NeuroImage: Clinical 46 (2025) 103775

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Efficacy of cognitive rehabilitation in cognition and brain networks: A randomised clinical trial in patients with multiple sclerosis

E. Lopez-Soley [a], E. Martinez-Heras [a], F. Vivo [a], A. Calvi [a], S. Alba-Arbalat [a], L. Romero-Pinel [b], S. Martínez-Yélamos [b,c], C. Ramo-Tello [d], S. Presas-Rodríguez [d], E. Munteis [e], J.E. Martínez-Rodríguez [e], J. Sastre-Garriga [f], E. Anglada [f], E.R. Meza-Murillo [f], M.J. Arévalo [f], R. Sánchez-Carrión [g], R. Pelayo [g], M. Bernabeu [g], N. Sola-Valls [h], M. Hervas [i], M. Sepulveda [a], A. Saiz [a], Y. Blanco [a], E. Solana [a,1,*], S. Llufriu [a,1,*]

[a] Neuroimmunology and Multiple Sclerosis Unit. Hospital Clinic Barcelona, Institut d'Investigacions Biomediques August Pi i Sunyer (IDIBAPS) and Universitat de Barcelona, Spain
[b] Multiple Sclerosis Unit, Department of Neurology, Hospital Universitari de Bellvitge. Neurology and Neurogenetics Group. Neuroscience Program, Institut d'Investigació Biomèdica de Bellvitge (IDIBELL), Spain
[c] Department of Clinical Sciences, School of Medicine, Universitat de Barcelona (UB), L'Hospitalet de Llobregat, Spain
[d] Multiple Sclerosis Unit, Department of Neurosciences, Hospital Universitari Germans Trias i Pujol, Spain
[e] Neurology Department, Hospital del Mar Medical Research Institute (IMIM), Spain
[f] Centre d'Esclerosi Múltiple de Catalunya (CEMcat), Hospital Universitari Vall d'Hebron, Spain
[g] Institut Guttmann, Institut Universitari de Neurorehabilitació Affiliated to the Universitat Autònoma de Barcelona and Fundació Institut d'Investigació en Ciències de la Salut Germans Trias i Pujol, Spain
[h] Neurology Department, Hospital Universitari Sant Joan de Reus, Clinical and Epidemiological Neuroscience Group (NeuroÈpia), Institut d'Investigació Sanitària Pere Virgili (IISPV), Spain
[i] Hospital de Sabadell Parc Taulí, Spain

ARTICLE INFO

Keywords:
Cognitive rehabilitation
Cognition
MRI
Structural networks
Multiple sclerosis

ABSTRACT

This study evaluated the efficacy of the computerised Guttmann, NeuroPersonalTrainer® (GNPT) cognitive rehabilitation (CR) and characterised the induced changes in cerebral networks in patients with multiple sclerosis (MS). This multicentre, double-blind, randomised clinical trial compared upward intensity training (active treatment) to low-intensity static training (static treatment). Cognition was assessed using the Brief Repeatable battery before and after 12 weeks of training and at 10-months follow-up, and patients were classified as having a mild or severe cognitive impairment (CI). Brain MRI pre- and post-CR were analysed using an advanced tractography algorithm, based on multishell diffusion MRI, to obtain node-based graph metrics (local efficiency and strength) from microscopic fractional anisotropy. Seventy MS patients completed the study (age 48.9 ± 8.8, disease duration 16.8 ± 9.0 years); active treatment: 36, static treatment: 34. Verbal memory improved significantly post-CR in both groups (55 % active; 34 % static treatment), accompanied by increases in local efficiency and strength in multimodal regions. At follow-up, verbal memory declined in both groups but remained above the pre-CR assessment (−25 % and −17 %, respectively). Patients with severe-CI (n = 36) showed improvement only with active treatment, while those with mild-CI (n = 34) improved regardless of intensity treatment. Network changes were more pronounced in patients in active treatment and in those with

Abbreviations: BRB-N, Brief Repeatable Battery of Neuropsychological Tests; CI, cognitive impairment; CR, cognitive rehabilitation; CRQ, cognitive Reserve Questionnaire; DMTs, disease-modifying therapies; DWI, diffusion-weighted imaging; EDSS, Expanded Disability Status Scale; FU, follow-up; GNPT, Guttmann, NeuroPersonalTrainner®; HADS, Hospital Anxiety Depression Scale; IPS, information processing speed; IQR, interquartile range; ITA, Intelligent Therapy Assistant; MFIS, Modified Fatigue Impact Scale; MRI, magnetic resonance imaging; MS, multiple sclerosis; MSQOL, multiple sclerosis quality of life; nGMv, normalized grey matter volume; nLv, normalized lesion volume; PASAT, Paced Auditory Serial Addition Test; RRMS, relapsing-remitting multiple sclerosis; SD, standard deviations; SDMT, Symbol Digit Modalities Test; SPART, 10/36 Spatial Recall Test; SPMS, secondary progressive multiple sclerosis; SRT, Selective Reminding Test; WLG, Word List Generation; μFA, microscopic fractional anisotropy.

* Corresponding authors.
E-mail addresses: elisabeth.solana@recerca.clinic.cat (E. Solana), sllufriu@clinic.cat (S. Llufriu).
[1] These authors share co-senior authorship.

https://doi.org/10.1016/j.nicl.2025.103775
Received 19 November 2024; Received in revised form 19 March 2025; Accepted 26 March 2025
Available online 1 April 2025

severe-CI. Quality of life did not change at post-CR, and cognitive improvement was influenced by cognitive reserve ($p = 0.011$). In MS, GNPT temporarily improves verbal memory and increases network connectivity, reinforcing the CR as a valuable tool for enhancing cognitive skills and promoting neuronal plasticity.

1. Introduction

Cognitive impairment (CI) is a common symptom in people with multiple sclerosis (MS), affecting 43–70 % of patients and significantly impacting their quality of life (Chiaravalloti and DeLuca 2008). This cognitive dysfunction is associated with a disconnection phenomenon due to structural damage in white and grey matter (Llufriu et al., 2014; 2017). Moreover, magnetic resonance imaging (MRI) studies suggest a reorganisation of functional (Rocca et al., 2016) and diffusion-based structural brain connections (Llufriu et al., 2017; Li et al., 2013; Solana et al., 2019) with compensatory or maladaptive mechanisms to cope with MS-related damage.

Given the inconclusive benefits of pharmacological therapies for CI, there is a need for alternative intervention approaches such as cognitive rehabilitation (CR) for MS patients (Chen et al., 2020). The CR includes behavioural treatments designed to improve cognitive functions and enhance the ability to manage cognitive deficits in daily life. Systematic reviews have demonstrated the positive effects of CR in various cognitive domains (Rosti-Otajärvi and Hämäläinen 2014; Mitolo et al., 2015; Chen, Chiaravalloti, and DeLuca 2021; DeLuca, Chiaravalloti, and Sandroff 2020). However, many studies have faced methodological shortcomings, such as small sample sizes, lack of randomisation, or inadequate control groups, prompting calls for robust randomised controlled trials with rigorous methodological standards. Additionally, reliable markers of the processes that underlie the beneficial effects of CR are needed to optimise patient management. Recent studies have suggested that CR may enhance neuroplasticity in MS (Sîrbu et al., 2022), with advanced MRI techniques linking task-related and resting-state functional connectivity changes to cognitive improvements after CR (DeLuca, Chiaravalloti, and Sandroff 2020). Nonetheless, it remains unclear whether CR can induce changes in structural connectivity by modifying white matter connections.

