.wnl.0000437295.97946.a8

Chiaravalloti, N., Stojanovic-Radic, J., & Deluca, J. (2013). The role of speed versus working memory in predicting learning new information in multiple sclerosis. *Journal of Clinical and Experimental Neuropsychology*, *35*. https://doi.org/10.1080/13803395.2012.760537

Chiu, C., Bishop, M., Pionke, J. J., Strauser, D., & Santens, R. L. (2017). Barriers to the Accessibility and Continuity of Health-Care Services in People with Multiple Sclerosis: A Literature Review. *International Journal of MS Care*, *19*(6), 313–321. https://doi.org/10.7224/1537-2073.2016-016

Conti, S., Bonazzi, S., Laiacona, M., Masina, M., & Coralli, M. V. (2015). Montreal Cognitive Assessment (MoCA)-Italian version: Regression based norms and equivalent scores. *Neurological Sciences*, *36*(2), 209–214. https://doi.org/10.1007/s10072-014-1921-3

Coolidge, F. L., Middleton, P. A., Griego, J. A., & Schmidt, M. M. (1996). The effects of interference on verbal learning in multiple sclerosis. *Archives of Clinical Neuropsychology*, *11*(7), 605–611. https://doi.org/10.1016/0887-6177(95)00047-X

Cotter, J., Firth, J., Enzinger, C., Kontopantelis, E., Yung, A. R., Elliott, R., & Drake, R. J. (2016). Social cognition in multiple sclerosis: A systematic review and meta-analysis. *Neurology*, *87*(16), 1727–1736. https://doi.org/10.1212/WNL.0000000000003236

Darwish, H., Zeinoun, P., Farran, N., Ghusn, H., Yamout, B., & Khoury, S. J. (2022). The Brief International Cognitive Assessment in Multiple Sclerosis (BICAMS): Validation in Arabic and Lebanese Normative Values. *Journal of the International Neuropsychological Society*, *28*(1), 94–103. https://doi.org/10.1017/S1355617721000102

De Giglio, L., De Luca, F., Prosperini, L., Borriello, G., Bianchi, V., Pantano, P., & Pozzilli, C. (2015). A Low-Cost Cognitive Rehabilitation With a Commercial Video Game Improves Sustained Attention and Executive Functions in Multiple Sclerosis: A Pilot Study. *Neurorehabilitation and Neural Repair*, *29*(5), 453–461. https://doi.org/10.1177/1545968314554623

De Luca, R., Russo, M., Gasparini, S., Leonardi, S., Foti Cuzzola, M., Sciarrone, F., Zichittella, C., Sessa, E., Maggio, M. G., De Cola, M. C., & Calabrò, R. S. (2021). Do people with multiple sclerosis benefit from PC-based neurorehabilitation? A pilot study. *Applied Neuropsychology: Adult*, *28*(4), 427–435. https://doi.org/10.1080/23279095.2019.1650747

Deluca, J., Barbieri-berger, S., & Johnson, S. K. (1994). The nature of memory impairments in multiple sclerosis: Acquisition versus retrieval. *Journal of Clinical and Experimental Neuropsychology*, *16*(2), 183–189. https://doi.org/10.1080/01688639408402629

Deluca, J., Chelune, G., Tulsky, D., Lengenfelder, J., & Chiaravalloti, N. (2004). Is Speed of Processing or Working Memory the Primary Information Processing Deficit in Multiple Sclerosis? *Journal of Clinical and Experimental Neuropsychology*, *26*, 550–562. https://doi.org/10.1080/13803390490496641

Demaree, H., Gaudino, E., Deluca, J., & Ricker, J. (2001). Learning Impairment is Associated With Recall Ability in Multiple Sclerosis. *Journal of Clinical and Experimental Neuropsychology*, *22*, 865–873. https://doi.org/10.1076/jcen.22.6.865.961

D'Esposito, M., Onishi, K., Thompson, H., Robinson, K., Armstrong, C., & Grossman, M. (1996). Working memory impairments in multiple sclerosis: Evidence from a dual-task paradigm. *Neuropsychology*, *10*(1), 51. https://psycnet.apa.org/journals/neu/10/1/51/

Dini, M., Gamberini, G., Tacchini, M., Boschetti, A., Gradassi, A., Chiveri, L., Rodegher, M., Comi, G., & Leocani, L. (2025). Development and validation of an electronic Symbol-Digit Modalities Test for remote monitoring of people with multiple sclerosis. *European Journal of Neurology*, *32*(1), e16454. https://doi.org/10.1111/ene.16454

Doig, G. S., & Simpson, F. (2005). Randomization and allocation concealment: A practical guide for researchers. *Journal of Critical Care*, *20*(2), 187–191

Dulau, C., Deloire, M., Diaz, H., Saubusse, A., Charre-Morin, J., Prouteau, A., & Brochet, B. (2017). Social cognition according to cognitive impairment in different clinical phenotypes of multiple sclerosis. *Journal of Neurology*, *264*(4), 740–748. https://doi.org/10.1007/s00415-017-8417-z

EFENDİ, H. (2015). Clinically Isolated Syndromes: Clinical Characteristics, Differential Diagnosis, and Management. *Nöro Psikiyatri Arşivi*, *52*(Suppl 1), S1–S11. https://doi.org/10.5152/npa.2015.12608

Filippi, M., Riccitelli, G., Mattioli, F., Capra, R., Stampatori, C., Pagani, E., Valsasina, P., Copetti, M., Falini, A., Comi, G., & Rocca, M. A. (2012a). Multiple Sclerosis: Effects of Cognitive Rehabilitation on Structural and Functional MR Imaging Measures—An Explorative Study. *Radiology*, *262*(3), 932–940. https://doi.org/10.1148/radiol.11111299

Filippi, M., Riccitelli, G., Mattioli, F., Capra, R., Stampatori, C., Pagani, E., Valsasina, P., Copetti, M., Falini, A., Comi, G., & Rocca, M. A. (2012b). Multiple Sclerosis: Effects of Cognitive Rehabilitation on Structural and Functional MR Imaging Measures—An Explorative Study. *Radiology*, *262*(3), 932–940. https://doi.org/10.1148/radiol.11111299

Fink, F., Rischkau, E., Butt, M., Klein, J., Eling, P., & Hildebrandt, H. (2010). Efficacy of an executive function intervention programme in MS: A placebo-controlled and pseudo-randomized trial. *Multiple Sclerosis Journal*, *16*(9), 1148–1151. https://doi.org/10.1177/1352458510375440

Fischer, M., Kunkel, A., Bublak, P., Faiss, J. H., Hoffmann, F., Sailer, M., Schwab, M., Zettl, U. K., & Köhler, W. (2014). How reliable is the classification of cognitive impairment across different criteria in early and late stages of multiple sclerosis? *Journal of the Neurological Sciences*, *343*(1–2), 91–99. https://doi.org/10.1016/j.jns.2014.05.042

Flavia, M., Stampatori, C., Zanotti, D., Parrinello, G., & Capra, R. (2010). Efficacy and specificity of intensive cognitive rehabilitation of attention and executive

functions in multiple sclerosis. *Journal of the Neurological Sciences*, *288*(1–2), 101–105. https://doi.org/10.1016/j.jns.2009.09.024

