Original research

Cognitive rehabilitation effects on grey matter volume and Go-NoGo activity in progressive multiple sclerosis: results from the CogEx trial

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ABSTRACT

Background Research on cognitive rehabilitation (CR) and aerobic exercise (EX) to improve cognition in progressive multiple sclerosis (PMS) remains limited. CogEx trial investigated the effectiveness of CR and EX in PMS: here, we present MRI substudy volumetric and task-related functional MRI (fMRI) findings.

Methods Participants were randomised to: 'CR plus EX', 'CR plus sham EX (EX-S)', 'EX plus sham CR (CR-S)' and 'CR-S plus EX-S' and attended 12-week intervention. All subjects performed physical/cognitive assessments at baseline, week 12 and 6 months post intervention (month 9). All MRI substudy participants underwent volumetric MRI and fMRI (Go-NoGo task).

Results 104 PMS enrolled at four sites participated in the CogEx MRI substudy; 84 (81%) had valid volumetric MRI and valid fMRI. Week 12/month 9 cognitive performances did not differ among interventions; however, 25–62% of the patients showed Symbol Digit Modalities Test improvements. Normalised cortical grey matter volume (NcGMV) changes at week 12 versus baseline were heterogeneous among interventions (p=0.05); this was mainly driven by increased NcGMV in 'CR plus EX-S' (p=0.02). Groups performing CR (ie, 'CR plus EX' and 'CR plus EX-S') exhibited increased NcGMV over time, especially in the frontal (p=0.01), parietal (p=0.04) and temporal (p=0.04) lobes, while those performing CR-S exhibited NcGMV decrease (p=0.008). In CR groups, increased NcGMV (r=0.36, p=0.01) at week 12 versus baseline correlated with increased California Verbal Learning Test (CVLT)-II scores. 'CR plus EX-S' patients exhibited Go-NoGo activity increase (p<0.05, corrected) at week 12 versus baseline in bilateral insula.

Conclusions In PMS, CR modulated grey matter (GM) volume and insular activity. The association of GM and CVLT-II changes suggests GM plasticity contributes to cognitive improvements.

Trial registration number NCT03679468.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Patients with progressive multiple sclerosis (MS) often present severe cognitive deficits, affecting their daily life activities and quality of life. Cognitive rehabilitation and physical exercise can be effective in improving cognition in MS; however, studies in progressive MS are still scanty.

⇒ MRI is a useful paraclinical tool, which has been employed during various rehabilitation protocols to quantify putative measures of plasticity following the intervention.

WHAT THIS STUDY ADDS

⇒ During the CogEx study, cognitive rehabilitation and physical exercise were both effective in improving the cognition of progressive MS participants, with no differences among interventions.

⇒ Groups performing cognitive rehabilitation showed increased grey matter volumetry (especially in frontal, parietal and temporal lobes) and insular functional MRI activity versus those performing sham cognitive rehabilitation.

⇒ Grey matter volume increase over time was correlated with concomitant improvements in cognitive performances.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Involving patients with progressive MS in intervention programmes requiring an enriched lifestyle is beneficial for their cognition, independent of treatment.

⇒ Grey matter plasticity may be one of the substrates explaining the observed cognitive improvements.

INTRODUCTION

Cognitive dysfunction is present in a large proportion of patients with multiple sclerosis (MS).[1] One of the most affected domains is information processing speed (IPS); however, visuospatial abilities, executive functions and working memory are also involved.[2] Progressive (P) MS often presents more severe cognitive deficits than relapsing-remitting (RR) patients.[3]

Cognitive rehabilitation (CR) effectively enhances cognition in MS, with various CR protocols showing benefits in the trained domains, especially in RRMS.[4 5] Preliminary data in other neurological conditions also report cognitive improvements after physical exercise (EX) rehabilitation[6]; however, evidences in MS are less straightforward.[7] MRI is valuable to assess MS-related abnormalities and was often used during rehabilitation to quantify putative measures of plasticity post intervention.[8 9] Numerous studies detected functional MRI (fMRI) activity and connectivity changes over time following cognitive/motor rehabilitation in MS, generally in brain regions subserving the trained function, suggesting that functional plasticity mechanisms underlie patients' improvements.[10–12] Results related to structural plasticity are more controversial.[10 11]

Most studies demonstrating the efficacy of CR, EX and combined CR/EX programmes on cognitive functions were conducted in patients with RRMS,[7 13] while investigations in PMS are still preliminary and limited by small sample size, cognitive status heterogeneity, lack of MRI monitoring and no medium-term observations.[14 15] To overcome such limitations, we recently conducted 'Improving Cognition in People With Progressive Multiple Sclerosis Using Aerobic Exercise and Cognitive Rehabilitation' (CogEx, ClinicalTrials.gov),[16] a multiarm, randomised, blinded and sham-controlled trial testing the effect of different CR and EX combinations on cognitive functions in patients with PMS. CogEx was run from 11 international research centres, and enrolled more than 300 patients with PMS with impaired IPS. Even though CogEx results failed to demonstrate improved efficacy of combined CR and EX on cognitive performances (especially on IPS, the trial's primary endpoint) over either interventions alone,[17] IPS improvements could be seen in a large proportion of participants,[17] ultimately suggesting that keeping patients with PMS active across multiple domains may contribute to cognitive amelioration.[17] In a CogEx subgroup at four selected sites, volumetric MRI and fMRI at all study time points were also acquired.[16] Our hypothesis was that modifications in grey matter (GM) volumes and fMRI activity occur in patients with PMS following rehabilitation, potentially explaining concomitant cognitive changes. To test this, we acquired three-dimensional (3D) T1-weighted MRI scans for tracking volumetry of whole-brain and tissue compartments. We also acquired fMRI scans during a sustained attention task (namely, the Go-NoGo task), already employed in MS to map functional substrates of cognitive impairment[18] and to track longitudinal activity changes after rehabilitation.[12] This paper presents findings of the CogEx volumetric MRI and active fMRI substudy.

MATERIALS AND METHODS

Patient consent

Written informed consent was obtained from subjects before participation.

Participants

Four centres participated in the CogEx MRI substudy: (1) IRCCS San Raffaele Hospital (Milan, Italy); (2) University of Genoa (Genoa, Italy); (3) University of Alabama at Birmingham (Birmingham, Alabama, USA) and (4) Kessler Foundation (East Hanover, New Jersey, USA).

Patients were enrolled between 14 December 2018 and 2 April 2022. Inclusion and exclusion CogEx criteria are reported elsewhere[16 17] and in the online supplemental methods. Among key inclusion criteria, there was a confirmed diagnosis of PMS and impaired IPS based on the Symbol Digit Modalities Test (SDMT) evaluation.

Study design and interventions

CogEx methodology has been previously described.[16 17] Patients were randomised (1:1:1:1) to four treatment arms: 'CR plus EX', 'CR plus sham EX (EX-S)', 'EX plus sham CR (CR-S)' and 'CR-S plus EX-S'. Participants attended 12 weeks of intervention. Clinical, neuropsychological and MRI assessments were conducted at baseline, immediately following intervention ('week 12') and 6 months post intervention ('month 9'). CR was provided using the RehaCom programme.[16 17] CR-S consisted of internet training, based on previous studies.[19] EX consisted of aerobic exercise performed on a recumbent arm-leg step ergometer (NuStep T5XR, Ann Arbor, Michigan, USA).[16 17] EX-S was focused on balance training and stretching.[16 17]

Clinical and neuropsychological assessment

At all time points (baseline, week 12 and month 9), experienced neurologists blinded to MRI findings performed a neurological examination with Expanded Disability Status Scale score rating and disease-modifying treatment recording (baseline only), as well as evaluation of walking capacity (6-minute walking test), physical activity and cardiorespiratory fitness.[16 17]

At the same time points, patients underwent a neuropsychological assessment through the Brief International Cognitive Assessment of Multiple Sclerosis,[20] including the SDMT for IPS evaluation, the Brief Visuospatial Memory Test Revised (BVMT-R) for visual memory evaluation and the California Verbal Learning Test-II (CVLT-II) for verbal memory evaluation. Corresponding z-scores were produced by country-specific regressions based on normative values.[21 22] At follow-up, subjects were considered SDMT-improved if their score increased by at least four points.[23] SDMT improvements ≥8 points were also tested.[23]

MRI acquisition

Using 3.0 Tesla scanners (IRCCS San Raffaele: Philips Ingenia; University of Genoa and University of Alabama: Siemens Prisma; Kessler Foundation: Siemens Skyra) and standardised guidelines for subjects' positioning, the following brain MRI sequences were acquired: (1) sagittal 3D fluid-attenuated inversion recovery (FLAIR); and (2) sagittal 3D T1-weighted sequence. Whenever possible, an axial T2*-weighted single-shot echo planar imaging sequence during a Go-NoGo fMRI task (total=160 volumes), was also acquired (online supplemental methods).