Technological advances have enabled the development of computer-assisted rehabilitation programmes, which are gaining interest due to their real-time adaptability and accessibility without needing extensive professional resources (Lampit et al., 2019). The Guttmann, NeuroPersonalTrainner® (GNPT) platform is a comprehensive programme that uses computer-based systems for CR and stimulation. It was designed to provide neuropsychological services with an asynchronous schedule, increasing the personalization and intensity of treatments for patients with neurological dysfunction (Solana et al., 2014; Fernandez-Gonzalo et al., 2015). Its efficacy has been previously demonstrated in patients with acquired brain injury, psychiatric disorders, and neurological diseases (Solana et al., 2014; Fernandez-Gonzalo et al., 2015; Gil-Pagés et al., 2022), but remains unexplored for MS.

Therefore, the primary objective was to assess the efficacy of GNPT with adaptive intensity compared to low-intensity static training on cognitive performance. The secondary objectives included: (1) to evaluate the efficacy of the CR according to the severity of cognitive dysfunction, (2) to explore changes in quality of life post-CR, (3) to analyse the influence of baseline clinical and psychological characteristics on cognitive modifications, and (4) to characterise the changes in brain structural connectivity driven by CR.

2. Methods

2.1. Participants

Participants were identified at 8 different centres in Catalonia and enrolled in the trial at the MS Unit of the Hospital Clinic Barcelona between January 2018 and November 2021. At the end of the recruitment, 120 participants were assessed for eligibility based on the following inclusion criteria: patients with relapsing–remitting (RRMS) or secondary progressive MS (SPMS) according to the 2017 McDonald criteria (Polman et al., 2011), with cognitive complaints and impaired results in at least two cognitive tests (see Assessment and outcome measures), aged between 18 and 65 years, and having access to a computer and internet connection to use GNPT from home. The exclusion criteria were: presenting any relapse or having received any corticosteroid therapy in the last 30 days prior to the baseline study visit, inability to undergo brain MRI, having a significant neurological, psychiatric condition or medication that could interfere with cognitive functioning, and having participated in CR within the 6 months prior to the study enrolment.

The Ethics Committee at the Hospital Clinic of Barcelona approved the study in 2016 (HCB/2016/0827), and eligible participants signed an informed consent form before their inclusion.

2.2. Study design and procedures

This multicentre, double-blind and randomised clinical trial to parallel groups, compared GNPT using upward-intensity training (active treatment) with low-intensity static training (static treatment). The study included 4 visits and two MRI scans (pre- and post-CR). Data was collected at baseline, 8 weeks (pre-CR), 20 weeks (post-CR) and 60 weeks follow-up (Fig. 1A). The time points were selected to balance obtaining long-term data while minimizing participant burden, given the demanding nature of the study.

At baseline, cognitive assessment and self-administered questionnaires were conducted, and participants were classified into cognitive groups (mild and severe-CI, criteria detailed in Assessment and outcome measures). After the baseline assessment, participants were assigned to each treatment group using a computer-generated random number at a ratio of 1:1 by an independent technician who also programmed and supervised the GNPT intervention. Patients were automatically allocated in blocks, balancing participants to ensure that the number of mild-CI and severe-CI patients was similar across the two treatment arms. The pre-CR visit included a cognitive assessment identical (with use of alternative versions of some tests) to the one performed at baseline to control for potential learning effects on cognitive tests. Additionally, a clinical assessment was conducted, and participants received instructions for the GNPT programme. Both groups received CR from home for three months. All assessment measures were repeated at post-CR and at follow-up. The same neuropsychologist, who was blinded to the treatment group, rated all the cognitive tests and conducted all visit assessments.

2.3. GNPT cognitive rehabilitation programme

The rehabilitation programme included three one-hour sessions per week, with a total of 36 sessions. Only those patients who attended more than 30 CR sessions were included in the analyses. The initial baseline performance of each patient was categorised as mild or severe-CI (see Assessment and outcome measures) and manually entered into the programme. Using this data, the software provided a personalised treatment proposal based on the Intelligent Therapy Assistant (ITA) (Solana et al., 2014). The ITA algorithm also determined and readjusted the most suitable difficulty configuration based on the patient's CI and evolution, ensuring task execution remained within the therapeutic range (task score between 65–85 % of correct answers) (Solana et al.,

2014). The active treatment group received a high-intensity rehabilitation programme adapted to the baseline cognitive status, with difficulty adjustments based on the ITA. In contrast, the static treatment group followed the same training programme but with a lower and not-incremental level of difficulty. The programme (https://gnpt.es) included 95 different tasks focused on attention, memory and executive functions (Solana et al., 2014).

2.4. Assessment and outcome measures

Demographic, clinical, cognitive, psychological and MRI information was recorded in the scheduled visits at the same centre. At baseline, collected data included sex, age, disease phenotype, disease duration, the number of relapses before study inclusion, and the use and type of disease-modifying therapies (DMTs). Clinical assessments included the neurological status as determined by the Expanded Disability Status Scale (EDSS) (Kurtzke 1983).

Participants underwent a cognitive assessment at each visit using the Brief Repeatable Battery of Neuropsychological Tests (BRB-N) (Rao et al. 1991). This battery includes different tests assessing cognitive domains as follows: (1) verbal memory: Selective Reminding Test (SRT, with two subtests: consistent long-term retrieval as an indicator of consolidation, and delayed retrieval); (2) visual memory: 10/36 Spatial Recall Test (SPART, with two subtests: immediate retrieval and for delayed retrieval); (3) attention and information processing speed (IPS): Symbol Digit Modalities Test (SDMT) and Paced Auditory Serial Addition Test (PASAT) 3 s per digit version; and (4) semantic fluency: Word List Generation (WLG). Raw values were transformed into z-scores by adjusting for age and education level according to the Spanish normative data, and were grouped in terms of each cognitive domain (Sepulcre et al., 2006). Patients were included in the clinical trial if they had at least two tests (being one from the attention-IPS domain) below −1 standard deviation (SD). Patients were classified as having a mild-CI with a performance z-score between −1 and −2 SD, or severe-CI with a performance z-score of <−2 SD. Alternate test versions were used for the SRT, SDMT, and PASAT.