Ghasemi, N., Razavi, S., & Nikzad, E. (2017). Multiple Sclerosis: Pathogenesis, Symptoms, Diagnoses and Cell-Based Therapy. *Cell Journal (Yakhteh)*, *19*(1), 1–10. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5241505/

Gich, J., Salavedra-Pont, J., Coll-Martinez, C., Quintana, E., Álvarez-Bravo, G., Robles-Cedeño, R., Buxó, M., Contreras-Rodriguez, O., & Ramió-Torrentà, L. (2024). The nature of memory impairment in multiple sclerosis: Understanding different patterns over the course of the disease. *Frontiers in Psychology*, *14*, 1269794. https://doi.org/10.3389/fpsyg.2023.1269794

Gilbert, S. J., & Burgess, P. W. (2008). Executive function. *Current Biology*, *18*(3), R110–R114

Gonzalez-Rosa, J. J., Vazquez-Marrufo, M., Vaquero, E., Duque, P., Borges, M., Gamero, M. A., Gomez, C. M., & Izquierdo, G. (2006). Differential cognitive impairment for diverse forms of multiple sclerosis. *BMC Neuroscience*, *7*, 39. https://doi.org/10.1186/1471-2202-7-39

Goretti, B., Niccolai, C., Hakiki, B., Sturchio, A., Falautano, M., Minacapelli, E., Martinelli, V., Incerti, C., Nocentini, U., Murgia, M., Fenu, G., Cocco, E., Marrosu, M. G., Garofalo, E., Ambra, F. I., Maddestra, M., Consalvo, M., Viterbo, R. G., Trojano, M., … Amato, M. P. (2014a). The brief international cognitive assessment for multiple sclerosis (BICAMS): Normative values with gender, age and education corrections in the Italian population. *BMC Neurology*, *14*(1), 171. https://doi.org/10.1186/s12883-014-0171-6

Goretti, B., Niccolai, C., Hakiki, B., Sturchio, A., Falautano, M., Minacapelli, E., Martinelli, V., Incerti, C., Nocentini, U., Murgia, M., Fenu, G., Cocco, E., Marrosu, M. G., Garofalo, E., Ambra, F. I., Maddestra, M., Consalvo, M., Viterbo, R. G., Trojano, M., … Amato, M. P. (2014b). The brief international cognitive assessment for multiple sclerosis (BICAMS): Normative values with gender, age and education corrections in the Italian population. *BMC Neurology*, *14*(1), 171. https://doi.org/10.1186/s12883-014-0171-6

Goverover, Y., Chiaravalloti, N. D., O'Brien, A. R., & DeLuca, J. (2018). Evidenced-Based Cognitive Rehabilitation for Persons With Multiple Sclerosis: An Updated Review of the Literature From 2007 to 2016. *Archives of Physical Medicine and Rehabilitation*, *99*(2), 390–407. https://doi.org/10.1016/j.apmr.2017.07.021

Hancock, L. M., Bruce, J. M., Bruce, A. S., & Lynch, S. G. (2015). Processing speed and working memory training in multiple sclerosis: A double-blind randomized controlled pilot study. *Journal of Clinical and Experimental Neuropsychology*, *37*(2), 113–127. https://doi.org/10.1080/13803395.2014.989818

Hanssen, K., Beiske, A., Landrø, N., Hofoss, D., & Hessen, E. (2016). Cognitive rehabilitation in multiple sclerosis: A randomized controlled trial. *Acta Neurologica Scandinavica*, *133*(1), 30–40

Hasomed GmbH. (2022). *RehaCom* (Version 6.10.3.0) [Computer software].

Hatcher-Martin, J. M., Adams, J. L., Anderson, E. R., Bove, R., Burrus, T. M., Chehrenama, M., Dolan O'Brien, M., Eliashiv, D. S., Erten-Lyons, D., Giesser, B. S., Moo, L. R., Narayanaswami, P., Rossi, M. A., Soni, M., Tariq, N., Tsao, J. W., Vargas, B. B., Vota, S. A., Wessels, S. R., … Govindarajan, R. (2020). Telemedicine in neurology. *Neurology*, *94*(1), 30–38. https://doi.org/10.1212/WNL.0000000000008708

Hedström, A., Bäärnhielm, M., Olsson, T., & Alfredsson, L. (2011). Exposure to environmental tobacco smoke is associated with increased risk for multiple sclerosis. *Multiple Sclerosis (Houndmills, Basingstoke, England)*, *17*, 788–793. https://doi.org/10.1177/1352458511399610

Hedström, A. K., Bäärnhielm, M., Olsson, T., & Alfredsson, L. (2009). Tobacco smoking, but not Swedish snuff use, increases the risk of multiple sclerosis. *Neurology*, *73*(9), 696–701. https://doi.org/10.1212/WNL.0b013e3181b59c40

Hilbert, S., Stadler, M., Lindl, A., Naumann, F., & Bühner, M. (2019). Analyzing longitudinal intervention studies with linear mixed models. *TPM - Testing, Psychometrics, Methodology in Applied Psychology*, *26*, 101–119. https://doi.org/10.4473/TPM26.1.6

Hildebrandt, H., Lanz, M., Hahn, H. K., Hoffmann, E., Schwarze, B., Schwendemann, G., & Kraus, J. A. (2007). Cognitive training in MS: Effects and

relation to brain atrophy. *Restorative Neurology and Neuroscience*, *25*(1), 33–43. https://content.iospress.com/articles/restorative-neurology-and-neuroscience/rnn00365

Hosseiny, M., Newsome, S. D., & Yousem, D. M. (2020). Radiologically Isolated Syndrome: A Review for Neuroradiologists. *AJNR: American Journal of Neuroradiology*, *41*(9), 1542–1549. https://doi.org/10.3174/ajnr.A6649

Hunter, J. D. (2007). Matplotlib: A 2D graphics environment. *Computing in Science & Engineering*, *9*(03), 90–95

Inglese, M., & Bester, M. (2010). Diffusion imaging in multiple sclerosis: Research and clinical implications. *NMR in Biomedicine*, *23*(7), 865–872. https://doi.org/10.1002/nbm.1515

Kesler, S. R., Adams, H. F., Blasey, C. M., & Bigler, E. D. (2003). Premorbid Intellectual Functioning, Education, and Brain Size in Traumatic Brain Injury: An Investigation of the Cognitive Reserve Hypothesis. *Applied Neuropsychology*, *10*(3), 153–162. https://doi.org/10.1207/S15324826AN1003_04

Koch-Henriksen, N., & Magyari, M. (2021). Apparent changes in the epidemiology and severity of multiple sclerosis. *Nature Reviews Neurology*, *17*, 1–13. https://doi.org/10.1038/s41582-021-00556-y

Kroll, T., Jones, G. C., Kehn, M., & Neri, M. T. (2006). Barriers and strategies affecting the utilisation of primary preventive services for people with physical disabilities: A qualitative inquiry. *Health & Social Care in the Community*, *14*(4), 284–293