MRI analysis

Structural MRI analysis

Focal T2-hyperintense white matter (WM) lesions were identified by a fully automated and validated approach using the 3D FLAIR and 3D T1-weighted as input.[24] Output lesion masks were visually checked (and edited, if necessary) by an experienced observer and T2-hyperintense WM lesion volume (LV) was obtained. At follow-up, new T2-hyperintense lesions versus previous scans were counted. At all time points, normalised GM volume (NGMV), normalised cortical GM (NcGMV), normalised WM volume (NWMV) and normalised brain volume (NBV, ie, the sum of NGMV and NWMV) were measured using SIENAx software on lesion-filled 3D T1-weighted sequences.[25] Five cortical masks (frontal, insular-cingulate, occipital, parietal and temporal) were derived using the Automated Anatomical Labeling (AAL) atlas.[26] Lobar GM volume was calculated by

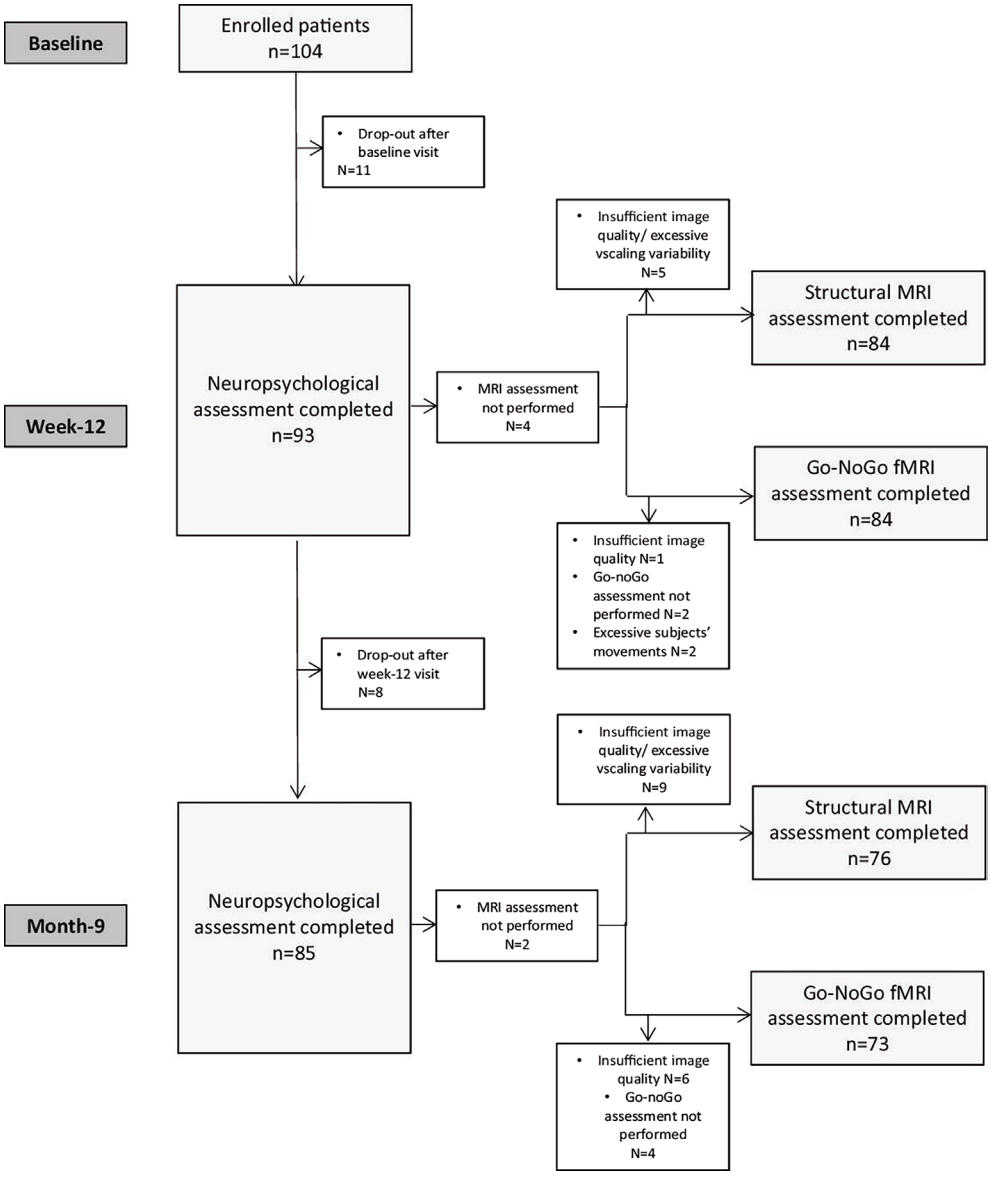

Figure 1 Flowchart showing the main steps of the CogEx MRI substudy. The number of patients with multiple sclerosis (MS) undergoing each step, as well as reasons for exclusion, are reported. fMRI, functional MRI.

applying these masks to single-subject GM maps, after back-transformation to native space, and was normalised using the SIENAx scaling factor. Segmentation of subcortical GM was performed using the FMRIB Software Library (FSL) FMRIB's Integrated Registration and Segmentation Tool (FIRST) tool[25]; volumes of these structures were calculated and normalised using the FSL SIENAx scaling factor. Given their possible relevance, normalised thalamic volume, normalised hippocampal volume and normalised volume of other deep GM nuclei (NDGMV, ie, the sum of the caudate nucleus, pallidum, putamen, amygdala and nucleus accumbens) entered subsequent analysis. At follow-up, percentage brain volume change (FSL SIENA) was calculated versus previous time points. Changes of NcGMV, lobar NcGMV, thalamic, hippocampal and NDGMV were calculated as percentage differences versus previous scans. Total NGMV and NWMV changes over time were not assessed, because of possible segmentation instability. The mean percentage change of the FSL SIENAx scaling factor at follow-up time points compared to baseline was 0.45% (SD=0.76%). To ensure longitudinal consistency, volumetric assessments were excluded from statistical analysis if the FSL SIENAx scaling factor showed excessive variability (>2 SD compared with the mean) across time points.

fMRI analysis

After pre-processing (online supplemental methods), changes in blood oxygenation level-dependent contrast during the Go-NoGo task were assessed using the general linear model and the theory of Gaussian fields. The first-level design matrix included motion parameters as regressors; average activations over all blocks were derived with appropriate linear contrasts.

Statistical analysis

Statistical analysis was performed using SPSS (IBM, V.26.0) and SAS V.9.0. Descriptives of each intervention group were reported as means (and SD) or median (and IQR) for continuous variables, while categorical variables were reported as frequencies. T2 LV was log-transformed.

Table 1 Main baseline demographic, clinical and neuropsychological characteristics of multiple sclerosis (MS) patients participating in the CogEx MRI substudy, divided according to received intervention

	'CR plus EX'	'CR plus EX-S'	'EX plus CR-S'	'CR-S plus EX-S'	P value
N	24	27	20	22	
Mean age (years) (SD)	51 (8.2)	52.5 (5.8)	52.1 (6.0)	51.7 (7.6)	0.89*
Sex (M/F)	11/13	10/17	6/14	9/13	0.74†
Median EDSS score (IQR)	5.0 (4.0–6.5)	6.0 (4.5–6.5)	5.5 (4.0–6.5)	6.0 (4.5–6.5)	0.72‡
Mean disease duration (years) (SD)	14.4 (10.1)	15.4 (9.0)	14.7 (11.3)	19.6 (9.9)	0.29*
Type of MS (primary/secondary progressive)	7/17	6/21	5/15	3/19	0.64†
6MWT total distance (m) (SD)	231.9 (146.6)	242.4 (102.5)	244.7 (140.8)	271.7 (140.6)	0.77*
VO_2 peak (mL/min/kg) (SD)	14.8 (5.3)	16.1 (6.0)	15.8 (4.5)	15.1 (7.8)	0.86*
Mean WR_{peak} (W) (SD)	74.5 (29.3)	73.1 (27.8)	76.2 (28.0)	74.7 (35.1)	0.98*
Average % in MVPA (SD)	1.7 (1.9)	1.2 (1.7)	2.3 (3.4)	1.3 (1.3)	0.40*
Education (total years of schooling) (SD)	12.5 (3.7)	13.9 (3.3)	14.2 (2.8)	14.1 (3.5)	0.32*
SDMT – mean number of correct responses (SD)	30.7 (7.4)	31.4 (6.5)	31.7 (6.3)	33.8 (8.3)	0.53*
SDMT z-score (SD)	−2.02 (0.5)	−2.05 (0.7)	−2.01 (0.6)	−1.85 (0.5)	0.67*
CVLT-II z-score (SD)	−1.08 (0.9)	−1.09 (1.2)	−1.01 (1.0)	−0.63 (1.1)	0.39*
BVMT-R z-score (SD)	−0.36 (0.8)	−0.67 (1.4)	−0.15 (1.2)	−0.45 (0.9)	0.45*

Only patients having baseline and week-12 neuropsychological assessments (n=93) are considered.
*Analysis of variance model.
†χ^2 test.
‡Kruskall-Wallis test.
BVMT-R, Brief Visuospatial Memory Test Revised; CR, cognitive rehabilitation; CR-S, sham cognitive rehabilitation; CVLT-II, California Verbal Learning Test-II; EDSS, Expanded Disability Status Scale; EX, physical exercise; EX-S, sham physical exercise; F, females; M, males; MVPA, moderate-to-vigorous physical activity; 6MWT, 6 min walking test; SDMT, Symbol Digit Modalities Test; WR_{peak}, peak work rate.

First, baseline demographic, clinical and neuropsychological variables were compared between patients participating in the CogEx MRI substudy and patients not participating, to test the representativeness of substudy population, using analysis of variance (ANOVA), χ^2 or Mann-Whitney U test, as appropriate. Such tests were also used to compare the four treatment arms (in terms of demographic, clinical, neuropsychological and baseline structural MRI variables) for MRI substudy patients. Only patients having at least baseline and week 12 valid neuropsychological assessments were considered.

A confirmatory analysis of the neuropsychological findings of the main trial[17] was performed. Briefly, the number of SDMT correct responses and SDMT, CVLT-II and BVMT-R z-scores were compared between interventions at week 12 using ANOVA models adjusted for baseline scores, while χ^2 tests assessed differences in the SDMT improvements among treatments.

Age-adjusted, sex-adjusted and site-adjusted linear mixed models were used to assess and compare among interventions longitudinal changes in volumetric MRI variables (at week 12 vs baseline and at month 9 vs week 12). To estimate mean percentage changes, we used as the dependent variable in each model the log-transformed volumes at the three time points. Intervention group, time and their interaction term were included as independent variables. We accounted for within-subject correlation with a compound symmetry correlation-type structure, according to information criteria. Such analyses were repeated: (1) by comparing all participants who received CR (ie, 'CR plus EX' and 'CR plus EX-S') versus those receiving CR-S (ie, 'EX plus CR-S' and 'CR-S plus EX-S'), regardless of the EX assigned; (2) by comparing all participants receiving EX (ie, 'CR plus EX' and 'EX plus CR-S') versus those receiving EX-S (ie, 'CR plus EX-S' and 'CR-S plus EX-S'), regardless of the CR assigned; and (3) by comparing SDMT-improved with not improved patients.

fMRI was analysed using SPM12 software. One-sample t-tests ($p<0.05$, family-wise error (FWE) corrected) assessed average Go-NoGo activity at different time points. Between-group comparisons of baseline activity and its longitudinal changes were assessed using age-adjusted, sex-adjusted and site-adjusted full factorial models for repeated measures. The same models produced F-contrasts assessing time-by-group interaction analysis. Results were tested at $p<0.001$, uncorrected and at $p<0.05$, FWE corrected. Analyses were repeated to test differences: (1) between CR versus CR-S patients; (2) between EX versus EX-S patients; and (3) between SDMT-improved versus not improved patients. Average fMRI activity z-score for significant regions were extracted using the REX toolbox (https://www.nitrc.org/projects/rex/) and used for correlation analysis.