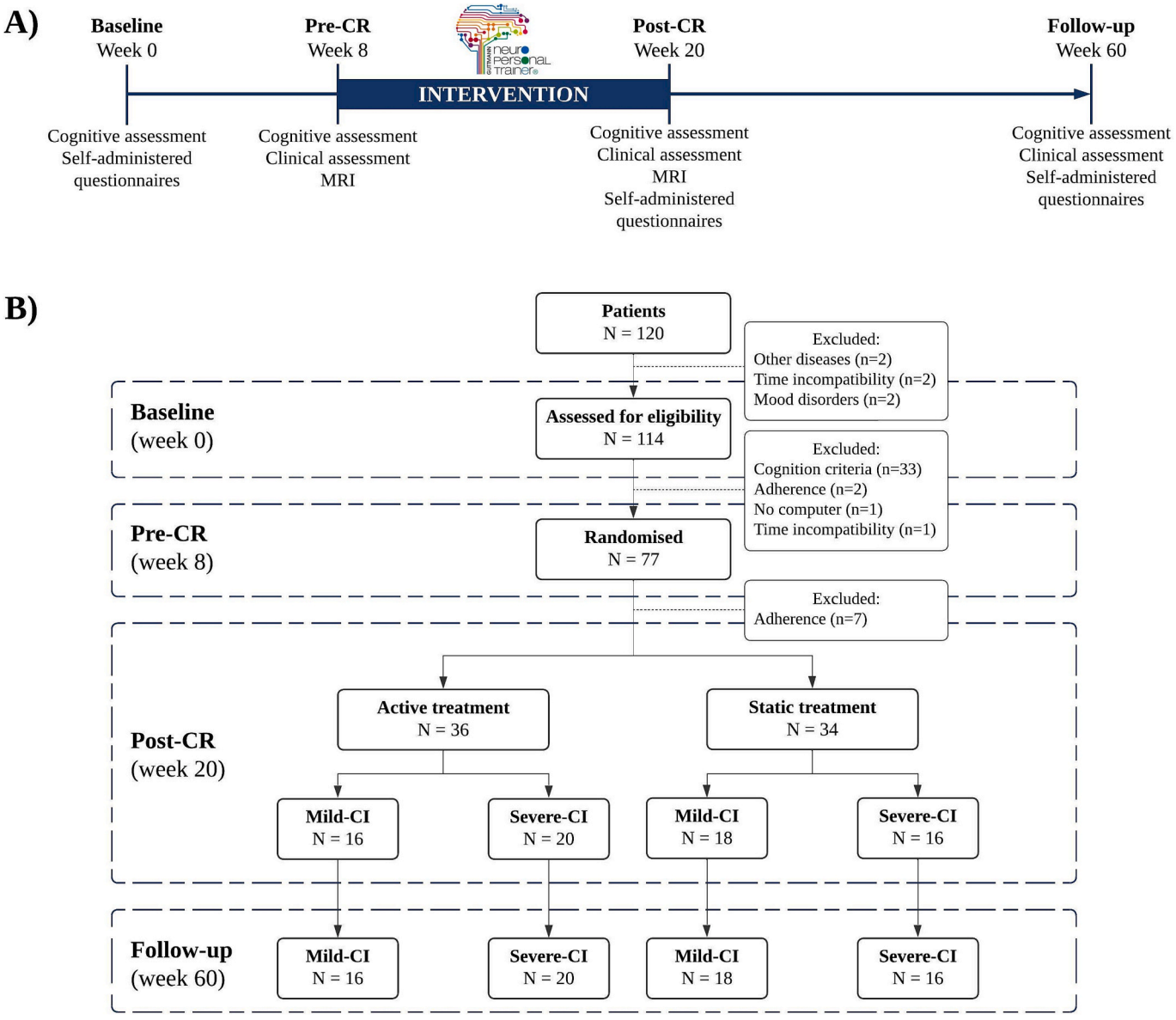

Fig. 1. Study design and participants. Fig. 1A shows the study design. Cognitive assessment was done using the Brief Repeatable Battery of Neuropsychological Tests. Self-administered questionnaires include the MS Quality of Life-54, Cognitive Reserve Questionnaire, Hospital Anxiety and Depression Scale, and Modified Fatigue Impact Scale. Clinical assessment included the Expanded Disability Status Scale. Fig. 1B is the flow diagram of participants through recruitment and study visits. CR: cognitive rehabilitation; MRI: magnetic resonance imaging; CI: cognitive impairment.

Patients also completed several surveys: MS Quality of Life-54 (MSQOL-54) (Vickrey et al. 1995), Cognitive Reserve Questionnaire (CRQ) (Rami González et al., 2011), Hospital Anxiety Depression Scale (HADS) (Zigmond and Snaith 1983) and the Modified Fatigue Impact Scale (MFIS) (Kos et al., 2005). The MSQOL-54 includes two composite scores: a physical composite reflecting physical health perceptions and function, and a mental composite, reflecting emotional well-being. Lastly, at the end of the intervention, participants rated their satisfaction with the CR on a scale from 0 to 10 points (with 10 being the best score). The questions included: 1) if they found rehabilitation useful, 2) if they had noticed changes in their daily life activities, and 3) if they would participate again in the study.

The primary outcome was the change in attention-IPS domain at post-CR. Secondary outcomes included changes in other cognitive domains at post-CR and at follow-up, quality of life, the influence of baseline clinical and psychological characteristics on cognitive performance, and network modifications.

2.5. Magnetic resonance imaging acquisition and processing

MRIs were acquired at pre- and post-CR on a 3-Tesla Magnetom Prisma (SIEMENS, Erlanger, Germany) scanner using a 64-channel phased-array head coil. The protocol involved a 3D-Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE), 3D-T2 fluid-attenuated inversion recovery (FLAIR), and diffusion-weighted imaging (DWI) sequences (details in Supplementary Material). White matter lesions were defined on the 3D-MPRAGE and 3D-FLAIR images using the Jim7 software (https://www.xinapse.com/). Lesion-filled images were parcellated into 62 grey matter regions and 14 subcortical regions using Mindboggle software (https://mindboggle.info), applying the Desikan–Killiany Tourville cortical labeling atlas. The automated subcortical segmentation was achieved with the FSL-FIRST package (fsl.fmrib.ox.ac.uk/fsl/fslwiki/FIRST) (Klein et al., 2017). These regions were then used to define the network nodes. SIENAX was used to compute normalized grey matter (nGMv) and lesion volume (nLv) (Smith et al., 2002).

2.6. Brain structural connectivity reconstruction and graph network analysis

DWI processing was performed as previously described (Tournier et al., 2019; Martinez-Heras et al., 2023). Major components in the pipeline included MP-PCA denoising, Gibbs ringing removal, eddy current and motion correction, geometrically unwarping procedure, and bias field correction. Following these corrections, microscopic fractional anisotropy (μFA) maps were calculated across three distinctive b-shells (1000, 2000 and 3000 s/mm^2) using the Multi-Compartment Spherical Mean Technique (MC-SMT) framework (https://github.com/ekaden/smt) (Kaden et al., 2016). Quantitative μFA connectivity matrices were generated by performing constrained-spherical deconvolution and probabilistic advanced diffusion tractography (Jeurissen et al., 2014). A set of 6 million streamlines was generated into the white matter mask to capture the entire white matter fibre trajectories, including both areas with lesions and without lesions (Solana et al., 2018). The parcellation scheme (76 nodes) from the anatomical image was aligned to the μFA map to determine which streamline connections needed to be selected between pairs of nodes to create the structural connectome. The mean μFA along each reconstructed fibre pathway was computed to establish the structural brain connectome between all pairs of grey matter regions.

Network graph measures were computed using the Brain Connectivity toolbox (https://sites.google.com/site/bctnet/). Node-based network measures investigated included local efficiency (the inverse of the shortest path distance between the nodes) and nodal strength (the sum of the edge weights connected to a node) (Rubinov and Sporns, 2010).

2.7. Statistical analysis

The sample size was calculated to detect differences in cognitive z-scores between study groups, with 80 % power and a significance level of $p = 0.05$. We estimated an effect size of 0.80 based on previous studies (Llufriu et al., 2014). Using the formula for independent t-tests, the estimated sample size was 25 participants per group. To account for a potential 20 % dropout rate, we increased the sample size to 35 participants per group.