Krupp, L. B., LaRocca, N. G., Muir-Nash, J., & Steinberg, A. D. (1989). The fatigue severity scale: Application to patients with multiple sclerosis and systemic lupus erythematosus. *Archives of Neurology*, *46*(10), 1121–1123

Kurtzke, J. F. (1983). Rating neurologic impairment in multiple sclerosis: An expanded disability status scale (EDSS). *Neurology*, *33*(11), 1444–1444

Kuznetsova, A., Brockhoff, P. B., & Christensen, R. H. B. (2017). lmerTest Package: Tests in Linear Mixed Effects Models. *Journal of Statistical Software*, *82*(13), 1–26. https://doi.org/10.18637/jss.v082.i13

Lamargue, D., Koubiyr, I., Deloire, M., Saubusse, A., Charre-Morin, J., Moroso, A., Coupé, P., Brochet, B., & Ruet, A. (2020). Effect of cognitive rehabilitation on neuropsychological and semiecological testing and on daily cognitive functioning in multiple sclerosis: The REACTIV randomized controlled study. *Journal of the Neurological Sciences*, *415*, 116929. https://doi.org/10.1016/j.jns.2020.116929

Lawson, D. W., Stolwyk, R. J., Ponsford, J. L., Baker, K. S., Tran, J., & Wong, D. (2022). Acceptability of telehealth in post-stroke memory rehabilitation: A qualitative analysis. *Neuropsychological Rehabilitation*, *32*(1), 1–21. https://doi.org/10.1080/09602011.2020.1792318

Leavitt, V. M., Wylie, G., Krch, D., Chiaravalloti, N., DeLuca, J., & Sumowski, J. F. (2014). Does slowed processing speed account for executive deficits in multiple sclerosis? Evidence from neuropsychological performance and structural neuroimaging. *Rehabilitation Psychology*, *59*(4), 422–428. https://doi.org/10.1037/a0037517

Litvan, I., Grafman, J., Vendrell, P., Martinez, J. M., Junqué, C., Vendrell, J. M., & Barraquer-Bordas, J. L. (1988). Multiple Memory Deficits in Patients With Multiple Sclerosis: Exploring the Working Memory System. *Archives of Neurology*, *45*(6), 607–610. https://doi.org/10.1001/archneur.1988.00520300025012

Liu, R., Du, S., Zhao, L., Jain, S., Sahay, K., Rizvanov, A., Lezhnyova, V., Khaibullin, T., Martynova, E., Khaiboullina, S., & Baranwal, M. (2022). Autoreactive lymphocytes in multiple sclerosis: Pathogenesis and treatment target. *Frontiers in Immunology*, *13*, 996469. https://doi.org/10.3389/fimmu.2022.996469

Lucas, R. M., Byrne, S. N., Correale, J., Ilschner, S., & Hart, P. H. (2015). Ultraviolet radiation, vitamin D and multiple sclerosis. *Neurodegenerative Disease Management*, *5*(5), 413–424. https://doi.org/10.2217/nmt.15.33

Macías Islas, M. Á., & Ciampi, E. (2019). Assessment and Impact of Cognitive Impairment in Multiple Sclerosis: An Overview. *Biomedicines*, *7*(1), Article 1. https://doi.org/10.3390/biomedicines7010022

Mani, A., Chohedri, E., Ravanfar, P., Mowla, A., & Nikseresht, A. (2018). Efficacy of group cognitive rehabilitation therapy in multiple sclerosis. *Acta Neurologica Scandinavica*, *137*(6), 589–597. https://doi.org/10.1111/ane.12904

Martin, K.-J., Lincoln, N., das Nair, R., & Kneebone, I. (2014). Group-based memory rehabilitation for people with multiple sclerosis: Subgroup analysis of the ReMiND trial. *International Journal of Therapy and Rehabilitation*, *21*(12), 590–596. https://doi.org/10.12968/ijtr.2014.21.12.590

Mattioli, F., Bellomi, F., Stampatori, C., Provinciali, L., Compagnucci, L., Uccelli, A., Pardini, M., Santuccio, G., Fregonese, G., Pattini, M., Allegri, B., Clerici, R., Lattuada, A., Montomoli, C., Corso, B., Gallo, P., Riccardi, A., Ghezzi, A., Roscio, M., … Capra, R. (2016). Two Years Follow up of Domain Specific Cognitive Training in Relapsing Remitting Multiple Sclerosis: A Randomized Clinical Trial. *Frontiers in Behavioral Neuroscience*, *10*. https://doi.org/10.3389/fnbeh.2016.00028

Mattioli, F., Stampatori, C., Scarpazza, C., Parrinello, G., & Capra, R. (2012). Persistence of the effects of attention and executive functions intensive rehabilitation in relapsing remitting multiple sclerosis. *Multiple Sclerosis and Related Disorders*, *1*(4), 168–173. https://doi.org/10.1016/j.msard.2012.06.004

McDoom, M. M., Koppelman, E., & Drainoni, M.-L. (2014). Barriers to accessible health care for medicaid eligible people with disabilities: A comparative analysis. *Journal of Disability Policy Studies*, *25*(3), 154–163

McGinley, M. P., Goldschmidt, C. H., & Rae-Grant, A. D. (2021). Diagnosis and Treatment of Multiple Sclerosis: A Review. *JAMA*, *325*(8), 765. https://doi.org/10.1001/jama.2020.26858

Messinis, L., Kosmidis, M. H., Nasios, G., Konitsiotis, S., Ntoskou, A., Bakirtzis, C., Grigoriadis, N., Patrikelis, P., Panagiotopoulos, E., Gourzis, P., Malefaki, S., & Papathanasopoulos, P. (2020). Do Secondary Progressive Multiple Sclerosis patients benefit from Computer- based cognitive neurorehabilitation? A randomized sham controlled trial. *Multiple Sclerosis and Related Disorders*, *39*, 101932. https://doi.org/10.1016/j.msard.2020.101932

Messinis, L., Nasios, G., Kosmidis, M. H., Zampakis, P., Malefaki, S., Ntoskou, K., Nousia, A., Bakirtzis, C., Grigoriadis, N., Gourzis, P., & Papathanasopoulos, P. (2017). Efficacy of a Computer-Assisted Cognitive Rehabilitation Intervention in Relapsing-Remitting Multiple Sclerosis Patients: A Multicenter Randomized Controlled Trial. *Behavioural Neurology*, *2017*, 1–17. https://doi.org/10.1155/2017/5919841

Minden, S. L., Frankel, D., Hadden, L., & Hoaglin, D. C. (2007). Access to health care for people with multiple sclerosis. *Multiple Sclerosis Journal*, *13*(4), 547–558. https://doi.org/10.1177/1352458506071306

Mitchell, A. J., Benito-León, J., González, J.-M. M., & Rivera-Navarro, J. (2005). Quality of life and its assessment in multiple sclerosis: Integrating physical and psychological components of wellbeing. *The Lancet Neurology*, *4*(9), 556–566. https://doi.org/10.1016/S1474-4422(05)70166-6

Mitolo, M., Venneri, A., Wilkinson, I. D., & Sharrack, B. (2015). Cognitive rehabilitation in multiple sclerosis: A systematic review. *Journal of the Neurological Sciences*, *354*(1), 1–9. https://doi.org/10.1016/j.jns.2015.05.004

Mondini, S., Mapelli, D., & Bisiacchi, P. (2003). *Esame neuropsicologico breve*.