Correlations between longitudinal changes in cognitive scores and concomitant changes in structural/functional MRI variables were assessed using Spearman's rank correlation coefficients.

Data availability statement

Anonymised data are available 1 year after publication, on reasonable request. Please make the request to the corresponding author, MAR. A CogEx Committee will review the request for approval. A data sharing agreement will be produced before any data are shared. The study protocol and statistical analysis plan were previously published.[16]

RESULTS

Demographic, clinical and cognitive characteristics

Figure 1 shows the study flowchart. 104 patients with PMS were initially included (IRCCS San Raffaele Hospital: n=41; University of Genoa: n=40; University of Alabama: n=13; Kessler Foundation: n=10). Of these, 93 patients (89%) completed baseline and week 12 neuropsychological evaluations and 84 (81%) completed baseline and week 12 structural MRI/fMRI. 79 PMS patients were right-handed and 5 (6%) were left-handed.

Patients participating in the CogEx MRI substudy were comparable versus those not participating for most of the clinical and neuropsychological characteristics (online supplemental table 1).

Table 2 Main structural MRI characteristics (baseline, week 12 and month 9) of the 88 patients with multiple sclerosis patients participating in the CogEx MRI substudy and having at least baseline and week 12 volumetric MRI scans

	'CR plus EX'	'CR plus EX-S'	'EX plus CR-S'	'CR-S plus EX-S'	P value	CR (ie, 'CR plus EX' and 'CR plus EX-S')	CR-S (ie, 'EX plus CR-S' and 'CR-S plus EX-S')	P value	EX (ie, 'CR plus EX' and 'EX plus CR-S')	EX-S (ie, 'CR plus EX-S' and 'CR-S plus EX-S')	P value
N	22	23	19	20		45	39		41	43	
Participants from centres: San Raffaele/Genoa/Alabama/Kessler (N)	9/9/2/2	10/7/3/3	9/7/2/1	8/7/4/1	0.98*	19/16/5/5	17/14/6/2	0.74*	18/16/4/3	18/14/4/7	0.80*
Mean T2 LV, baseline (mL) (SD)	9.0 (8.5)	12.2 (10.3)	15.9 (11.7)	8.2 (8.6)	0.17†	10.6 (9.5)	12.0 (10.8)	0.90†	12.2 (10.6)	10.3 (9.6)	0.52†
Mean NBV, baseline (mL) (SD)	1477 (68)	1449 (60)	1482 (72)	1503 (57)	0.03†	1463 (65)	1493 (65)	0.02†	1479 (69)	1474 (64)	0.57†
PBVC, week 12 vs baseline (%) (SD)	−0.01 (0.7)	−0.17 (0.6)	−0.34 (0.7)	−0.13 (0.4)	0.33†	−0.09 (0.6)	−0.22 (0.5)	0.32†	−0.16 (0.7)	−0.15 (0.5)	0.98†
PBVC, month 9 vs week 12 (%) (SD)	−0.46 (0.8)	−0.29 (0.6)	−0.41 (0.6)	−0.25 (0.8)	0.65†	−0.39 (0.7)	−0.34 (0.7)	0.56†	−0.44 (0.7)	−0.27 (0.7)	0.25†
Mean NcGMV, baseline (mL), (SD)	614 (41)	600 (41)	612 (46)	626 (30)	0.22†	607 (41)	619 (39)	0.18†	613 (42)	612 (38)	0.92†
Mean % NcGMV change, week 12 vs baseline (estimate, 95% CI)	0.41 (−0.46 to 1.27)	0.94 (0.10 to 1.78)	−0.47 (−1.38 to 0.45)	−0.51 (−1.39 to 0.39)	0.05‡	0.69 (0.09 to 1.29)	−0.49 (−1.12 to 0.14)	0.008†	−0.01 (−0.65 to 0.63)	0.27 (−0.35 to 0.89)	0.54‡
Mean % NcGMV change, month 9 vs week 12 (estimate, 95% CI)	−0.08 (−1.02 to 0.87)	−0.28 (−1.26 to 0.70)	−0.31 (−1.28 to 0.67)	0.01 (−0.96 to 0.98)	0.96‡	−0.18 (−0.85 to 0.49)	−0.15 (−0.83 to 0.53)	0.94‡	−0.20 (−0.89 to 0.49)	−0.17 (−0.87 to 0.54)	0.94‡
Mean NWMV, baseline (mL) (SD)	663 (40)	652 (30)	673 (45)	676 (43)	0.07†	657 (35)	674 (43)	0.02†	667 (42)	663 (38)	0.42†
Mean HippV, baseline (mL), (SD)	9.4 (1.2)	8.6 (1.6)	9.4 (1.5)	9.9 (1.4)	0.03†	8.9 (1.5)	9.6 (1.5)	0.06†	9.4 (1.3)	9.1 (1.6)	0.48†
Mean % HippV change, week 12 vs baseline, (estimate, 95% CI)	1.85 (−0.42 to 4.18)	0.77 (−1.43 to 3.01)	0.03 (−2.31 to 2.44)	0.10 (−2.18 to 2.45)	0.67‡	1.29 (−0.29 to 2.89)	0.07 (−1.56 to 1.74)	0.29‡	0.98 (−0.64 to 2.64)	0.45 (−1.13 to 2.06)	0.64‡
Mean % HippV change, month 9 vs week 12, (estimate, 95% CI)	−0.26 (2.67 to 2.21)	0.03 (−2.50 to 2.62)	−1.14 (−3.62 to 1.39)	1.37 (−1.16 to 3.96)	0.57‡	−0.09 (−1.83 to 1.68)	0.10 (−1.66 to 1.90)	0.87‡	−0.70 (2.42 to 1.06)	0.72 (−1.07 to 2.53)	0.26‡
Mean ThalV, baseline (mL) (SD)	19.1 (2.8)	18.3 (2.7)	19.1 (2.3)	20.1 (2.7)	0.14†	18.7 (2.8)	19.6 (2.5)	0.10†	19.1 (2.6)	19.2 (2.8)	0.89†
Mean % ThalV change, week 12 vs baseline (estimate, 95% CI)	−0.04 (−0.76 to 0.69)	−0.27 (0.97 to 0.44)	0.35 (−0.41 to 1.12)	0.17 (−0.58 to 0.92)	0.67‡	−0.15 (−0.66 to 0.34)	0.26 (−0.27 to 0.78)	0.26‡	0.14 (−0.38 to 0.67)	−0.06 (−0.57 to 0.45)	0.58‡
Mean % ThalV change, month 9 vs week 12 (estimate, 95% CI)	−0.56 (−1.35 to 0.22)	−0.25 (−1.07 to 0.58)	−0.14 (−0.95 to 0.68)	−0.40 (−1.21 to 0.41)	0.88‡	−0.41 (−0.97 to 0.14)	−0.27 (−0.83 to 0.30)	0.72‡	−0.36 (−0.92 to 0.21)	−0.32 (−0.89 to 0.26)	0.92‡
Mean NDGMV, baseline (mL) (SD)	29.3 (3.8)	27.4 (4.5)	29.2 (2.8)	30.5 (3.3)	0.06†	28.4 (4.3)	29.9 (3.1)	0.08†	29.3 (3.3)	28.9 (4.2)	0.58†
Mean % NDGMV change, week 12 vs baseline (estimate, 95% CI)	0.80 (−0.33 to 1.96)	−0.36 (−1.46 to 0.75)	−0.79 (−1.99 to 0.43)	0.35 (−0.83 to 1.55)	0.22‡	0.21 (−0.58 to 1.00)	−0.20 (−1.05 to 0.65)	0.48‡	0.06 (−0.76 to 0.90)	−0.03 (−0.84 to 0.78)	0.87‡
Mean % NDGMV change, month 9 vs week 12 (estimate, 95% CI)	−1.21 (−2.42 to 0.01)	−0.20 (−1.41 to 1.02)	0.14 (−1.13 to 1.42)	−0.40 (−1.68 to 0.90)	0.47‡	−0.70 (−1.56 to 0.16)	−0.14 (−1.04 to 0.77)	0.37‡	−0.58 (−1.45 to 0.30)	−0.29 (−1.17 to 0.60)	0.65‡

Patients were first divided according to intervention, and then grouped according to the received type of treatment (ie, cognitive rehabilitation (CR) or physical exercise (EX)).
*χ^2 test.
†Analysis of variance adjusted for age, sex and acquisition scanner.
‡Linear mixed effect model adjusted for age, sex and acquisition scanner.
CR, cognitive rehabilitation; CR-S, sham cognitive rehabilitation; EX, physical exercise; EX-S, sham physical exercise; HippV, normalised hippocampal volume; LV, lesion vol; NBV, normalised brain volume; NcGMV, normalised cortical grey matter volume; NDGMV, normalised vol of other deep grey matter nuclei (see text for further description); NGMV, normalised grey matter volume; NWMV, normalised white matter volume; PBVC, percentage brain volume change; ThalV, normalised thalamic volume.

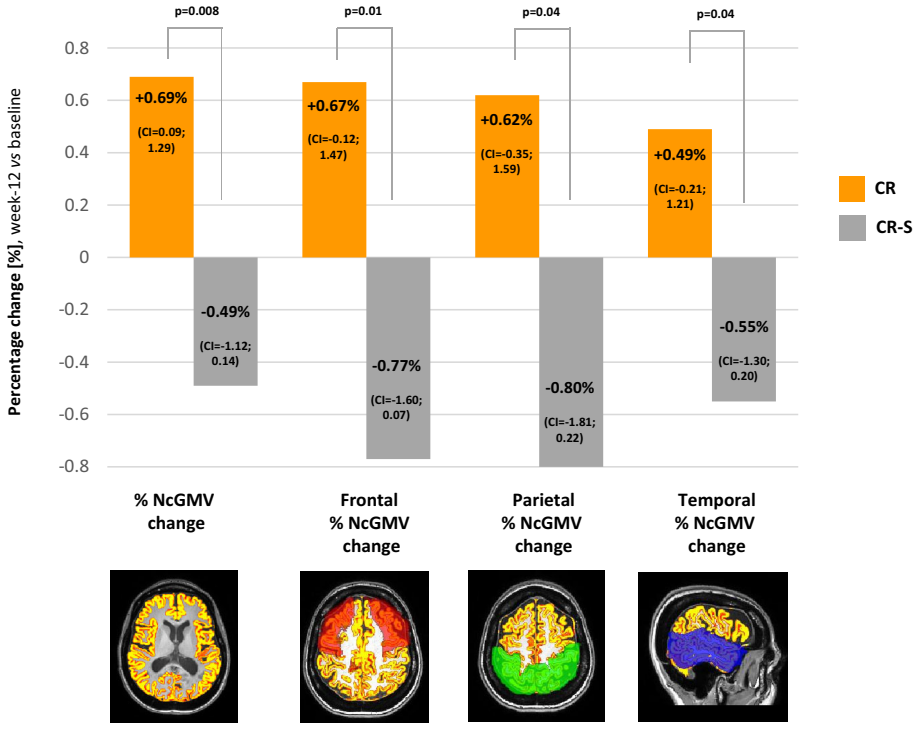

Figure 2 Results from volumetric analysis. Changes at week 12 versus baseline of normalised cortical grey matter volume (NcGMV), frontal NcGMV, parietal NcGMV and temporal NcGMV in patients performing cognitive rehabilitation (CR, N=45) versus those performing sham cognitive rehabilitation (CR-S, N=39) are shown.