Descriptive statistics were used to explore the demographic, clinical, cognitive and MRI characteristics before CR. Group comparisons were conducted using the Chi-squared test, Wilcoxon-Mann-Whitney *U* test or Student's *t*-test, as appropriate.

Linear mixed-effect regression models with subject-specific random intercepts were used to study longitudinal changes in: (1) cognitive performance, (2) quality of life, and (3) structural graph metrics across visits. In all these models, study visits (visit numbers, categorical variable) were included as a fixed-effect predictor. Separately, (4) we used mixed-effect models to assess the influence of the treatment type (active or static, as a fixed variable) on cognitive performance between pre- and post-CR. Additionally, mixed-effect models were employed to explore the associations between (5) baseline clinical characteristics (disease duration, EDSS, use of DMTs –categorised by no DMT, moderate-efficacy or high-efficacy DMTs–, CRQ, HADS, MFIS, nLv and nGMv) and cognitive performance after CR, and (6) structural connectivity changes with cognitive performance, considering only variables that showed significant differences in the longitudinal analysis. Continuous variables were standardised to enhance model interpretability. An additional two-sample test for equality of proportions with continuity correction was conducted to compare the proportions of nodes with significant changes between groups. Analyses were conducted for each treatment and cognitive group separately (active treatment, static treatment, mild and severe-CI).

Furthermore, linear spline models were used to visualise the cognitive changes between study visits and the effect size of the cognitive and MRI metrics differences was described using the Hedges' g.

All the analyses were performed using the R statistical software (version 4.2.2), setting the level of significance at $p < 0.05$ and correcting multiple comparisons for the false discovery rate when appropriate.

3. Results

Fig. 1B depicts the flow diagram of participants through recruitment and study visits. Out of the 120 MS participants assessed for eligibility, 114 completed the baseline visit. After excluding those who did not meet inclusion criteria, 77 participants began the CR, and 70 completed it, resulting in an attrition rate of 9.09 % due to voluntary withdrawal (n = 7). Of the 70 patients, 36 were randomly assigned to the active treatment group, and 34 to the static treatment group. In the MRI analyses, 4 of the 70 patients were excluded due to artefacts in MRI acquisition (n = 66).

None of the demographic or clinical measures pre-CR differed between active and static treatment groups (Table 1). However, patients in the active treatment group exhibited worse z-scores in verbal memory compared to those in the static treatment group ($p = 0.016$), while no differences were found in other cognitive domains at pre-CR (Supplementary Table 1). Additionally, no learning effects were observed in cognitive scores between the baseline and pre-CR visits, indeed, a significant decline in verbal memory was observed in the second assessment (p = 0.015) (Table 2).

3.1. Cognitive performance results

3.1.1. Efficacy of the CR on cognitive performance by treatment group

The mixed-effect model analyses did not reveal an improvement in

Table 1
Demographic and clinical characteristics of patients before CR.

	Entire cohort (n = 70)	Active treatment (n = 36)	Static treatment (n = 34)	*p* value
Female, n (%)	47 (67)	25 (69)	22 (65)	0.867[c]
Age (years)	49.2 (43.9–55.1)	48.5 (45.2–53.5)	50.1 (42.9–55.1)	0.603[b]
Type of MS, n (%)				
RRMS	57 (81)	29 (81)	28 (82)	0.999[c]
SPMS	13 (19)	7 (19)	6 (18)	
Disease duration (years)	16.1 (9.87–23.4)	14.8 (11.5–18.4)	18.2 (8.2–24.5)	0.518[a]
EDSS (range)	3.0 (1.0–7.5)	3.5 (2.0–7.5)	3.0 (1.0–6.5)	0.110[a]
Number of previous relapses (range)	5 (3–7)	5 (3–7)	4.5 (3–8.5)	0.611[b]
DMTs line, n (%)				
No DMTs	15 (21)	7 (20)	8 (24)	0.915[c]
Moderate-efficacy DMTs	23 (33)	12 (33)	11 (32)	
High-efficacy DMTs	32 (46)	17 (47)	15 (44)	
Cognitive status, n (%)				
Mild-CI	34 (49)	16 (44)	18 (53)	0.637[c]
Severe-CI	36 (51)	20 (56)	16 (47)	
MSQOL-54				
Physical composite	47.1 (35.4–57.1)	45.6 (36.8–56.0)	48.2 (33.0–57.7)	0.898[a]
Mental composite	47.9 (35.9–68.0)	44.5 (35.8–66.8)	52.9 (36.2–68.2)	0.874[b]
CRQ score	14 (12–17)	14.5 (13–17)	13 (11–16)	0.205[a]
nLv (cm^3)	11.62 (4.56–27.0)	11.8 (4.56–33.1)	11.0 (4.93–20.3)	0.425[b]
nGMv (cm^3)	690.9 (646–725)	696 (637–723)	686 (661–726)	0.534[b]

The data represents the absolute numbers and proportions of the qualitative data, and the median and IQR for the quantitative data, unless otherwise specified. MS: multiple sclerosis; RRMS: relapsing-remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis; EDSS: Expanded Disability Status Scale; DMTs: Disease Modifying Therapies; CI: cognitive impairment; MSQOL-54: MS Quality of Life-54; CRQ: cognitive reserve questionnaire; nLv: normalized lesion volume; nGMv: normalized grey matter volume.
[a] : Students' *t*-test, [b]: Wilcoxon Mann Whitney Test; [c]: Chi-squared test.

Table 2
Cognitive differences between baseline and pre-CR.

Cognitive tests	Baseline	Pre-CR	Adj. p value
Verbal memory	−1.52 (1.06)	−2.04 (1.01)	0.015[a]
Visual memory	−0.86 (1.03)	−0.79 (0.96)	0.672[a]
Attention and IPS	−0.89 (0.99)	−0.66 (1.06)	0.365[a]
Semantic fluency	−1.17 (0.89)	−1.04 (0.91)	0.482[b]

The data represents the mean and standard deviation. CR: cognitive rehabilitation; IPS: information processing speed. P-values are adjusted using the FDR multiple testing correction method.
[a] : Students' *t*-test, [b]: Wilcoxon Mann Whitney Test.

attention-IPS performance at post-CR either in the active and static treatment group (p > 0.05). However, an improvement in verbal memory at post-CR in both the active (β = 1.099, 95 % CI 0.80–1.40, $p < 0.001$, median change of 55 %, g = 0.95) and in the static treatment (β = 0.718, 95 %CI 0.41–1.03, $p < 0.001$, median change of 34 %, g = 0.64) groups was observed. At follow-up, this increase was followed by a performance decrease in both groups (active treatment: β = −0.652, 95 %CI −0.95–−0.35, $p < 0.001$, median change of −25 %, g = −0.56; static treatment: β = −0.460, 95 %CI −0.79–−0.13, $p = 0.010$, median change of −17 %, g = −0.37), although results remained above the pre-CR z-scores. Changes between pre- and post-CR did not reach statistical significance in other cognitive domains (Fig. 2, Supplementary Fig. 1 and Supplementary Table 2), and there were no differences between treatment groups ($p > 0.05$) (Supplementary Table 3).

To further assess the impact of CR and confirm the improvement in verbal memory observed between pre- and post-CR, verbal memory changes between baseline and post-CR were also examined. The results indicate that verbal memory significantly improved from baseline to post-CR in both the active (β = 0.241, 95 % CI 0.13–0.36, p < 0.001) and the static treatment group (β = 0.168, 95 % CI 0.02–0.32, p = 0.036).