Morrison, E. H., George, V., & Mosqueda, L. (2008). Primary care for adults with physical disabilities: Perceptions from consumer and provider focus groups. *Family Medicine*, *40*(9), 645–651. https://escholarship.org/uc/item/84d223gt

Munger, K. L., Levin, L. I., Hollis, B. W., Howard, N. S., & Ascherio, A. (2006). Serum 25-Hydroxyvitamin D Levels and Risk of Multiple Sclerosis. *JAMA*, *296*(23), 2832–2838. https://doi.org/10.1001/jama.296.23.2832

Naeeni Davarani, M., Arian Darestani, A., Hassani-Abharian, P., Vaseghi, S., Zarrindast, M.-R., & Nasehi, M. (2022). RehaCom rehabilitation training improves a wide-range of cognitive functions in multiple sclerosis patients. *Applied Neuropsychology: Adult*, *29*(2), 262–272. https://doi.org/10.1080/23279095.2020.1747070

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., Cummings, J. L., & Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society*, *53*(4), 695–699

Nucci, M., Mapelli, D., & Mondini, S. (2012). Cognitive Reserve Index questionnaire (CRIq): A new instrument for measuring cognitive reserve. *Aging Clinical and Experimental Research*, *24*(3), 218–226. https://doi.org/10.1007/BF03654795

O'Connell, K., Langdon, D., Tubridy, N., Hutchinson, M., & McGuigan, C. (2015). A preliminary validation of the brief international cognitive assessment for multiple

sclerosis (BICAMS) tool in an Irish population with multiple sclerosis (MS). *Multiple Sclerosis and Related Disorders*, *4*(6), 521–525. https://doi.org/10.1016/j.msard.2015.07.012

Okuda, D. T., Mowry, E. M., Beheshtian, A., Waubant, E., Baranzini, S. E., Goodin, D. S., Hauser, S. L., & Pelletier, D. (2009). Incidental MRI anomalies suggestive of multiple sclerosis. *Neurology*, *72*(9), 800–805. https://doi.org/10.1212/01.wnl.0000335764.14513.1°

Olsson, T., Barcellos, L. F., & Alfredsson, L. (2017). Interactions between genetic, lifestyle and environmental risk factors for multiple sclerosis. *Nature Reviews Neurology*, *13*(1), 25–36. https://doi.org/10.1038/nrneurol.2016.187

Orton, S.-M., Wald, L., Confavreux, C., Vukusic, S., Krohn, J. P., Ramagopalan, S. V., Herrera, B. M., Sadovnick, A. D., & Ebers, G. C. (2011). Association of UV radiation with multiple sclerosis prevalence and sex ratio in France. *Neurology*, *76*(5), 425–431. https://doi.org/10.1212/WNL.0b013e31820a0a9f

Ozakbas, S., Cagiran, I., Ormeci, B., & Idiman, E. (2004). Correlations between multiple sclerosis functional composite, expanded disability status scale and health-related quality of life during and after treatment of relapses in patients with multiple sclerosis. *Journal of the Neurological Sciences*, *218*(1), 3–7. https://doi.org/10.1016/j.jns.2003.09.015

Parisi, L., Rocca, M. A., Mattioli, F., Copetti, M., Capra, R., Valsasina, P., Stampatori, C., & Filippi, M. (2014). Changes of brain resting state functional connectivity predict the persistence of cognitive rehabilitation effects in patients with multiple sclerosis. *Multiple Sclerosis Journal*, *20*(6), 686–694. https://doi.org/10.1177/1352458513505692

Pedullà, L., Brichetto, G., Tacchino, A., Vassallo, C., Zaratin, P., Battaglia, M. A., Bonzano, L., & Bove, M. (2016). Adaptive vs. non-adaptive cognitive training by means of a personalized App: A randomized trial in people with multiple sclerosis. *Journal of NeuroEngineering and Rehabilitation*, *13*(1), 88. https://doi.org/10.1186/s12984-016-0193-y

Pennington, C. R., Oxtoby, M. C.-S.-Y., & Shaw, D. J. (2023). Social cognitive disruptions in multiple sclerosis: The role of executive (dys) function. *Neuropsychology*

Peretti, A., Amenta, F., Tayebati, S. K., Nittari, G., & Mahdi, S. S. (2017). Telerehabilitation: Review of the State-of-the-Art and Areas of Application. *JMIR Rehabilitation and Assistive Technologies*, *4*(2), e7511. https://doi.org/10.2196/rehab.7511

Pirani, A., Nasreddine, Z., Neviani, F., Fabbo, A., Rocchi, M. B., Bertolotti, M., Tulipani, C., Galassi, M., Belvederi Murri, M., & Neri, M. (n.d.). MoCA 7.1: Multicenter Validation of the First Italian Version of Montreal Cognitive Assessment. *Journal of Alzheimer's Disease Reports*, *6*(1), 509–520. https://doi.org/10.3233/ADR-210053

Polychroniadou, E., Bakirtzis, C., Langdon, D., Lagoudaki, R., Kesidou, E., Theotokis, P., Tsalikakis, D., Poulatsidou, K., Kyriazis, O., Boziki, M., Papadopoulos, G., Boura, E., Sintila, L., Hatzigeorgiou, S., Ziamos, C., Ioannidis, P., Karacostas, D., & Grigoriadis, N. (2016). Validation of the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) in Greek population with multiple sclerosis. *Multiple Sclerosis and Related Disorders*, *9*, 68–72. https://doi.org/10.1016/j.msard.2016.06.011

Pusswald, G., Mildner, C., Zebenholzer, K., Auff, E., & Lehrner, J. (2014). A neuropsychological rehabilitation program for patients with Multiple Sclerosis based on the model of the ICF. *NeuroRehabilitation*, *35*(3), 519–527. https://doi.org/10.3233/NRE-141145

Rao, S. M., Grafman, J., DiGiulio, D., Mittenberg, W., Bernardin, L., Leo, G. J., Luchetta, T., & Unverzagt, F. (1993). Memory dysfunction in multiple sclerosis: Its relation to working memory, semantic encoding, and implicit learning. *Neuropsychology*, *7*(3), 364–374. https://doi.org/10.1037/0894-4105.7.3.364

Rao, S. M., Leo, G. J., Ellington, L., Nauertz, T., Bernardin, L., & Unverzagt, F. (1991). Cognitive dysfunction in multiple sclerosis.: II. Impact on employment and social functioning. *Neurology*, *41*(5), 692–696. https://doi.org/10.1212/WNL.41.5.692

Remy, C., Valet, M., Stoquart, G., El Sankari, S., Van Pesch, V., De Haan, A., & Lejeune, T. (2020). Telecommunication and rehabilitation for patients with multiple sclerosis: Access and willingness to use. A cross-sectional study. *European Journal of Physical and Rehabilitation Medicine*, *56*(4). https://doi.org/10.23736/S1973-9087.20.06061-X