Table 1 shows the main baseline demographic, clinical and neuropsychological variables of MRI substudy patients, divided according to treatment allocation. No between-group differences were found.

Cognitive outcomes

Online supplemental table 2 shows the cognitive scores of the 93 patients completing baseline and week-12 neuropsychological evaluation. Similarly to the main study,[17] no between-group differences in neuropsychological scores were found among interventions at week 12 and month 9, for any treatment subdivision.

The percentage of patients showing SDMT improvements ranged from 43% to 62% at week 12 and from 25% to 41% at month 9, depending on cut-off, with no difference among any group (online supplemental table 2).

Structural MRI findings

Seven 3D T1-weighted MRIs were excluded because of insufficient quality and 7 MRIs were excluded because of excessive variability in the FSL SIENAx scaling factor.

Table 2 summarises lesional and atrophy measures divided according to the intervention and grouped for treatment type (ie, groups performing CR vs those performing CR-S, and groups performing EX vs those performing EX-S). The distribution of centres among treatment groups was homogeneous (p=range 0.74–0.98, table 2).

Most of the baseline lesional and volumetric characteristics were similar among the four interventions, except for NBV and normalised hippocampal volume (both p=0.03).

The median new T2 lesion number at week 12 and month 9 was 0 (IQR=0–0) in all groups.

Considering atrophy, no significant heterogeneity was found in volumetric changes over time among treatment groups (p=range 0.22–0.96, table 2), except for NcGMV at week 12 versus baseline (p=0.05). A post hoc analysis revealed that such heterogeneity was mainly driven by increased NcGMV over time within 'CR plus EX-S' patients (p=0.02).

When assessing groups performing CR versus those performing CR-S, a significantly divergent behaviour was found for NcGMV changes at week 12 versus baseline (p=0.008, table 2 and figure 2), with the CR group showing NcGMV increase and the CR-S group showing NcGMV decrease over time. The analysis of lobar GM atrophy revealed that NcGMV differences between groups were mainly located in the frontal (p=0.01), parietal (p=0.04) and temporal (p=0.04) lobes (online supplemental table 3 and figure 2). The remaining structural MRI variables did not show any significant difference between CR and CR-S patients, neither at week 12 versus baseline (p=range 0.26–0.48, table 2), nor at month 9 versus week 12 (p=range 0.37–0.94, table 2).

Also, no differences were found for EX versus EX-s group comparisons (p=range 0.26–0.94; table 2) and for SDMT-improved versus not improved patients (data not shown).

fMRI findings

Behavioural performances during the Go-NoGo fMRI task were comparable across interventions (online supplemental table 4).

Online supplemental figure 1 shows the average fMRI activation, which was mainly located (p<0.05, FWE corrected) in frontal, parietal, occipital, temporal and insular cortices and did not differ between interventions (p<0.05, FWE corrected).

Table 3 and figure 3 report longitudinal changes of Go-NoGo fMRI activation in the four intervention groups.

In 'CR plus EX-S', fMRI activity increased at week 12 versus baseline in the left insula (p<0.05, FWE corrected), left postcentral gyrus (p<0.001, uncorrected) and right insula (p<0.001, uncorrected), this latter being significant at time-by-group

Table 3 Changes over time of functional MRI (fMRI) activation during the Go-NoGo task in patients enrolled in the different intervention groups (post hoc t-tests from SPM12 full factorial model for repeated measures, adjusted for age, sex and acquisition site, p<0.001, uncorrected, cluster extent k=10)

Changes over time of task-related fMRI activation						
Group	Contrast	Areas	BA	MNI space coordinates (x y z)	K	T value
'CR plus EX'	Week 12>baseline	–		–	–	–
	Baseline>week 12	–		–	–	–
	Month 9>week 12	–		–	–	–
	Week 12>month 9	L medial SFG	32	–12 28 34	52	3.73
'EX plus CR-S'	Week 12>baseline	–		–	–	–
	Baseline>week 12	–		–	–	–
	Month 9>week 12	–		–	–	–
	Week 12>month 9	–		–	–	–
'CR plus EX-S'	Week 12>baseline	L Insula*	13	–36 –28 26*	195*	4.51
		L Postcentral gyrus	48	–50 –14 26	63	3.56
		R Insula	**13**	**44 –36 20**	**33**	**3.55**
	Baseline>week 12	–		–	–	–
	Month 9>week 12	–		–	–	–
	Week 12>month 9	–		–	–	–
'CR-S plus EX-S'	Week 12>baseline	–		–	–	–
	Baseline>week 12	L SFG	46	–28 52 16	30	3.89
	Month 9>week 12	–		–	–	–
	Week 12>month 9	–		–	–	–

Results surviving at p<0.05, family-wise error corrected for multiple comparisons, are marked with*. Clusters in **bold** were significant in the time-by-group interaction analysis. BA, Brodmann area; CR, cognitive rehabilitation; CR-S, sham cognitive rehabilitation; EX, physical exercise; EX-S, sham physical exercise; L, left; MFG, middle frontal gyrus; MNI, Montreal Neurological Institute; R, right; SFG, superior frontal gyrus.

interaction analysis. Within 'CR plus EX', fMRI activity decreased (p<0.001, uncorrected) in the left superior frontal gyrus (SFG) at month 9 versus week 12. Likewise, within 'CR-S plus EX-S', fMRI activity decreased (p<0.001, uncorrected) in the left SFG at week 12 versus baseline. No changes were detected in 'EX plus CR-S'.

An increased fMRI activity in the bilateral insula at week 12 versus baseline (Montreal Neurological Institute (MNI) space coordinates, left: −36 −26 28, k=32, right: 40 −36 20, k=24, p<0.001 uncorrected) was also found within patients performing CR, being significant for the right insula at the time-by-group interaction analysis *vs* CR-S patients.

A sensitivity analysis performed by repeating all comparisons with the exclusion of five left-handed patients with PMS confirmed the previous results (data not shown). Finally, no fMRI differences were found between SDMT improved and not improved patients (data not shown).

Correlation analysis

In groups performing CR, increased CVLT-II scores at week 12 versus baseline correlated with increased NcGMV (r=0.36, p=0.01).

No further correlations were found between structural and task-related fMRI variables versus concomitant changes in cognitive scores.

DISCUSSION

Here, we analysed volumetric MRI and Go-NoGo fMRI data from CogEx MRI substudy. After the intervention, groups performing CR (and, in particular, the 'CR plus EX-S' group) had increased cortical GM volume in frontal, parietal and temporal lobes, and increased insular fMRI activity versus those performing CR-S. Cortical GM volume changes correlated with concomitant changes in cognitive performances, suggesting that GM plasticity may partially explain observed cognitive improvements.

In line with the main study,[17] combined CR and EX treatments did not show additional cognitive benefits compared with treatments in isolation or sham treatments. Previous MS reports did not give a definite indication about the superiority of combined cognitive/motor training versus single-modality trainings.[27 28] However, since cognitive impairment in MS is due to deficits of communications among multimodal regions, we hypothesised that a multidomain rehabilitation including both cognitive and aerobic components would be more effective than single CR/EX interventions. Despite this, the CogEx study did not confirm such a hypothesis. Nevertheless, a large proportion of patients[17] presented enhanced SDMT performances at follow-up, suggesting that involving patients with PMS in enriched lifestyle interventions results in cognitive improvements.[17]

Moving to MRI, the most intriguing result pertained to cortical GM changes at week 12 versus baseline: they were significantly heterogeneous among the four treatment arms, with an indication towards increased cortical GM volume in 'CR plus EX-S' patients. A divergent behaviour was also present when comparing all patients undergoing CR, who exhibited increased GM volume, and those undergoing CR-S, who showed the opposite trend. This is notable, since previous MS studies exploring the effects of CR on GM volumetry found no significant changes.[10 11] On the other hand, action-observation[29] or resistance training[30] modulated cortical GM volume. The notion that cortical GM volumetry is relevant for cognition is well-established: studies consistently linked smaller neocortical volumes with cognitive deficits in MS,[31 32] with a preferential cortical involvement in PMS.[32] Longitudinal studies indicated