3.1.2. *Efficacy of the CR on cognitive performance in patients with different cognitive status (mild and severe-CI)*

In the mild-CI group (n = 34), changes in verbal memory domain were maintained (Supplementary Table 4 and Supplementary Fig. 2). Patients improved verbal memory z-score between pre- and post-CR in both the active (n = 16, β = 1.230, 95 %CI 0.75–1.71, $p < 0.001$, median change of 59 %, g = 1.44) and the static treatment group (n = 18, β = 0.997, 95 %CI 0.63–1.36, $p < 0.001$, median change of 42 %, g = 1.16). Both groups experienced a decrease from post-CR to follow-up (active treatment: β = −0.950, 95 %CI −1.42–−0.48, $p < 0.001$, median change of −31 %, g = −1.04; static treatment: β = −0.544, 95 %CI −0.97–−0.12, $p = 0.020$, median change of −18 %, g = −0.59), though z-scores remained above their pre-CR levels.

In patients with severe-CI (n = 36), changes in verbal memory were observed only in those patients who received active treatment (n = 20, pre- vs. post-CR: β = 0.995, 95 %CI 0.61–1.38, $p < 0.001$, median change of 50 %, g = 0.35; post-CR vs. follow-up: β = −0.402, 95 %CI −0.78–−0.03, $p = 0.043$, median change of −16 %, g = −0.33) (Supplementary Table 5 and Supplementary Fig. 2). No differences were found between pre- and post-CR in other cognitive domains, and no differences were detected between treatment groups in either the mild or severe-CI group ($p > 0.05$) (Supplementary Table 3).

3.1.3. *Impact of CR on patient's quality of life and influence of clinical and psychological characteristics on cognitive performance*

Post-CR, there were no significant changes in either the physical or mental MSQOL-54 composite scores ($p > 0.05$) (Supplementary Table 6). Moreover, participants positively rated the usefulness of CR (median of 9/10 points, interquartile range (IQR) 7–10), the impact on their daily life activities (median 6/10, IQR 3–8), and their willingness to participate again (median 10/10, IQR 8–10).

The effect of CR on verbal memory performance was confirmed in a multiple linear mixed-effect model that included baseline characteristics as covariates. The results showed that only study visits (β = 0.899, 95 % CI 0.67–1.13, $p < 0.001$) and cognitive reserve (β = 0.366, 95 % CI 0.07–0.66, $p = 0.018$) influenced cognitive performance at post-CR in the entire cohort (Table 3).

3.2. *Brain structural connectivity*

At pre-CR, differences between mild and severe-CI groups were found in local efficiency in 5 (7 %) nodes (mean value for mild-CI group = 0.742 ± 0.04; mean value for severe-CI group = 0.715 ± 0.05). There were also differences in strength in 25 (33 %) nodes (mean value for mild-CI group = 63.847 ± 9.39; mean value for severe-CI group = 57.056 ± 13.08), mostly involving the parietal, frontal and temporal cortex (p < 0.05). However, these differences disappeared after correcting for multiple comparisons.

3.2.1. *Structural connectivity changes induced by CR according to treatment and cognitive groups*

Brain connectivity changes between pre- and post-CR, measured with nodal local efficiency and strength, were analysed by mixed-effect models. In the active treatment group, increases in both local efficiency and strength were noted in 19 (25 %) (g range 0.12–0.38) and 18 (24 %) (g range 0.15–0.45) nodes, respectively. Notable changes were observed in the deep grey matter, frontal, temporal, parietal, and cingulate cortex (Fig. 3A). Conversely, the static treatment group showed differences in

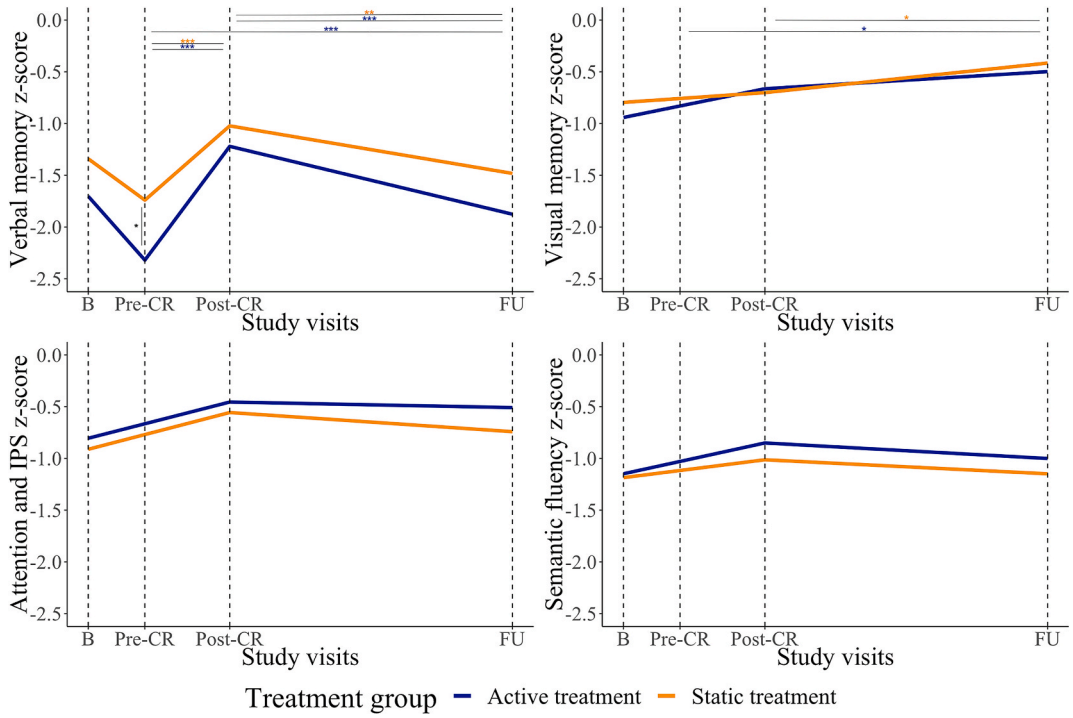

Fig. 2. Cognitive domains z-score at the study visits in each treatment group. The cognitive z-scores were modelled by spline models with two knots indicating each study visit and represented by dotted black vertical lines. The active treatment group is represented in blue and the static treatment group in orange. All models were fitted using the lme4 package in R version 4.2.2 (R Foundation for Statistical Computing: *p < 0.05). Vertical asterisk represents significant differences between treatment groups at pre-CR. Horizontal asterisks represents significant differences from the analyses of pre-CR, post-CR and FU. Baseline time point was not part of the statistical analyses. B: baseline; CR: cognitive rehabilitation; FU: follow-up; IPS: information processing speed. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 3
Effect of pre-CR characteristics on verbal memory performance at post-CR in the entire cohort.