Rilo, O., Peña, J., Ojeda, N., Rodríguez-Antigüedad, A., Mendibe-Bilbao, M., Gómez-Gastiasoro, A., DeLuca, J., Chiaravalloti, N., & Ibarretxe-Bilbao, N. (2018). Integrative group-based cognitive rehabilitation efficacy in multiple sclerosis: A randomized clinical trial. *Disability and Rehabilitation*, *40*(2), 208–216. https://doi.org/10.1080/09638288.2016.1250168

Rodrigues, P., da Silva, B., & Trevisan, G. (2023). A systematic review and meta-analysis of neuropathic pain in multiple sclerosis: Prevalence, clinical types, sex dimorphism, and increased depression and anxiety symptoms. *Neuroscience & Biobehavioral Reviews*, *154*, 105401. https://doi.org/10.1016/j.neubiorev.2023.105401

Rogante, M., Grigioni, M., Cordella, D., & Giacomozzi, C. (2010). Ten years of telerehabilitation: A literature overview of technologies and clinical applications. *NeuroRehabilitation*, *27*(4), 287–304. https://doi.org/10.3233/NRE-2010-0612

Rosti-Otajärvi, E. M., & Hämäläinen, P. I. (2014). Neuropsychological rehabilitation for multiple sclerosis. *Cochrane Database of Systematic Reviews*. https://doi.org/10.1002/14651858.CD009131.pub3

Ruano, L., Portaccio, E., Goretti, B., Niccolai, C., Severo, M., Patti, F., Cilia, S., Gallo, P., Grossi, P., Ghezzi, A., Roscio, M., Mattioli, F., Stampatori, C., Trojano, M., Viterbo, R. G., & Amato, M. P. (2017). Age and disability drive cognitive impairment in multiple sclerosis across disease subtypes. *Multiple Sclerosis Journal*, *23*(9), 1258–1267. https://doi.org/10.1177/1352458516674367

Sachdev, P. S., Blacker, D., Blazer, D. G., Ganguli, M., Jeste, D. V., Paulsen, J. S., & Petersen, R. C. (2014). Classifying neurocognitive disorders: The DSM-5 approach. *Nature Reviews Neurology*, *10*(11), 634–642. https://doi.org/10.1038/nrneurol.2014.181

Scheer, J., Kroll, T., Neri, M. T., & Beatty, P. (2003). Access Barriers for Persons with Disabilities: The Consumer's Perspective. *Journal of Disability Policy Studies*, *13*(4), 221–230. https://doi.org/10.1177/104420730301300404

Schreiner, T.-G., & Genes, T.-M. (2021). Obesity and Multiple Sclerosis—A Multifaceted Association. *Journal of Clinical Medicine*, *10*(12), Article 12. https://doi.org/10.3390/jcm10122689

Schultheis, M. T., Garay, E., & DeLuca, J. (2001). The influence of cognitive impairment on driving performance in multiple sclerosis. *Neurology*, *56*(8), 1089–1094. https://doi.org/10.1212/WNL.56.8.1089

Schultheis, M. T., Garay, E., Millis, S. R., & DeLuca, J. (2002). Motor vehicle crashes and violations among drivers with multiple sclerosis. *Archives of Physical Medicine and Rehabilitation*, *83*(8), 1175–1178. https://doi.org/10.1053/apmr.2002.34279

Shatil, E., Metzer, A., Horvitz, O., & Miller, A. (2010). Home-based personalized cognitive training in MS patients: A study of adherence and cognitive performance. *NeuroRehabilitation*, *26*(2), 143–153. https://doi.org/10.3233/NRE-2010-0546

Shevil, E., & Finlayson, M. (2006). Perceptions of persons with multiple sclerosis on cognitive changes and their impact on daily life. *Disability and Rehabilitation*, *28*(12), 779–788. https://doi.org/10.1080/09638280500387013

Soelberg Sorensen, P., Giovannoni, G., Montalban, X., Thalheim, C., Zaratin, P., & Comi, G. (2019). The Multiple Sclerosis Care Unit. *Multiple Sclerosis Journal*, *25*(5), 627–636. https://doi.org/10.1177/1352458518807082

Solari, A., Motta, A., Mendozzi, L., Pucci, E., Forni, M., Mancardi, G., & Pozzilli, C. (2004). Computer-aided retraining of memory and attention in people with multiple sclerosis: A randomized, double-blind controlled trial. *Journal of the Neurological Sciences*, *222*(1–2), 99–104. https://doi.org/10.1016/j.jns.2004.04.027

Soldan, S. S., & Lieberman, P. M. (2023). Epstein–Barr virus and multiple sclerosis. *Nature Reviews Microbiology*, *21*(1), 51–64. https://doi.org/10.1038/s41579-022-00770-5

Stern, Y. (2009). Cognitive reserve☆. *Neuropsychologia*, *47*(10), 2015–2028. https://doi.org/10.1016/j.neuropsychologia.2009.03.004

Stroop, J. R. (1935). Studies of interference in serial verbal reactions. *Journal of Experimental Psychology*, *18*(6), 643–662. https://doi.org/10.1037/h0054651

Taylor, L. A., Mhizha-Murira, J. R., Smith, L., Potter, K.-J., Wong, D., Evangelou, N., Lincoln, N. B., & das Nair, R. (2021). Memory rehabilitation for people with multiple sclerosis. *Cochrane Database of Systematic Reviews*, *10*

Team, R. C. (2020). RA language and environment for statistical computing, R Foundation for Statistical. *Computing*

Tesar, N., Bandion, K., & Baumhackl, U. (2005). Efficacy of a neuropsychological training programme for patients with multiple sclerosis – a randomised controlled trial. *Wiener Klinische Wochenschrift*, *117*(21–22), 747–754. https://doi.org/10.1007/s00508-005-0470-4

Thompson, A. J., Banwell, B. L., Barkhof, F., Carroll, W. M., Coetzee, T., Comi, G., Correale, J., Fazekas, F., Filippi, M., Freedman, M. S., Fujihara, K., Galetta, S. L., Hartung, H. P., Kappos, L., Lublin, F. D., Marrie, R. A., Miller, A. E., Miller, D. H., Montalban, X., … Cohen, J. A. (2018). Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *The Lancet Neurology*, *17*(2), 162–173. https://doi.org/10.1016/S1474-4422(17)30470-2

Tinnefeld, M., Treitz, F. H., Haase, C. G., Wilhelm, H., Daum, I., & Faustmann, P. M. (2005). Attention and memory dysfunctionsin mild multiple sclerosis. *European Archives of Psychiatry and Clinical Neuroscience*, *255*(5), 319–326. https://doi.org/10.1007/s00406-005-0565-y

Van Schependom, J., D'hooghe, M. B., Cleynhens, K., D'hooge, M., Haelewyck, M.-C., De Keyser, J., & Nagels, G. (2015). Reduced information processing speed as primum movens for cognitive decline in MS. *Multiple Sclerosis Journal*, *21*(1), 83–91. https://doi.org/10.1177/1352458514537012