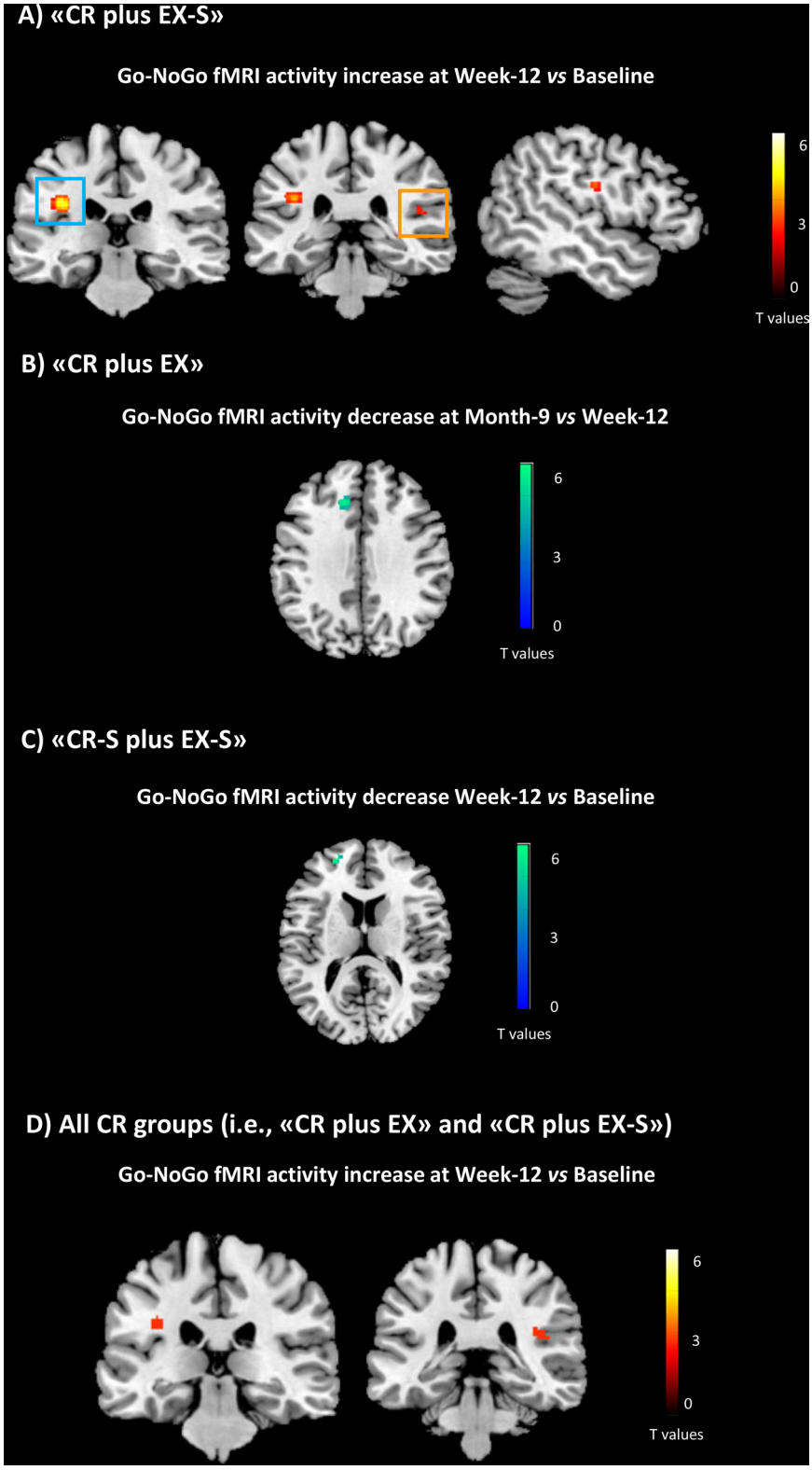

Figure 3 Changes over time of functional MRI activations during the Go-NoGo task in the different intervention groups. Clusters showing significant changes over time of functional MRI (fMRI) activation during the Go-NoGo task in the different intervention groups (post hoc t-tests from SPM12 full factorial model for repeated measures, adjusted for age, sex and acquisition site, p<0.001, uncorrected, cluster extent k=10). Increase of activation is reported using a red-yellow scale, while decrease of activation is reported using a blue-lightblue scale. (A) Changes occurring in the 'CR plus EX-S' group; (B) Changes occurring in the 'CR plus EX' group; (C) Changes occurring in the 'CR-S plus EX-S' group; (D) Changes occurring in all CR groups (ie, 'CR plus EX' and 'CR plus EX-S'). The blue box highlights the cluster surviving at p<0.05, family-wise error corrected for multiple comparisons, while the orange box highlights the cluster significant at the time-by-group interaction analysis. Images are in neurological convention. CR, cognitive rehabilitation; CR-S, sham cognitive rehabilitation; EX, physical exercise; EX-S, sham physical exercise.

greater neocortical volume decrease in cognitively deteriorating than in stable patients with MS.[33] Since GM atrophy development characterises cognitively worsening MS, the opposite trend (ie, increased or stable cortical GM volume) might be beneficial for cognitive performances. This is further reinforced by our correlation between increased NcGMV at week 12 versus baseline and concomitant CLVT-II changes. Interestingly, lobar GM analysis indicated increased cortical GM volume in the frontal, parietal and temporal lobes. This is noteworthy, since frontal, temporal and parietal regions are relevant for several cognitive functions, including those involved by the cognitive training of this study (ie, divided and sustained attention, vigilance and concentration).[17]

We found no significant volumetric change for hippocampus, thalamus and other deep GM nuclei, probably because of a relatively small sample size or to inherent measurement variability. However, hippocampal and deep GM atrophy might be more important for explaining cognition in RRMS,[34] where these structures might deplete their reserve for adaptive plasticity early on,[35] rather than in patients with PMS, where cortical damage is more relevant.[32 33] Another factor that might explain this result might be related to deep GM long-standing involvement in atrophy processes: it starts to occur at very early MS stages[36] and is therefore very pronounced in PMS. As such, it is likely that deep GM atrophy is a difficult process to be reversed by rehabilitation programmes in this phenotype.

Among fMRI findings, the most relevant result was the increase of Go-NoGo fMRI activity in insular regions after training. The insula is a multimodal brain region being a hub of the salience network, having a key role in integrating information from the default-mode and executive control networks.[37] Furthermore, the insula participates in interoception and cognitive control.[38] As such, an abnormal insular activity in MS has been linked with cognitive disturbances.[39] Our finding of increased insular activity during the Go-NoGo task immediately after CR is in line with recent findings in patients with MS remaining cognitively stable after 3 years,[40] while reduced insular connectivity characterised cognitively deteriorating patients.[40] As such, it is conceivable to hypothesise that an improved insular function might be one of the substrates of the cognitive improvements observed in patients undergoing CR. The absence of significant associations between insular activity and concomitant cognitive changes might indicate that, while reflecting changes in brain activation after CR in patients with PMS, the Go-NoGo task might not be sensitive to improvements in more complex cognitive tests. Nevertheless, future studies exploring insular connectivity in this cohort may provide additional insights into changes taking place in the insular network post rehabilitation.

This study has some limitations. First, sample size of treatment arms was relatively small: enrolling patients with PMS with controlled characteristics and willing to participate in an intensive training programme was difficult. Also, the COVID-19 emergency somewhat hampered recruitment.[17] While this did not impact our cognitive findings (the same observations were made on a larger cohort[17]), this might explain the lack of correlation between active fMRI and cognitive metrics. Second, we detected a significant correlation between cortical GM volume and concomitant CVLT-II changes over time in CR patients; however, CVLT-II improvements were not different across treatments, somehow limiting interpretability. Third, left-handedness was not an exclusion criterion. However, a few left-handed patients did not excessively contaminate fMRI findings, as shown by the sensitivity analysis reported in the Results section. Finally, global and lobar structural damage was assessed on 3D T1-weighted scans and, even if we used some precautions to improve the consistency of volumetry changes over time, we used a method not optimised for longitudinal assessment. Also, volumetric MRI results did not survive correction for multiple comparisons, thus advocating replication of these findings in larger populations.

To conclude, the CogEx MRI substudy showed no synergistic effect of CR and EX on cognitive performances or structural MRI and fMRI measures of PMS. However, CR modulated cortical GM volumes (especially in frontal, parietal and temporal lobes) and insular fMRI activity. Also, there was some association between increased cortical volume and improved CVLT-II scores in groups undergoing CR, suggesting that GM still retains a certain degree of plasticity even in this rather advanced PMS population, and that such plasticity might be one of the substrates explaining observed cognitive improvements.

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REFERENCES

1 Feinstein A. *Mind, mood and memory. The neurobehavioral consequences of multiple sclerosis*. Johns Hopkins University Press, 2022.
2 Benedict RHB, Amato MP, DeLuca J, *et al*. Cognitive impairment in multiple sclerosis: clinical management, MRI, and therapeutic avenues. *Lancet Neurol* 2020;19:860–71.
3 Huijbregts SCJ, Kalkers NF, de Sonneville LMJ, *et al*. Differences in cognitive impairment of relapsing remitting, secondary, and primary progressive MS. *Neurology* 2004;63:335–9.