Pre-CR characteristics	β (95 %CI)	*p* value
Study visits	0.899 (0.67–1.13)	<0.001
Treatment group	−0.356 (−0.92–0.21)	0.221
Disease duration	0.178 (−0.13–0.49)	0.266
EDSS	0.055 (−0.26–0.37)	0.734
DMTs (line)	−0.234 (−0.64–0.17)	0.262
CRQ score	0.366 (0.07–0.66)	0.018
HADS	0.249 (−0.11–0.61)	0.184
MFIS	−0.157 (−0.51–0.20)	0.392
nLv	−0.101 (−044–0.23)	0.557
nGMv	0.248 (−0.08–0.58)	0.148

Beta coefficients and 95 % confidence intervals (CI) from a mixed-effect model. CR: cognitive rehabilitation; EDSS: Expanded Disability Status Scale; DMTs: Disease Modifying Therapies; HADS: Hospital Anxiety and Depression Scale; MFIS: Modified Fatigue Impact Scale; CRQ: cognitive reserve questionnaire; nLv: normalized lesion volume; nGMv: normalized grey matter volume.

local efficiency and strength in 8 (11 %) (g range −0.24–0.30) and 7 (9 %) (g range 0.20–0.33) nodes, respectively, predominantly involving the temporal, occipital, and cingulate cortex (Fig. 3B). Patients in the static group showed lower proportion of nodes with changes in both local efficiency (Chi-squared = 4.503, 95 %CI 0.01–0.28, $p = 0.034$) and strength (Chi-squared = 4.787, 95 %CI 0.02–0.27, $p = 0.029$) compared with those receiving active treatment.

Differences between pre- and post-CR were also analysed separately in patients with different cognitive status. In the mild-CI group, post-CR analysis revealed an increase in local efficiency and strength in 3 (4 %) (g range 0.12–0.26) and 4 (5 %) (g range 0.27–0.42) nodes, respectively, mainly involving the temporal, occipital, and parietal cortex (Fig. 3C). Patients with severe-CI showed differences in local efficiency and strength in 23 (30 %) (g range 0.12–0.30) and 28 (37 %) (g range 0.15–0.43) nodes, respectively, particularly including the temporal, frontal and cingulate cortex (Fig. 3D). Thus, patients with severe-CI had more nodes with changes in local efficiency (Chi-squared = 16.750, 95 %CI 0.14–0.39, $p < 0.001$) and strength (Chi-squared = 20.940, 95 %CI 0.18–0.45, $p < 0.001$) after CR compared with the mild-CI group.

3.2.2. Changes in structural connectivity associated with verbal memory performance

Associations between improvements in verbal memory and statistically significant changes in connectivity were explored, highlighting associations ($p < 0.05$) in Fig. 3.

When the analysis was restricted to the active treatment group only, associations were found between verbal memory performance and local efficiency in 8/19 (42 %) nodes and in strength in 8/18 (44 %) nodes, mostly including the frontal cortex. Conversely, within the static treatment group, only changes in local efficiency in 3/8 nodes (38 %), primarily in the parietal cortex, were associated with verbal memory performance.

Further stratification based on cognitive status showed no associations between changes in structural connectivity and verbal memory performance among patients with mild-CI. However, in patients with severe-CI, associations were found between improvements in verbal memory and changes in local efficiency in 16/23 nodes (70 %) and strength in 16/28 nodes (57 %). These associations were particularly prominent in the frontal and temporal cortex.

4. Discussion

In this double-blind randomised clinical trial, we aimed to assess the efficacy of GNPT in the rehabilitation of cognitive dysfunction and characterise its impact on brain networks among MS patients, comparing upward intensity treatment to low-intensity static treatment.

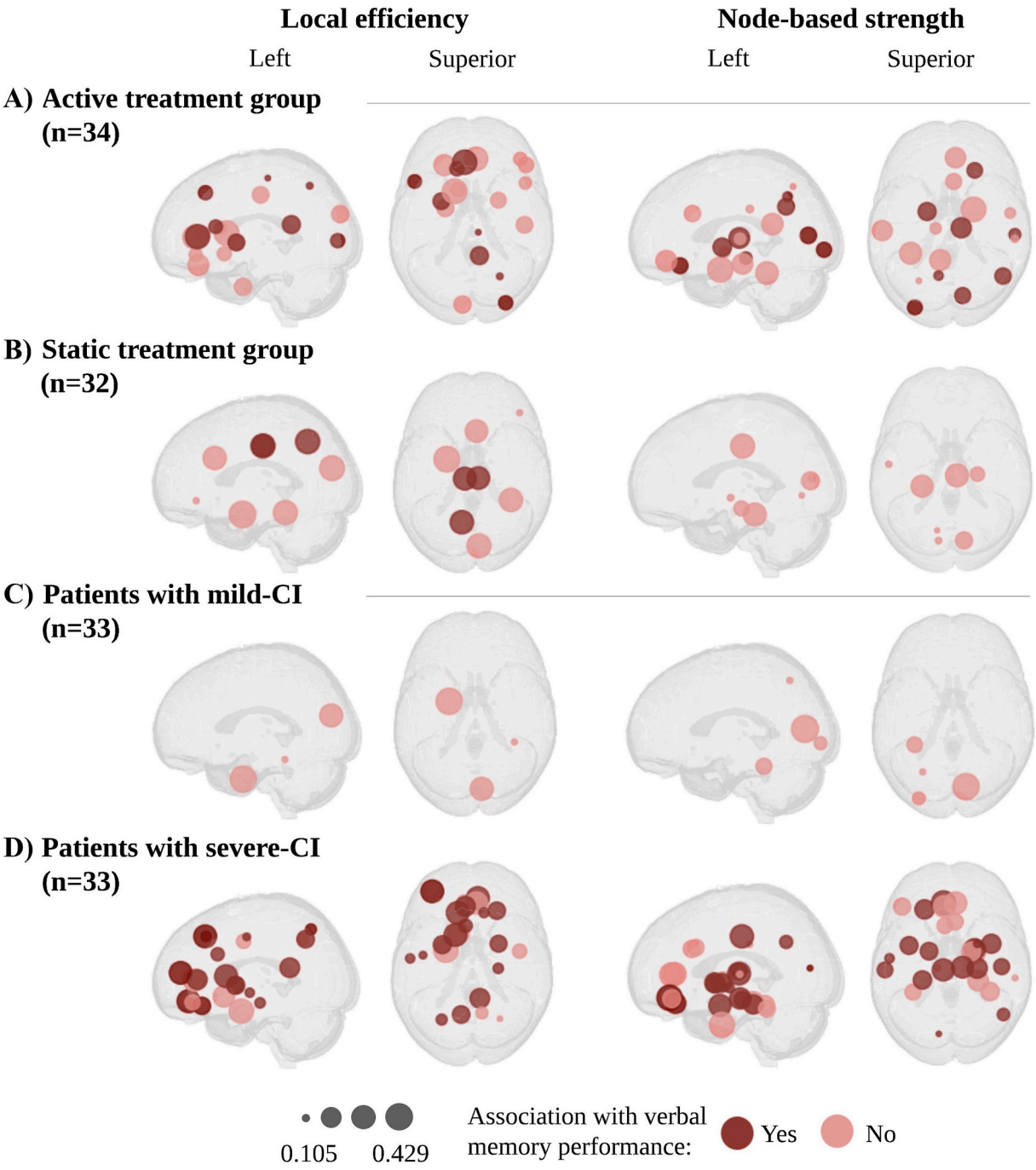

Fig. 3. Microstructural connectivity changes induced by CR and its association with verbal memory performance. Depiction of statistically significant nodes between pre- and post-CR using μFA. The circle size depends on the estimated β value and the circle colour depends on the association with verbal memory performance. The figure was generated using Netplotbrain, a Python-based tool accessible at https://www.netplotbrain.org. CI: cognitive impairment.