Vargas, D., & Tyor, W. (2017). Update on Disease-Modifying Therapies for Multiple Sclerosis. *Journal of Investigative Medicine*, *65*, jim-2016. https://doi.org/10.1136/jim-2016-000339

Vilou, I., Bakirtzis, C., Artemiadis, A., Ioannidis, P., Papadimitriou, M., Konstantinopoulou, E., Aretouli, E., Messinis, L., Nasios, G., Dardiotis, E., Kosmidis,

M., & Grigoriadis, N. (2020). Computerized cognitive rehabilitation for treatment of cognitive impairment in multiple sclerosis: An explorative study. *Journal of Integrative Neuroscience*, *19*(2), Article 2. https://boris.unibe.ch/149357/

Vogt, A., Kappos, L., Calabrese, P., Stöcklin, M., Gschwind, L., Opwis, K., & Penner, I.-K. (2009). Working memory training in patients with multiple sclerosis – comparison of two different training schedules. *Restorative Neurology and Neuroscience*, *27*(3), 225–235. https://doi.org/10.3233/RNN-2009-0473

Walker, L. A. S., Osman, L., Berard, J. A., Rees, L. M., Freedman, M. S., MacLean, H., & Cousineau, D. (2016). Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS): Canadian contribution to the international validation project. *Journal of the Neurological Sciences*, *362*, 147–152. https://doi.org/10.1016/j.jns.2016.01.040

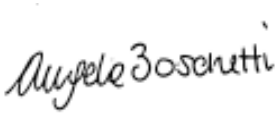
Walton, C., King, R., Rechtman, L., Kaye, W., Leray, E., Marrie, R. A., Robertson, N., La Rocca, N., Uitdehaag, B., Van Der Mei, I., Wallin, M., Helme, A., Angood Napier, C., Rijke, N., & Baneke, P. (2020). Rising prevalence of multiple sclerosis worldwide: Insights from the Atlas of MS, third edition. *Multiple Sclerosis Journal*, *26*(14), 1816–1821. https://doi.org/10.1177/1352458520970841

Wickham, H., & Wickham, H. (2016). *Data analysis*. Springer

Willer, C. J., Dyment, D. A., Risch, N. J., Sadovnick, A. D., Ebers, G. C., & The Canadian Collaborative Study Group. (2003). Twin concordance and sibling recurrence rates in multiple sclerosis. *Proceedings of the National Academy of Sciences*, *100*(22), 12877–12882. https://doi.org/10.1073/pnas.1932604100

Xiang, X. M., & Bernard, J. (2021). Telehealth in Multiple Sclerosis Clinical Care and Research. *Current Neurology and Neuroscience Reports*, *21*(4), 14. https://doi.org/10.1007/s11910-021-01103-4

Zucchella, C., Federico, A., Martini, A., Tinazzi, M., Bartolo, M., & Tamburin, S. (2018). Neuropsychological testing. *Practical Neurology*, *18*(3), 227–237.



7. Appendices

7.1 Appendix 1

Table 12. **Full LMM results for neuropsychological outcome measures**. The table shows LMM results presenting the effects of "Group", "Time", their interactions, and covariates age and education for the neuropsychological outcomes. For each predictor, the table includes the coefficient (b), standard error (SE), *t*-statistic, adjusted *p-value*, 95% confidence intervals (CIs), and standardised coefficients ($b_{standardised}$).

Montreal Cognitive Assessment (MoCA)						
Predictor	***b***	**SE**	***t***	$p_{adjusted}$	**95% CIs**	$b_{standardised}$
Group	-0.912	0.879	-1.038	*0.609*	[-1.14, 0.36]	-0.39
Time r-T1	0.200	0.773	0.259	*0.797*	[-0.57, 0.74]	0.09
Time r-T2	0.713	0.831	0.858	*0.633*	[-0.41, 1.01]	0.30
Group × r-T1	-0.400	0.997	-0.401	*0.789*	[-1.02, 0.68]	-0.17
Group × r-T2	0.749	1.087	0.689	*0.659*	[-0.61, 1.25]	0.32
Age	-0.069	0.037	-1.848	*0.210*	[-0.56, 0.02]	-0.27
Education	0.202	0.079	2.547	*0.075*	[0.08, 0.67]	0.37
Symbol Digit Modalities Test (SDMT)						
Predictor	***b***	**SE**	***t***	$p_{adjusted}$	**95% CIs**	$b_{standardised}$
Group	-2.744	4.227	-0.649	*0.835*	[-1.08, 0.55]	-0.27
Time r-T1	1.400	1.859	0.753	*0.835*	[-0.22, 0.50]	0.14
Time r-T2	5.942	2.021	2.940	***0.043****	[0.18, 0.97]	0.57
Group × r-T1	0.133	2.400	0.056	*0.956*	[-0.45, 0.48]	0.01
Group × r-T2	-6.697	2.646	-2.532	***0.047****	[-1.16, -0.14]	-0.65
Age	-0.036	0.222	-0.163	*0.956*	[-0.42, 0.36]	-0.03
Education	-0.031	0.474	-0.064	*0.956*	[-0.42, 0.38]	-0.01
California Verbal Learning Test-2º Edition (CVLT-II)						
Predictor	***b***	**SE**	***t***	$p_{adjusted}$	**95% CIs**	$b_{standardised}$
Group	-3.122	4.753	-0.657	*0.788*	[-1.08, 0.55]	-0.27
Time r-T1	1.600	3.147	0.508	*0.788*	[-0.40, 0.67]	0.14
Time r-T2	4.639	3.410	1.360	*0.483*	[-0.19, 0.98]	0.40

Group × r-T1	-1.600	4.063	-0.394	*0.788*	[-0.83, 0.56]	-0.14
Group × r-T2	1.206	4.462	0.270	*0.788*	[-0.66, 0.87]	0.10
Age	-0.125	0.230	-0.542	*0.788*	[-0.46, 0.26]	-0.10
Education	0.954	0.491	1.940	*0.266*	[-0.01, 0.72]	0.35

Brief Visuospatial Memory Test-Revised (BVMT-R)

Predictor	***b***	**SE**	***t***	$p_{adjusted}$	**95% CIs**	$b_{standardised}$
Group	-3.384	3.047	-1.110	*0.768*	[-1.27, 0.36]	-0.45
Time r-T1	-1.100	2.104	-0.523	*0.805*	[-0.71, 0.42]	-0.15
Time r-T2	0.597	2.277	0.262	*0.835*	[-0.53, 0.69]	0.08
Group × r-T1	-0.567	2.716	-0.209	*0.835*	[-0.80, 0.65]	-0.08
Group × r-T2	2.632	2.980	0.883	*0.768*	[-0.45, 1.15]	0.35
Age	-0.126	0.146	-0.868	*0.768*	[-0.51, 0.20]	-0.16
Education	0.223	0.311	0.719	*0.768*	[-0.23, 0.49]	0.13