4 Feinstein A, Freeman J, Lo AC. Treatment of progressive multiple sclerosis: what works, what does not, and what is needed. *Lancet Neurol* 2015;14:194–207.
5 Lampit A, Heine J, Finke C, *et al*. Computerized cognitive training in multiple sclerosis: a systematic review and meta-analysis. *Neurorehabil Neural Repair* 2019;33:695–706.
6 Petersen RC, Lopez O, Armstrong MJ, *et al*. Practice guideline update summary: mild cognitive impairment: report of the guideline development, dissemination, and implementation subcommittee of the American academy of neurology. *Neurology* 2018;90:126–35.
7 Gharakhanlou R, Wesselmann L, Rademacher A, *et al*. Exercise training and cognitive performance in persons with multiple sclerosis: a systematic review and multilevel meta-analysis of clinical trials. *Mult Scler* 2021;27:1977–93.
8 Rocca MA, Preziosa P, Filippi M. Application of advanced MRI techniques to monitor pharmacologic and rehabilitative treatment in multiple sclerosis: current status and future perspectives. *Expert Rev Neurother* 2019;19:835–66.
9 Zatorre RJ, Fields RD, Johansen-Berg H. Plasticity in gray and white: neuroimaging changes in brain structure during learning. *Nat Neurosci* 2012;15:528–36.
10 Campbell J, Langdon D, Cercignani M, *et al*. A randomised controlled trial of efficacy of cognitive rehabilitation in multiple sclerosis: a cognitive, behavioural, and MRI study. *Neural Plast* 2016;2016:4292585.
11 Filippi M, Riccitelli G, Mattioli F, *et al*. Multiple sclerosis: effects of cognitive rehabilitation on structural and functional MR imaging measures--an explorative study. *Radiology* 2012;262:932–40.
12 Sulpizio V, Berchicci M, Di Russo F, *et al*. Effect of Exoskeleton-assisted rehabilitation over prefrontal cortex in multiple sclerosis patients: a neuroimaging pilot study. *Brain Topogr* 2021;34:651–63.
13 Prosperini L, Di Filippo M. Beyond clinical changes: rehabilitation-induced neuroplasticity in MS. *Mult Scler* 2019;25:1348–62.
14 Chiaravalloti ND, Moore NB, DeLuca J. The efficacy of the modified story memory technique in progressive MS. *Mult Scler* 2020;26:354–62.
15 Messinis L, Kosmidis MH, Nasios G, *et al*. Do secondary progressive multiple sclerosis patients benefit from computer- based cognitive neurorehabilitation? A randomized sham controlled trial. *Mult Scler Relat Disord* 2020;39:101932.
16 Feinstein A, Amato MP, Brichetto G, *et al*. Study protocol: improving cognition in people with progressive multiple sclerosis: a multi-arm, randomized, blinded, sham-controlled trial of cognitive rehabilitation and aerobic exercise (COGEx). *BMC Neurol* 2020;20:204.
17 Feinstein A, Amato MP, Brichetto G, *et al*. A multi-arm, randomized, blinded, sham-controlled trial of cognitive rehabilitation and aerobic exercise (the CogEx trial) for cognitive impairment in people with progressive multiple sclerosis. *Lancet Neurol* 2023.
18 Koini M, Filippi M, Rocca MA, *et al*. Correlates of executive functions in multiple sclerosis based on structural and functional MR imaging: insights from a multicenter study. *Radiology* 2016;280:869–79.
19 Edwards JD, Wadley VG, Vance DE, *et al*. The impact of speed of processing training on cognitive and everyday performance. *Aging Ment Health* 2005;9:262–71.
20 Langdon DW, Amato MP, Boringa J, *et al*. Recommendations for a brief International cognitive assessment for multiple sclerosis (BICAMS). *Mult Scler* 2012;18:891–8.
21 Goretti B, Niccolai C, Hakiki B, *et al*. The brief international cognitive assessment for multiple sclerosis (BICAMS): normative values with gender, age and education corrections in the Italian population. *BMC Neurol* 2014;14:171.
22 Parmenter BA, Testa SM, Schretlen DJ, *et al*. The utility of regression-based norms in interpreting the minimal assessment of cognitive function in multiple sclerosis (MACFIMS). *J Int Neuropsychol Soc* 2010;16:6–16.
23 Strober LB, Bruce JM, Arnett PA, *et al*. A much needed metric: defining reliable and statistically meaningful change of the oral version Symbol Digit Modalities Test (SDMT). *Mult Scler Relat Disord* 2022;57:103405.
24 Valverde S, Cabezas M, Roura E, *et al*. Improving automated multiple sclerosis lesion segmentation with a cascaded 3D convolutional neural network approach. *Neuroimage* 2017;155:159–68.
25 Jenkinson M, Beckmann CF, Behrens TEJ, *et al*. Fsl. *Neuroimage* 2012;62:782–90.
26 Yamin MA, Valsasina P, Tessadori J, *et al*. Discovering functional connectivity features characterizing multiple sclerosis phenotypes using explainable artificial intelligence. *Hum Brain Mapp* 2023;44:2294–306.
27 Argento O, Piacentini C, Bossa M, *et al*. Motor, cognitive, and combined rehabilitation approaches on MS patients' cognitive impairment. *Neurol Sci* 2023;44:1109–18.
28 Moustafaa EBS, Darwish MH, El-Tamawy MS, *et al*. Fatigue, cognition and inflammatory biomarkers changes in response to computer-based cognitive training in multiple sclerosis patients: a randomized controlled trial. *NeuroRehabilitation* 2022;51:315–24.
29 Rocca MA, Meani A, Fumagalli S, *et al*. Functional and structural plasticity following action observation training in multiple sclerosis. *Mult Scler* 2019;25:1472–87.
30 Kjølhede T, Siemonsen S, Wenzel D, *et al*. Can resistance training impact MRI outcomes in relapsing-remitting multiple sclerosis? *Mult Scler* 2018;24:1356–65.
31 Amato MP, Bartolozzi ML, Zipoli V, *et al*. Neocortical volume decrease in relapsing-remitting MS patients with mild cognitive impairment. *Neurology* 2004;63:89–93.
32 Riccitelli G, Rocca MA, Pagani E, *et al*. Cognitive impairment in multiple sclerosis is associated to different patterns of gray matter atrophy according to clinical phenotype. *Hum Brain Mapp* 2011;32:1535–43.
33 Eijlers AJC, Dekker I, Steenwijk MD, *et al*. Cortical atrophy accelerates as cognitive decline worsens in multiple sclerosis. *Neurology* 2019;93:e1348–59.
34 Damjanovic D, Valsasina P, Rocca MA, *et al*. Hippocampal and deep gray matter nuclei atrophy is relevant for explaining cognitive impairment in MS: a multicenter study. *AJNR Am J Neuroradiol* 2017;38:18–24.
35 Vollmer TL, Nair KV, Williams IM, *et al*. Multiple sclerosis phenotypes as a continuum: the role of neurologic reserve. *Neurol Clin Pract* 2021;11:342–51.
36 Rocca MA, Valsasina P, Meani A, *et al*. Association of gray matter atrophy patterns with clinical phenotype and progression in multiple sclerosis. *Neurology* 2021;96:e1561–73.
37 Uddin LQ, Kinnison J, Pessoa L, *et al*. Beyond the tripartite cognition-emotion-interoception model of the human insular cortex. *J Cogn Neurosci* 2014;26:16–27.
38 Cole MW, Schneider W. The cognitive control network: integrated cortical regions with dissociable functions. *Neuroimage* 2007;37:343–60.
39 Weygandt M, Meyer-Arndt L, Behrens JR, *et al*. Stress-induced brain activity, brain atrophy, and clinical disability in multiple sclerosis. *Proc Natl Acad Sci U S A* 2016;113:13444–9.
40 Azzimonti M, Preziosa P, Pagani E, *et al*. Functional and structural brain MRI changes associated with cognitive worsening in multiple sclerosis: a 3-year longitudinal study. *J Neurol* 2023;270:4296–308.

Online Supplemental Methods

Participants: inclusion criteria. Inclusion criteria of CogEx study were: a) a confirmed diagnosis of PMS;[1] b) age between 25 and 65 years; c) corrected visual acuity >20/70; d) intact language comprehension based on Token Test scores >28 and ability to understand instructions; e) insufficient physical activity (i.e., Health Contribution Score of the Godin Leisure-Time Exercise Questionnaire <23 units); f) impaired IPS (i.e., Symbol Digit Modalities Test [SDMT] scores ≥1.282 standard deviations below the age-, sex-, and education-adjusted normative score[2]). Exclusion criteria were: a) wheelchair dependency (Expanded Disability Status scale [EDSS] score≥7.0); b) history of significant neurological or psychiatric conditions other than PMS; c) relapses or steroid treatment in the past 3 months; d) MRI contraindications (e.g., pregnancy, pacemaker, breast-feeding, etc.); e) use of drugs potentially affecting cognition (excluding cannabis); f) severe depression (i.e., Beck Depression Inventory II scores <29).

MRI acquisition. Using 3.0 Tesla scanners (IRCCS San Raffaele: Philips Ingenia CX; University of Genoa and University of Alabama: Siemens Prisma; Kessler Foundation: Siemens Skyra) and standardized procedures for subjects positioning, the following brain MRI sequences were acquired from MS patients during a single session at each study time point: a) variable flip angle 3D T2-weighted fluid-attenuated inversion recovery (FLAIR) turbo spin echo (Philips scanner: repetition time [TR]=4800 ms; echo time [TE]=270 ms; inversion time [TI]=1650 ms; matrix size=256 × 256; field of view [FOV]=256 × 256 mm^2; echo train length [ETL]=167; 192 contiguous sagittal slices, 1 mm thick; Siemens scanners: TR=5000 ms; TE=395 ms; TI=1800 ms; matrix size=256 × 256; FOV=256 × 256 mm^2; ETL=284; 192 contiguous sagittal slices, 1.05 mm thick), b) sagittal 3D T1-weighted sequence: (Philips scanner: TR=7 ms; TE=3.2 ms; TI=1000 ms; flip angle=8°; matrix size=256 × 256; FOV=256 × 256 mm^2; 204 contiguous sagittal slices, 1 mm thick; Siemens scanners: TR=2300 ms; TE=2.98 ms; TI=900 ms; flip angle=9°; matrix size=256 × 256; FOV=256

× 256 mm^2; 204 contiguous sagittal slices, 1 mm thick). Whenever possible, an axial T2*-weighted single-shot EPI sequence during the execution of a Go-NoGo fMRI task was acquired using the following parameters on all scanners: TR=3000 ms; TE=30 ms, flip angle=85°; matrix size=96×96; FOV=240 x 240 mm^2; 30 contiguous axial slices, 4 mm thick, number of volumes=160).

FMRI experimental design. During the Go-NoGo stimulus-response discrimination task, subjects had to react as fast as possible to a predefined target, either a cross or a square, pressing a button with their right index-finger. The paradigm, implemented as a block design and described in details in the online Supplemental methods, consisted of eight 30s active conditions and eight interspersed 24s rest phases. where an exclamation mark was presented. A 3s non-verbal instruction presented prior to each active run indicated the target. In every active block, one stimulus constituted the target while the other stimulus required response suppressing, ended by a 3s “stop”-signal. Targets, shown for 300ms, had varying inter-stimulus intervals to modulate severity (1000, 2000, 2500, 1000, 2500, 1500, 2000, and 1500ms). Reaction times (RT), omission errors (no response although required), commission errors (false response without adequate cue), and the proportion of correct responses were recorded. Prior to scanning, participants were familiarized with the paradigm outside the scanner.

fMRI pre-processing. FMRI data were pre-processed using SPM12 software. Pre-processing steps included realignment, co-registration to lesion-filled 3D T1-weighted sequence, normalization into the Montreal Neurological Institute (MNI) space, and smoothing with a 10-mm, 3D-Gaussian filter. Subjects were discarded (n=2) if they had a maximum cumulative translation higher than 3.0 mm in the x,y,z planes or a maximum cumulative rotation of 0.5 degrees.

References

1. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. Neurology 2014;83:278-286.
2. Strober L, DeLuca J, Benedict RH, et al. Symbol Digit Modalities Test: A valid clinical trial endpoint for measuring cognition in multiple sclerosis. Mult Scler 2019;25:1781-1790.

Online Supplemental Table 1. Main baseline demographic, clinical and neuropsychological characteristics of multiple sclerosis (MS) patients participating to the CogEx MRI sub-study compared to those not participating to the MRI sub-study.