The results revealed that 12-week training with the computer-assisted programme had no benefits on attention-IPS, but improved verbal memory in both treatment groups, being patients with higher cognitive reserve those who benefit more from CR. When stratified by CI severity, patients with mild-CI improved similarly regardless of the treatment received, while verbal memory improvement in severe-CI patients occurred only in those who received active treatment. Furthermore, cognitive improvements, particularly in verbal memory, were accompanied by increased diffusion-based structural network connectivity in multimodal regions, with higher network efficiency in the frontal and temporal cortex being associated with verbal memory improvement. These findings reinforce the CR as a valuable tool to enhance cognitive skills and promote neuronal plasticity in people with MS.

The positive results regarding the improvement of verbal memory are in concordance with other clinical trials in MS, which have shown greater memory improvement compared to other cognitive domains (Shatil et al., 2010; Brissart et al., 2020; Vilou et al., 2020). In the present study, these differences did not extend to other cognitive domains, contrary to findings from other studies reporting changes also in executive function, attention and IPS (Gich et al., 2015; Sharbafshaaer et al., 2022). These discrepancies may be explained by the complex nature of CI in MS patients, as it is driven by declining verbal memory and IPS over time (Lopez-Soley et al., 2021; Wojcik et al., 2022). Additionally, a significant decrease in verbal memory scores was observed between

baseline and pre-CR, which may initially seem unexpected given that learning effects are typically observed in repeated cognitive testing. However, we hypothesize that this decline may reflect the heterogeneity of cognitive performance in individuals with MS, where fluctuations are common due to factors such as fatigue, attentional variability, and disease progression (Chen et al., 2022). Despite this variability, the beneficial effects of CR were observed regardless of whether baseline or pre-CR values were considered, reinforcing the robustness of the intervention. Moreover, the verbal memory domain showed the poorest performance at the pre-CR stage, particularly in the active treatment group, potentially contributing to a greater improvement in this domain. Interestingly, we did not observe significant differences in terms of efficacy between active versus static treatment, even though the active treatment group had worse cognitive scores before CR. This could be because the static treatment group was not a waiting list group, but a group that underwent the same training programme as the active treatment group with different intensity. This suggests that CR benefits MS patients with CI, even if the programme is suboptimal. Furthermore, the results showed a persistent, though gradually decreasing, improvement in verbal memory for 10 months after rehabilitation. A finding that supports the long-lasting benefits of CR and underscores the importance of conducting periodic CR in clinical practice to maintain these improvements (Mousavi et al., 2020).

Stratifying patients by cognitive status revealed that verbal memory improvement in mild-CI patients was achieved with both therapeutic strategies. However, among patients with severe-CI, improvement in verbal memory was only evident in the active treatment group, since in the static treatment group the 24 % increase did not reach statistical significance. These results suggest that patients with more severe cognitive dysfunction may require more intensive rehabilitation to demonstrate measurable improvement. Although, we cannot rule out that the small sample size may have limited the ability to detect progress within this group. Moreover, the results showed that patients with higher cognitive reserve are those who benefit more from CR. Cognitive reserve could be enhancing their response to the rehabilitation, as its protective effect on cognitive performance has been well demonstrated (Sumowski and Leavitt, 2013).

Despite no significant changes in the MSQOL-54 composite scores post-CR, participants rated the intervention highly in terms of usefulness and willingness to participate again. The MSQOL-54 captures a broad range of aspects that may not be directly impacted by CR alone, suggesting that interventions targeting multiple domains (e.g., physical, emotional, or social) may yield more pronounced effects. The positive subjective ratings, however, indicate that participants perceived value in the intervention, encouraging the future implementation of similar interventions.

Following CR, neuroimaging studies have demonstrated functional changes in patterns of brain organisation, which have been associated with improved cognitive functioning, suggesting training-related neuroplasticity (Prosperini and Di Filippo, 2019; Rocca et al., 2019). Despite methodological differences between studies, findings are consistent pointing out the role of the cingulate cortex, precuneus, thalamus and cerebellum in functional brain plasticity enhanced by CR (Rocca et al., 2019). By contrast, structural MRI studies are still limited and have yielded inconsistent results (Prosperini and Di Filippo, 2019). Specifically, one study reported no effects of CR on structural plasticity measured with white matter diffusivity in normal appearing tissue (Filippi et al., 2012), while others found diffusion tensor imaging changes on corpus callosum after video game-based CR (De Giglio et al., 2016) and increased parahippocampal volume after visual imagery training (Ernst et al., 2018).

In the present study, increments of nodal local efficiency and strength, measured with μFA, after CR were found in cognitive relevant regions, both in active and static treatment groups, regardless of patient's cognitive status. However, the CR strategy with increasing task difficulty enhanced more changes in core nodes of the structural network than the static protocol. All in all, CR seems to enhance the effectiveness of local information transfer between multimodal regions, which could be reflecting structural brain reorganisation and compensation mechanisms. Results are encouraging, as CI in MS may be the result of more rigid and overloaded central structures that interfere with information flow, and lead to a network collapse (Zhang et al., 2021; Schoonheim et al., 2022). The present results are in line with a recent study that reported changes in graph parameters using grey matter networks after a 5-week CR in 15 MS patients (Frieske et al., 2022). The authors suggest that CR might help prevent network deterioration by increasing local efficiency and facilitating compensation mechanisms. Furthermore, our results show that improvements in verbal memory after CR are related to increased nodal connectivity, predominantly in the temporal cortex. These findings support the ability of CR to modify white matter connections and consequently enhance the connectivity of several brain regions through plasticity mechanisms.

Interestingly, we observed differences in structural connectivity changes after CR between patients with mild and severe-CI. Patients with mild-CI showed minimal increases in connectivity post-CR, which were not associated with verbal memory improvement. This might imply that, in patients with mild cognitive dysfunction, other mechanisms such as cognitive reserve (Lopez-Soley et al., 2020) or functional modifications may modulate the cognitive improvements. Conversely, patients with severe-CI had poorer connectivity prior to training and exhibited changes in a larger number of nodes, particularly in the frontal and temporal cortex, which were associated with verbal memory improvement. These findings suggest an interplay between cognitive status and the degree of neural plasticity, where more overrated networks may show more cognitive disruption and a more marked impact after CR (Schoonheim et al., 2022).

This study has important strengths, including the robust design as a multicentre, double-blind, randomised clinical trial. A key advantage of this approach was providing at-home access to the intervention, which contributed to a high adherence rate and demonstrated its potential for cost-effective clinical use. Furthermore, the study included a low-intensity treatment group as a comparator, instead of a waiting-list control group. However, adding a purely passive control group without CR could have provided additional insights into the benefits of rehabilitation. In addition, the microstructural connectivity derived from μFA maps was used, leveraging its previously demonstrated superiority over standard fractional anisotropy due to its enhanced sensitivity and specificity in detecting and characterising brain tissue changes (Vivó et al., 2024).

Nonetheless, our study also has some limitations that should be considered. The stratified groups were small, and the cohort predominantly consisted of relapsing-remitting MS patients, reflecting the typical real-world MS population. Even so, our study included an adequately powered sample, highlighting the inclusion of patients with different cognitive status and the challenging recruitment due to the time-consuming nature of participation. Moreover, future research should incorporate long-term connectivity analyses to determine the persistence and potential evolution of brain network modifications following CR.