Stroop Test Word-Reading Item

Predictor	***b***	**SE**	***t***	$p_{adjusted}$	**95% CIs**	$b_{standardised}$
Group	-9.141	5.186	-1.763	*0.357*	[-1.57, 0.10]	-0.73
Time r-T1	1.100	2.772	0.397	*0.792*	[-0.36, 0.53]	0.09
Time r-T2	1.687	3.009	0.561	*0.792*	[-0.35, 0.62]	0.14
Group × r-T1	0.644	3.680	0.175	*0.862*	[-0.54, 0.64]	0.05
Group × r-T2	-3.566	4.098	-0.870	*0.779*	[-0.94, 0.37]	-0.29
Age	-0.130	0.263	-0.496	*0.792*	[-0.49, 0.30]	-0.10
Education	0.531	0.558	0.952	*0.779*	[-0.21, 0.59]	0.19

Stroop Test Word-Reading Time

Predictor	***b***	**SE**	***t***	$p_{adjusted}$	**95% CIs**	$b_{standardised}$
Group	6.952	6.882	1.010	*0.810*	[-0.41, 1.25]	0.42
Time r-T1	-3.966	6.048	-0.656	*0.810*	[-0.97, 0.49]	-0.24
Time r-T2	-2.882	6.505	-0.443	*0.810*	[-0.96, 0.61]	-0.17
Group × r-T1	1.939	8.004	0.242	*0.810*	[-0.85, 1.08]	0.12
Group × r-T2	12.470	8.813	1.415	*0.660*	[-0.31, 1.81]	0.75

Age	0.073	0.289	0.253	*0.810*	[-0.28, 0.37]	0.04
Education	-0.459	0.608	-0.754	*0.810*	[-0.45, 0.20]	-0.12

Stroop Test Colour-Naming Item

Predictor	***b***	**SE**	***t***	$p_{adjusted}$	**95% CIs**	$b_{standardised}$
Group	-1.721	3.620	-0.475	*0.730*	[-1.10, 0.68]	-021
Time r-T1	0.800	1.506	0.531	*0.730*	[-0.27, 0.47]	0.10
Time r-T2	-2.612	1.637	-1.595	*0.477*	[-0.72, 0.08]	-0.32
Group × r-T1	-1.338	2.003	-0.668	*0.730*	[-0.66, 0.33]	-0.16
Group × r-T2	2.281	2.003	1.021	*0.730*	[-0.27, 0.83]	0.28
Age	-0.174	0.190	-0.917	*0.730*	[-0.64, 0.24]	-0.20
Education	0.133	0.397	0.344	*0.742*	[-0.37, 0.52]	0.07

Stroop Test Colour-Naming Time

Predictor	***b***	**SE**	***t***	$p_{adjusted}$	**95% CIs**	$b_{standardised}$
Group	5.629	7.657	0.735	*0.751*	[-0.56, 1.22]	0.33
Time r-T1	0.700	3.177	0.220	*0.827*	[-0.33, 0.41]	0.04
Time r-T2	7.215	3.454	2.089	*0.175*	[0.02, 0.82]	0.42
Group × r-T1	-2.392	4.226	-0.566	*0.766*	[-0.63, 0.35]	-0.14
Group × r-T2	-5.227	4.714	-1.109	*0.733*	[-0.85, 0.25]	-0.30
Age	0.313	0.401	0.780	*0.751*	[-0.27, 0.61]	0.17
Education	0.192	0.839	0.229	*0.827*	[-0.39, 0.49]	0.05

Stroop Test Colour-Word Interference Item

Predictor	***b***	**SE**	***t***	$p_{adjusted}$	**95% CIs**	$b_{standardised}$
Group	0.755	2.739	0.276	*0.806*	[-0.71, 0.93]	0.11
Time r-T1	-1.100	1.156	-0.952	*0.666*	[-0.51, 0.18]	-0.16
Time r-T2	1.034	1.257	0.822	*0.666*	[-0.22, 0.53]	0.15
Group × r-T1	2.715	1.538	1.766	*0.229*	[-0.06, 0.87]	0.41
Group × r-T2	-0.992	1.715	-0.579	*0.755*	[-0.66, 0.37]	-0.15
Age	-0.341	0.143	-2.383	*0.112*	[-0.88,-0.08]	-0.48
Education	-0.074	0.300	-0.248	*0.806*	[-0.46, 0.36]	-0.05

Stroop Test Colour-Word Interference Time						
Predictor	***b***	**SE**	***t***	$p_{adjusted}$	**95% CIs**	$b_{standardised}$
Group	-32.730	25.164	-1.301	*0.356*	[-1.38, 0.29]	-0.54
Time r-T1	-16.400	13.203	-1.242	*0.356*	[-0.71, 0.17]	-0.27
Time r-T2	-18.462	14.336	-1.288	*0.356*	[-0.78, 0.17]	-0.31
Group × r-T1	18.015	17.562	1.026	*0.416*	[-0.28, 0.88]	0.30
Group × r-T2	36.068	19.554	1.845	*0.312*	[-0.05, 1.24]	0.60
Age	2.375	1.274	1.864	*0.312*	[-0.03, 0.76]	0.37
Education	-0.141	2.665	-0.053	*0.958*	[-0.41, 0.39]	-0.01

7.2 Appendix 2

Table 13. **Full LMM results for PROMs**. The table shows LMM results presenting the effects of "Group", "Time", their interactions, and covariates age and education for the PROMs. For each predictor, the table includes the coefficient (b), standard error (SE), *t*-statistic, adjusted *p-value*, 95% confidence intervals (CIs), and standardised coefficients ($b_{standardised}$).

Modified Fatigue Impact Scale 21 (MFIS-21)						
MFIS-21						
Predictor	***b***	**SE**	***t***	$p_{adjusted}$	**95% CIs**	$b_{standardised}$
Group	2.138	7.905	0.270	*0.888*	[-0.77, 1.02]	0.12
Time r-T1	3.400	5.342	0.636	*0.888*	[-0.41, 0.80]	0.19
Time r-T2	0.819	5.785	0.142	*0.888*	[-0.61, 0.70]	0.05
Group × r-T1	-5.312	6.977	-0.761	*0.888*	[-1.09, 0.49]	-0.30
Group × r-T2	-5.727	7.718	-0.742	*0.888*	[-1.20, 0.55]	-0.32
Age	-0.101	0.378	-0.267	*0.888*	[-0.45, 0.34]	-0.05
Education	-0.465	0.804	-0.578	*0.888*	[-0.51, 0.28]	-0.11
MFIS-21 Physical Subscale						
Predictor	***b***	**SE**	***t***	$p_{adjusted}$	**95% CIs**	$b_{standardised}$
Group	-0.641	3.722	-0.172	*0.921*	[-0.95, 0.80]	-0.08
Time r-T1	2.000	3.044	0.657	*0.921*	[-0.48, 0.95]	0.23
Time r-T2	-0.328	3.282	-0.100	*0.921*	[-0.81, 0.73]	-0.04
Group × r-T1	-2.707	3.970	-0.682	*0.921*	[-1.25, 0.62]	-0.32
Group × r-T2	-0.532	4.377	-0.121	*0.921*	[-1.09, 0.97]	-0.06