	Total CogEx population	**No MRI sub-study**	**MRI sub-study**	**p**
N	311	207	104	
Mean age [years] (SD)	52.6 (7.2)	53.0 (7.2)	51.9 (7.0)	0.19*
Sex (M/F)	117/194	79/128	38/66	0.78^{+}
Median EDSS score (IQR)	6.0 (4.5-6.5)	6.0 (4.5-6.5)	6.0 (4.0-6.5)	0.99^{++}
Mean disease duration [years] (SD)	14.5 (9.6)	14.0 (9.4)	15.6 (10.1)	0.18*
Type of MS (Primary/Secondary progressive)	84/227	59/148	25/79	0.40^{+}
6MWT total distance [m] (SD)	265.5 (141.0)	276.5 (142.8)	243.8 (135.4)	0.06*
VO_2 peak [mL/min/kg] (SD)	17.5 (6.3)	18.5 (6.3)	15.4 (5.9)	<0.001*
Mean WR_{peak} [W] (SD)	81.0 (33.6)	84.8 (35.1)	73.5 (29.3)	0.005*
Average % in MVPA (SD)	1.7 (2.3)	1.7 (2.4)	1.7 (2.3)	0.91*
Education [total years of schooling] (SD)	13.9 (3.3)	14.0 (3.3)	13.8 (3.4)	0.68*
SDMT z-score (SD)	-2.10 (0.75)	-2.20 (0.82)	-2.00 (0.59)	0.037*
SDMT – mean number of correct responses (SD)	33.3 (8.2)	34.2 (8.5)	31.6 (7.2)	0.011*
CVLT II z-score (SD)	-1.05 (1.2)	-1.09 (1.3)	-0.97 (1.2)	0.39*
BVMT-R z-score (SD)	-0.68 (1.3)	-0.82 (1.3)	-0.40 (1.1)	0.005*

*ANOVA model;$^{+}$Chi-square test; $^{++}$Kruskall Wallis test.

Abbreviations: SD=standard deviation; IQR=interquartile range; M=males; F=females; EDSS=Expanded Disability Status scale; 6MWT=6-minute walking test; WR_{peak}=peak work rate; MVPA=moderate-to-vigorous physical activity; SDMT=symbol digit modalities test; CVLT II=California verbal learning test II; BVMT-R=brief visuospatial memory test revised.

Online Supplemental Table 2. Between-group comparison of cognitive scores at different study time points for patients (n=93) having a valid neuropsychological assessment at baseline and week 12 visits. Patients were first divided into the four intervention groups, and then grouped into participants receiving CR (i.e., "CR plus EX" and "CR plus EX-S") *vs* those receiving CR-S (i.e., "EX plus CR-S" and "CR-S plus EX-S") as well as into participants receiving EX (i.e., "CR plus EX" and "EX plus CR-S") *vs* those receiving EX-S (i.e., "CR plus EX-S" and "CR-S plus EX-S").

		Intervention groups				
		"CR plus EX"	**"CR plus EX-S"**	**"EX plus CR-S"**	**"CR-S plus EX-S"**	**p**
N		24	27	20	22	
SDMT - mean number of correct responses (SD)	**Baseline**	30.7 (7.4)	31.4 (6.5)	31.7 (6.3)	33.8 (8.3)	0.53*
	Week-12	36.6 (11.9)	39.7 (11.0)	37.6 (13.1)	40.2 (12.8)	0.64**
	Month-9	34.1 (9.5)	34.1 (12.8)	33.7 (11.0)	37.6 (13.9)	0.98**
Number (%) of patients showing SDMT improvements	**Week-12 (cut-off: 4 points)**	16 (67%)	20 (74%)	9 (45%)	13 (59%)	0.89^{+}
	Week-12 (cut-off: 8 points)	9 (37%)	14 (52%)	7 (35%)	10 (45%)	0.37^{+}
	Month-9 (cut-off: 4 points)	11 (46%)	13 (48%)	7 (35%)	7 (32%)	0.54^{+}
	Month-9 (cut-off: 8 points)	5 (21%)	7 (26%)	5 (25%)	6 (27%)	0.61^{+}
SDMT z-score (SD)	**Baseline**	-2.02 (0.5)	-2.05 (0.7)	-2.01 (0.6)	-1.85 (0.5)	0.67*
	Week-12	-1.39 (1.2)	-1.12 (1.3)	-1.18 (1.3)	-1.04 (1.0)	0.65**
	Month-9	-1.68 (0.9)	-1.49 (1.2)	-1.46 (1.2)	-1.23 (1.1)	0.63**
CVLT-II z-	**Baseline**	-1.08 (0.9)	-1.09 (1.2)	-1.01 (1.0)	-0.63 (1.1)	0.39*

score (SD)	**Week-12**	-0.68 (0.7)	-0.82 (1.2)	-0.63 (1.2)	-0.71 (1.0)	0.19**
	Month-9	-0.64 (1.0)	-0.52 (1.3)	-0.62 (0.9)	-0.51 (1.1)	0.12**
BVMT-R z-score (SD)	**Baseline**	-0.36 (0.8)	-0.67 (1.4)	-0.15 (1.2)	-0.45 (0.9)	0.45*
	Week-12	-0.39 (0.9)	-0.61 (1.3)	-0.17 (0.9)	-0.35 (1.1)	0.94**
	Month-9	-0.40 (1.2)	-0.69 (1.4)	-0.50 (0.9)	-0.59 (1.1)	0.93**
		Interventions grouped by:				
		CR (i.e., "CR plus EX" and "CR plus EX-S")		**CR-S (i.e., "EX plus CR-S" and "CR-S plus EX-S")**		**p**
N		51		42		
SDMT - mean number of correct responses (SD)	**Baseline**	31.1 (6.9)		32.8 (7.4)		0.26*
	Week-12	38.3 (11.4)		38.9 (12.8)		0.38**
	Month-9	34.1 (11.2)		35.7 (12.6)		0.90**
Number (%) of patients showing SDMT improvements	**Week-12 (cut-off: 4 points)**	36 (70%)		22 (52%)		0.06^{+}
	Week-12 (cut-off: 8 points)	23 (45%)		17 (40%)		0.40^{+}
	Month-9 (cut-off: 4 points)	24 (47%)		14 (33%)		0.13^{+}
	Month-9 (cut-off: 8 points)	12 (23%)		11 (26%)		0.47^{+}
SDMT z-score (SD)	**Baseline**	-2.03 (0.5)		-1.92 (0.6)		0.37*
	Week-12	-1.25 (1.2)		-1.10 (1.2)		0.95**
	Month-9	-1.58 (1.0)		-1.34 (1.2)		0.54**
CVLT-II z-score (SD)	**Baseline**	-1.09 (1.1)		-0.86 (1.1)		0.31*
	Week-12	-0.76 (1.0)		-0.67 (1.1)		0.65**
	Month-9	-0.57 (1.2)		-0.56 (0.9)		0.29**
BVMT-R z-	**Baseline**	-0.53 (1.1)		-0.31 (1.0)		0.34*

score (SD)	**Week-12**	-0.51 (1.1)	-0.27 (1.0)	0.62**
	Month-9	-0.55 (1.3)	-0.55 (1.0)	0.53**
		Interventions grouped by:		
		EX (i.e., "CR plus EX" and "EX plus CR-S")	**EX-S (i.e., "CR plus EX-S" and "CR-S plus EX-S")**	**p**
N		44	49	
SDMT - mean number of correct responses (SD)	**Baseline**	31.2 (6.9)	32.5 (7.4)	0.39*
	Week-12	37.1 (12.3)	39.9 (11.7)	0.48**
	Month-9	33.9 (10.0)	35.7 (13.3)	0.96**
Number (%) of patients showing SDMT improvements	**Week-12 (cut-off: 4 points)**	25 (57%)	33 (67%)	0.20+
	Week-12 (cut-off: 8 points)	16 (36%)	24 (49%)	0.15+
	Month-9 (cut-off: 4 points)	18 (41%)	20 (41%)	0.58+
	Week-12 (cut-off: 8 points)	10 (23%)	13 (26%)	0.42+
SDMT z-score (SD)	**Baseline**	-2.01 (0.6)	-1.95 (0.6)	0.64*
	Week-12	-1.3 (1.2)	-1.08 (1.1)	0.47**
	Month-9	-1.59 (1.0)	-1.37 (1.1)	0.28**
CVLT-II z-score (SD)	**Baseline**	-1.09 (0.9)	-0.89 (1.2)	0.37*
	Week-12	-0.66 (0.9)	-0.77 (1.1)	0.07**
	Month-9	-0.63 (0.9)	-0.51 (1.2)	0.99**
BVMT-R z-score (SD)	**Baseline**	-0.26 (1.0)	-0.57 (1.2)	0.18*
	Week-12	-0.29 (0.9)	-0.49 (1.2)	0.72**
	Month-9	-0.44 (1.1)	-0.64 (1.3)	0.94**

*ANOVA model; **ANOVA adjusted for baseline scores; +Chi-square test.

Abbreviations: CR=cognitive rehabilitation; CR-S=sham cognitive rehabilitation; EX=physical exercise; EX-S=sham physical exercise; SD=standard deviation; SDMT=Symbol Digit Modalities Test; CVLT-II=California Verbal Learning Test-II; BVMT-R=Brief Visuospatial Memory Test Revised.

Online Supplemental Table 3 Changes over time of lobar grey matter (GM) atrophy in patients participating to the CogEx MRI sub-study and having at least baseline and week 12 volumetric MRI scans. Patients were first divided according to intervention, and then grouped according to the received type of treatment (i.e., cognitive rehabilitation (CR) or physical exercise (EX)).