5. Conclusion

Our study demonstrates that CR using GNPT in MS patients with cognitive dysfunction not only induced temporary positive effects on verbal memory, but also increased the underlying microstructural network connectivity in multimodal cognition-related regions. Such results are encouraging, given that benefits were observed regardless of the treatment intensity, suggesting adaptability to most MS patients. However, in patients with severe-CI, improvement depends on more intensive CR. Moreover, patients with higher cognitive reserve derive greater benefit from CR, supporting the promotion of mentally stimulating activities from the time of diagnosis. Overall, findings reinforce

the CR as a valuable tool to enhance cognitive skills and neuronal plasticity, reaffirming its usefulness as a reliable intervention for the clinical management of cognitive deficits in MS patients.

CRediT authorship contribution statement

E. Lopez-Soley: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **E. Martinez-Heras:** Writing – review & editing, Writing – original draft, Software, Methodology, Formal analysis, Data curation, Conceptualization. **F. Vivo:** Writing – review & editing, Software, Methodology, Formal analysis, Data curation. **A. Calvi:** Writing – review & editing, Data curation. **S. Alba-Arbalat:** Writing – review & editing, Data curation. **L. Romero-Pinel:** Writing – review & editing, Data curation. **S. Martínez-Yélamos:** Writing – review & editing, Data curation. **C. Ramo-Tello:** Writing – review & editing, Data curation. **S. Presas-Rodríguez:** Writing – review & editing, Data curation. **E. Munteis:** Writing – review & editing, Data curation. **J.E. Martínez-Rodríguez:** Writing – review & editing, Data curation. **J. Sastre-Garriga:** Writing – review & editing, Data curation. **E. Anglada:** Writing – review & editing, Data curation. **E.R. Meza-Murillo:** Writing – review & editing, Data curation. **M.J. Arévalo:** Writing – review & editing, Data curation. **R. Sánchez-Carrión:** Writing – review & editing, Data curation. **R. Pelayo:** Writing – review & editing, Data curation. **M. Bernabeu:** Writing – review & editing, Data curation. **N. Sola-Valls:** Writing – review & editing, Data curation. **M. Hervas:** Writing – review & editing, Data curation. **M. Sepulveda:** Writing – review & editing, Data curation. **A. Saiz:** Writing – review & editing, Data curation. **Y. Blanco:** Writing – review & editing, Data curation. **E. Solana:** Writing – review & editing, Writing – original draft, Visualization, Software, Methodology, Formal analysis, Data curation, Conceptualization. **S. Llufriu:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Funding acquisition, Data curation, Conceptualization.

Funding

This work was sponsored by the Instituto Carlos III (ISCIII) and co-funded by the European Union through the Plan Estatal de Investigación Científica y Técnica y de Innovación 2015–2024 (PI15/00587 to SL and AS; PI18/01030 to SL and AS; PI21/01189 to SL and AS), by AGAUR SGR-Cat 2021, by the Red Española de Esclerosis Múltiple (REEM – RD16/0015/0002, RD16/0015/0003), by Bristol-Myers Squibb, the Ayudas Merck de Investigación 2017 from the Fundación Merck Salud and the Proyecto Societat Catalana Neurologia 2017.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: EMH, FV, SAA, EA, ERMM, MJA, RSC and MB declare nothing to disclose; ELS holds a grant 100028ID1 AGAUR INVESTIGO22: Programa Investigo. Mecanismo de Recuperación, Transformación y Resiliencia. Funded by the European Union, Next Generation EU. Previously holded a grant from the University of Barcelona predoctoral grant (APIF) and received travel reimbursement from ECTRIMS and Sanofi; AC is supported by the ECTRIMS post-doc fellowship (2022), previously received a UK MS Society PhD studentship (2020), a Guarantors of Brain "Entry" clinical fellowship (2019), and an ECTRIMS-MAGNIMS fellowship (2018). He received travel reimbursement from UK MS society, ECTRIMS, NAIMS; LRP has received in the last three years funding for travel and congress expenses and honoraria for lectures from Biogen, Bristol Myers Squibb, Novartis, Merck, Roche and Teva; SMY has received in the last three years support for congress attendance from Biogen, Bristol Myers Squibb, Janssen, Merck, Novartis, Roche and Sandoz. The institution where LRP and SMY work (Hospital Universitari de Bellvitge/ Institut d'Investigació Biomèdica de Bellvitge) has received in the last three years and dedicated exclusively to support the research of the Unit, fees for advisory council, collaborations, donations and advice from Almirall, Bayer, Biogen, Bristol Myers Squibb, Celgene, Genzyme, Horizon/Amgen, Janssen, Kern Pharma, Lilly, Merck, Novaxpharm, Novartis, Roche, Sandoz and Sanofi; CRT received research support or compensation for consulting fees, speaker honoraria, support for attending meetings and/or travel, participation on advisory board and research grants for her institution from Biogen Idec, Novartis, Sanofi, Janssen, Bristol, Roche, Almirall, Sandoz and Merck. She holds grants from the ISCIII (PI21/00944; RICORS 21/0002), European grant H2020 (RESTORE – 779316), AGAUR (2021SGR00002); SPR has received travel and congress expenses from Biogen, Novartis and Merck and speaker fees from Biogen and Merck; EM received speaker honoraria from Merck; JM has received personal fees for consulting services and lectures from Novartis, Biogen Idec, Sanofi and Merck-Serono; JSG received compensation in the last 24 months for consulting services and speaking honoraria from BMS, Sanofi, Merck, Janssen, Novartis, and Roche, is scientific director of Revista de Neurología and member of the editorial committee of Multiple Sclerosis Journal. He has received research support from Fondo de Investigación en Salud (PI19/00950 and PI22/00750) from Instituto de Salud Carlos III, Spain; RP receives a grant from the ISCIII (PI19/01634); NSV received funding from the Spanish Government (Instituto de Salud Carlos III, Spain, and Fondo Europeo de Desarrollo Regional [FEDER, FI16/00251] and speaker honoraria from Sanofi, Novartis, Bristol, Myer Squibb, Johnson and Johnson, Biogen-idec, Merck-Serono and Roche; MH received speaker honoraria from Biogen-Idec, Novartis, Merck-Serono, and Sanofi-Genzyme; MS received speaking honoraria from Roche, Biogen, Bial and Horizon Therapeutics and travel reimbursement from Biogen, Sanofi, Merck, Bial and Roche for national and international meetings; AS received compensation for consulting services and speaker honoraria from Merck, Biogen-Idec, Sanofi- Novartis, Roche, Janssen and Horizon Therapeutics; YB received compensation for consulting services and speaker honoraria from Biogen, Novartis, Bristol Myer Squibb Genzyme, Sanofi, Johnson & Johnson, Sandoz and Merck. ES received travel reimbursement from Sanofi, Merck and ECTRIMS; SL received compensation for consulting services and speaker honoraria from Biogen Idec, Novartis, TEVA, Genzyme, Sanofi, Merck and Bristol-Myers Squibb, and holds grants from the Instituto de Salud Carlos III, AGAUR and EME-REEM.

Acknowledgments

The authors are grateful to the Fundació Clínic per a la recerca biomèdica-IDIBAPS and Hospital Clinic Barcelona (Barcelona, Spain), which are supported by the CERCA Programme/Generalitat de Catalunya. We are also grateful to all patients and families for their participation in this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2025.103775.

Data availability

The datasets generated and/or analysed in the current study, as well as the code, are available from the corresponding authors upon reasonable request.

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