Age	-0.062	0.163	-0.381	*0.921*	[-0.42, 0.29]	-0.07
Education	-0.184	0.346	-0.533	*0.921*	[-0.45, 0.26]	-0.09
MFIS-21 Cognitive Subscale						
Predictor	***b***	**SE**	***t***	$p_{adjusted}$	**95% CIs**	$b_{standardised}$
Group	3.439	4.452	0.772	*0.795*	[-0.56, 1.26]	0.35
Time r-T1	1.700	2.478	0.686	*0.795*	[-0.33, 0.68]	0.17
Time r-T2	0.422	2.690	0.157	*0.876*	[-0.51, 0.59]	0.04
Group × r-T1	-2.647	3.239	-0.817	*0.795*	[-0.93, 0.39]	-0.27
Group × r-T2	-3.277	3.590	-0.913	*0.795*	[-1.07, 0.40]	-0.33
Age	-0.048	0.224	-0.216	*0.876*	[-0.47, 0.38]	-0.05
Education	-0.143	0.478	-0.298	*0.876*	[-0.49, 0.36]	-0.06
MFIS-21 Psycho-social Subscale						
Predictor	***b***	**SE**	***t***	$p_{adjusted}$	**95% CIs**	$b_{standardised}$
Group	-0.593	1.027	-0.577	*0.949*	[-1.09, 0.60]	-0.24
Time r-T1	-0.200	0.697	-0.287	*0.949*	[-0.66, 0.49]	-0.08
Time r-T2	-0.071	0.754	-0.094	*0.949*	[-0.65, 0.59]	-0.03
Group × r-T1	-0.111	0.910	-0.122	*0.949*	[-0.79, 0.70]	-0.05
Group × r-T2	0.065	1.006	0.065	*0.949*	[-0.80, 0.86]	0.03
Age	-0.011	0.049	-0.221	*0.949*	[-0.41, 0.33]	-0.04
Education	-0.157	0.104	-1.509	*0.587*	[-0.66, 0.09]	-0.28
Fatigue Impact Scale (FSS)						
Predictor	***b***	**SE**	***t***	$p_{adjusted}$	**95% CIs**	$b_{standardised}$
Group	0.006	5.497	0.001	*0.999*	[-0.87, 0.87]	0.00
Time r-T1	-0.333	4.817	-0.069	*0.999*	[-0.79, 0.74]	-0.03
Time r-T2	-1.829	5.013	-0.365	*0.999*	[-0.94, 0.65]	-0.14
Group × r-T1	1.333	6.134	0.217	*0.999*	[-0.86, 1.08]	0.11
Group × r-T2	1.850	6.656	0.278	*0.999*	[-0.91, 1.20]	0.15
Age	0.025	0.240	0.106	*0.999*	[-0.33, 0.37]	0.02
Education	-0.405	0.512	-0.791	*0.999*	[-0.49, 0.21]	-0.14
Beck's Depression Inventory-II (BDI-II)						
Predictor	***b***	**SE**	***t***	$p_{adjusted}$	**95% CIs**	$b_{standardised}$
Group	3.621	3.665	0.988	*0.538*	[-0.44, 1.31]	0.43
Time r-T1	2.900	2.193	1.322	*0.538*	[-0.18, 0.87]	0.35
Time r-T2	0.000	2.379	0.000	*1.000*	[-0.57, 0.57]	-0.00
Group × r-T1	-2.767	2.832	-0.977	*0.538*	[-1.01, 0.35]	-0.33
Group × r-T2	3.079	3.164	0.973	*0.538*	[-0.39, 1.12]	0.37
Age	-0.021	0.183	-0.113	*1.000*	[-0.43, 0.38]	-0.02
Education	-0.197	0.390	-0.505	*0.826*	[-0.51, 0.30]	-0.10
Multiple Sclerosis Quality of Life-29 Questionnaire (MSQOL-29)						
MSQOL-29						

Predictor	*b*	SE	*t*	$p_{adjusted}$	95% CIs	$b_{standardised}$
Group	2.437	3.458	0.705	*0.682*	[-0.54, 1.12]	0.29
Time r-T1	2.156	3.252	0.663	*0.682*	[-0.52, 1.04]	0.26
Time r-T2	-0.197	3.487	-0.056	*0.955*	[-0.86, 0.82]	-0.02
Group × r-T1	-7.350	4.235	-1.736	*0.363*	[-1.90, 0.14]	-0.88
Group × r-T2	-0.563	4.667	-0.121	*0.955*	[-1.19, 1.06]	-0.07
Age	-0.192	0.136	-1.415	*0.461*	[-0.52, 0.09]	-0.21
Education	0.343	0.289	1.185	*0.501*	[-0.12, 0.48]	0.18

MSQOL-29 Physical Composite Score

Predictor	*b*	SE	*t*	$p_{adjusted}$	95% CIs	$b_{standardised}$
Group	4.434	3.194	1.388	*0.367*	[-0.25, 1.38]	0.56
Time r-T1	2.960	2.797	1.058	*0.475*	[-0.34, 1.09]	0.38
Time r-T2	1.915	3.009	0.636	*0.604*	[-0.52, 1.01]	0.24
Group × r-T1	-4.938	3.643	-1.356	*0.367*	[-1.56, 0.30]	-0.63
Group × r-T2	-3.057	4.033	-0.758	*0.604*	[-1.42, 0.64]	-0.39
Age	-0.311	0.133	-2.330	*0.125*	[-0.68, -0.05]	-0.37
Education	-0.003	0.284	-0.012	*0.991*	[-0.32, 0.31]	-0.00

MSQOL-29 Mental Composite Score

Predictor	*b*	SE	*t*	$p_{adjusted}$	95% CIs	$b_{standardised}$
Group	0.923	4.419	0.209	*0.959*	[-0.77, 0.95]	0.09
Time r-T1	3.140	3.855	0.814	*0.840*	[-0.44, 1.05]	0.30
Time r-T2	0.818	4.148	0.197	*0.959*	[-0.73, 0.89]	0.08
Group × r-T1	-6.643	5.021	-1.323	*0.774*	[-1.62, 0.33]	-0.64
Group × r-T2	0.287	5.560	0.052	*0.959*	[-1.05, 1.11]	0.03
Age	0.065	0.185	0.350	*0.959*	[-0.27, 0.39]	0.06
Education	0.328	0.394	0.831	*0.840*	[-0.20, 0.47]	0.14

Patient Determined Disease Steps (PDDS)

Predictor	*b*	SE	*t*	$p_{adjusted}$	95% CIs	$b_{standardised}$
Group	-0.419	0.576	-0.728	*0.755*	[-1.09, 0.51]	-0.29
Time r-T1	-0.100	0.308	-0.325	*0.878*	[-0.50, 0.36]	-0.07
Time r-T2	0.072	0.334	0.215	*0.878*	[-0.41, 0.51]	0.05
Group × r-T1	0.311	0.402	0.775	*0.755*	[-0.34, 0.77]	0.22
Group × r-T2	-0.069	0.450	-0.154	*0.878*	[-0.67, 0.58]	-0.05
Age	0.027	0.029	0.911	*0.755*	[-0.20, 0.55]	0.17
Education	-0.104	0.062	-1.667	*0.441*	[-0.69, 0.06]	-0.32