	"CR plus EX"	**"CR plus EX-S"**	**"EX plus CR-S"**	**"CR-S plus EX-S"**	**p**	**CR (i.e., "CR plus EX" and "CR plus EX-S")**	**CR-S (i.e., "EX plus CR-S" and "CR-S plus EX-S")**	**p**	**EX (i.e., "CR plus EX" and "EX plus CR-S")**	**EX-S (i.e., "CR plus EX-S" and "CR-S plus EX-S")**	**p**
N	22	23	19	20		45	39		41	43	
Mean % Frontal NcGMV change, week-12 *vs* baseline (estimate, 95% CI)	0.23 (-0.92;1.40)	1.07 (-0.04;2.19)	-0.85 (-2.05;0.36)	-0.68 (-1.86;0.50)	0.07*	0.67 (-0.12;1.47)	-0.77 (-1.60;0.07)	0.01*	-0.28 (-1.13;0.57)	0.25 (-0.57;1.07)	0.37*
Mean % Frontal NcGMV change, month-9 *vs* week-12 (estimate, 95% CI)	0.02 (-1.23;1.29)	-0.49 (-1.79;0.82)	-0.08 (-1.37;1.23)	-0.01 (-1.30;1.29)	0.94*	-0.24 (-1.13;0.66)	-0.05 (-0.95;0.86)	0.76*	-0.03 (-0.94;0.88)	-0.29 (-1.21;0.64)	0.69*
Mean % Insular-Cingulate NcGMV change, week-12 *vs* baseline (estimate, 95% CI)	1.02 (-0.48;2.55)	0.18 (-1.24;1.63)	-0.33 (-1.89;1.25)	-0.48 (-1.99;1.06)	0.50*	0.58 (-0.46;1.64)	-0.41 (-1.51;0.71)	0.20*	0.37 (-0.73;1.49)	-0.12 (-1.18;0.95)	0.52*
Mean % Insular-	1.26 (-	-0.94 (-	-0.78 (-	0.06 (-	0.23*	0.24 (-0.93;1.44)	-0.36 (-1.55;0.84)	0.47*	0.25 (-0.93;1.45)	-0.44 (-1.65;0.77)	0.41*

Cingulate NcGMV change, month-9 *vs* week-12 (estimate, 95% CI)	0.37;2.92)	2.61;0.75)	2.44;0.90)	1.60;1.75)							
Mean % Occipital NcGMV change, week-12 *vs* baseline (estimate, 95% CI)	-0.67 (-1.52;0.19)	0.49 (-0.33;1.33)	0.05 (-0.86;0.96)	-0.57 (-1.45;0.31)	0.18*	-0.06 (-0.66;0.54)	-0.27 (-0.90;0.37)	0.63*	-0.33 (-0.96;0.31)	-0.01 (-0.61;0.61)	0.46*
Mean % Occipital NcGMV change, month-9 *vs* week-12 (estimate, 95% CI)	0.81 (-0.13;1.76)	0.32 (-0.66;1.31)	-0.42 (-1.38;0.55)	-0.16 (-1.12;0.81)	0.29*	0.55 (-0.13;1.23)	-0.28 (-0.97;0.40)	0.09*	0.21 (-0.47;0.91)	0.04 (-0.65;0.74)	0.73*
Mean % Parietal NcGMV change, week-12 *vs* baseline (estimate, 95% CI)	-0.26 (-1.64;1.15)	1.42 (0.07;2.79)	-1.08 (-2.53;0.38)	-0.53 (-1.94;0.91)	0.07*	0.62 (-0.35;1.59)	-0.80 (-1.81;0.22)	0.04*	-0.65 (-1.66;0.37)	0.51 (-0.47;1.51)	0.10*
Mean % Parietal NcGMV change, month-9 *vs* week-12 (estimate, 95% CI)	0.11 (-1.39;1.65)	-0.78 (-2.34;0.80)	-0.30 (-1.85;1.28)	-0.53 (-2.07;1.04)	0.86*	-0.35 (-1.43;0.70)	-0.42 (-1.51;0.69)	0.93*	-0.09 (-1.18;1.01)	-0.70 (-1.81;0.41)	0.43*
Mean % Temporal	0.23 (-	0.74 (-	-0.53 (-	-0.57 (-	0.22*	0.49 (-0.21;1.21)	-0.55 (-1.30;0.20)	0.04*	-0.13 (-0.88;0.63)	0.13 (-0.60;0.86)	0.62*

NcGMV change, week-12 *vs* baseline (estimate, 95% CI)	0.80;1.28)	0.26;1.74)	1.61;0.57)	1.62;0.49)							
Mean % Temporal NcGMV change, month-9 *vs* week-12 (estimate, 95% CI)	-0.34 (-1.46;0.79)	-0.80 (-2.97;0.37)	-0.61 (-1.77;0.55)	-0.01 (-1.16;1.16)	0.79*	-0.57 (-1.37;0.23)	-0.31 (-1.12;0.50)	0.65*	-0.48 (-1.28;0.35)	-0.43 (-1.25;0.40)	0.93*

*Linear mixed effect model adjusted for age, sex and acquisition scanner.

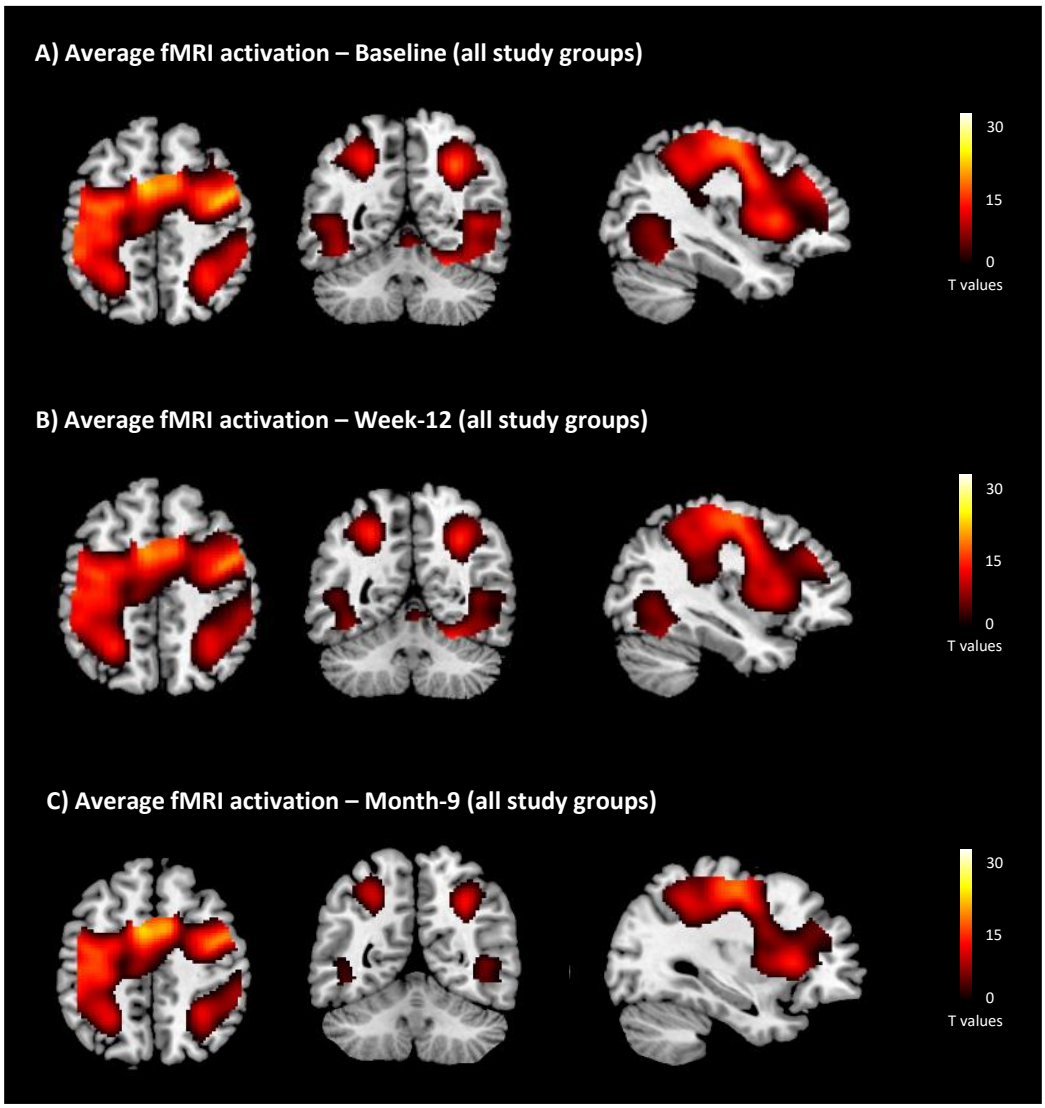
Abbreviation: NcGMV=normalized cortical grey matter volume.

Online Supplemental Table 4. Behavioural performances of patients while performing the Go-NoGo functional MRI task at the different study time points.

	"CR plus EX"	**"CR plus EX-S"**	**"EX plus CR-S"**	**"CR-S plus EX-S"**	**p***
Baseline					
CorrResp [%] (SD)	87 (16)	89 (16)	89 (15)	82 (22)	0.52
OmErr [#] (SD)	12.5 (15.6)	14.9 (15.6)	9.6 (14.6)	14.5 (19.2)	0.74
CommErr [#] (SD)	9.9 (12.5)	8.0 (12.8)	8.6 (13.3)	13.1 (15.8)	0.67
RT [ms] (SD)	445 (65)	429 (56)	475 (103)	435 (98)	0.31
Week-12					
CorrResp [%] (SD)	90 (16)	94 (14)	92 (13)	90 (16)	0.79
OmErr [#] (SD)	11.6 (15.8)	11.5 (16.8)	6.6 (13.4)	8.3 (15.2)	0.67
CommErr [#] (SD)	7.3 (12.5)	4.1 (10.6)	6.3 (10.9)	7.6 (12.7)	0.77
RT [ms] (SD)	445 (62)	429 (43)	444 (74)	411 (64)	0.28
Month-9					
CorrResp [%] (SD)	96 (4)	93 (13)	91 (20)	88 (19)	0.59
OmErr [#] (SD)	3 (3.6)	14.1 (17.3)	12.5 (19.7)	9.4 (15.3)	0.17
CommErr [#] (SD)	3.1 (3.8)	4.6 (9.4)	6.6 (15.5)	8.9 (15.4)	0.54
RT [ms] (SD)	439 (72)	443 (48)	465 (101)	424 (82)	0.53

*ANOVA model

Abbreviations: CR=cognitive rehabilitation; EX=physical exercise; CR-S=sham cognitive rehabilitation; EX-S=sham physical exercise; SD=standard deviation; CorrResp=percentage of correct responses; OmErr=omission errors; CommErr=commission errors; RT=reaction time.



Online Supplemental Figure 1. Average spatial maps of functional MRI (fMRI) activations from subjects participating to the CogEx Go-NoGo fMRI sub-study at the different time points (A: baseline; B: week-12; C: month-9; T contrasts for positive effects of interest from SPM12 repeated-measure ANOVA models, adjusted for age, sex, and acquisition site, $p<0.05$ family-wise error corrected). Activations are reported using a red-yellow scale. Images are in neurological convention.