

Results

Recruitment began in December 2021 and is ongoing, with data collection concluding by mid-2025. Owing to COVID-19 restrictions, recruitment in 2021 was slow, but 70 PwMS and 53 HC have been enrolled to date. Data analysis is in progress, with preliminary results anticipated by late 2024. The up-to-date progress in enrollment is illustrated in Figure 1.

[Place Supplementary Figure 1 here]

Figure 1. A. Consolidated Standards of Reporting Trials Diagram showing the up-to-date flow of the participants through each stage of the MS-NEUROPLAST study. PwMS: People with Multiple Sclerosis; HC: Healthy Controls; PwMS-CON: active control group; PwMS-CCT: intervention group.

Tables 1 and 5 list demographics and disease-related information, Tables 2 and 6 list cognitive performance, Tables 3 and 7 list responses to PROMs, and Tables 4 and 8 list physical performance for the up-to-date study population. Stratification, as presented in Tables 1 and 2, is evaluated via χ^2 tests, independent Student's t-tests or Mann-Whitney U tests, depending on score distributions.

Table 1. Demographic and disease-related information for the experimental (PwMS-CCT) and control (PwMS-CON) groups of PwMS.

	PwMS-CCT (N=35)	PwMS-CON (N=35)	p
	Demographics		
Age (years)	43 (11.45)	39 (11.90)	0.137
Sex (women)	30 (86%)	29 (83%)	0.743
Education (years)*	16 (4)	16 (4)	0.455
	Disease-related characteristics		
MS type (RRMS/PMS)	24/11 (69/31%)	27/8 (77/23%)	0.420
EDSS*	3 (2.63)	3 (1.5)	0.884
Disease Duration (years)*	5 (8)	10 (12.5)	0.431
DMT (Yes/No/Unspecified)	27/5/3 (77/14/9%)	30/3/2 (86/8/6%)	0.651

Sex and MS types are indicated as N (%). The mean and standard deviation are presented for most variables, while * denotes the cases where the median and the interquartile range are presented. Significant differences between the groups ($p < 0.05$) are denoted with bold type.

Abbreviations: RRMS: Relapsing-Remitting MS; PMS: Progressive MS; EDSS: Expanded

Disability Status. Disease duration is defined as the time elapsed between the official diagnosis and the date of the first visit. Note: No significant differences between PwMS-CCT and PwMS-CON ($p > 0.05$).

Table 2. Cognitive performance for the experimental (PwMS-CCT) and control (PwMS-CON) groups of PwMS.

Cognitive Performance	Raw scores			Standardised scores (z-scores)		
	PwMS-CCT	PwMS-CON	p	PwMS-CCT	PwMS-CON	p
Overall Cognition						
MMSE*	29 (1.5)	29 (3)	0.808	–	–	–
Memory						
GVLТ	52.63 (11.55)	55.34 (14.10)	0.228	0.20 (0.73)	0.41 (0.80)	0.246
BVMT-R	24.63 (6.53)	22.74 (8.53)	0.309	0.06 (1.21)*	-0.08 (2.32)*	0.285
AFO	55.34 (9.91)	51.54 (11.70)	0.144	0.12 (0.94)	-0.16 (1.13)	0.307
Attention						
DSF*	9 (3)	8 (2)	0.372	0.00 (1.00)	-0.33 (1.00)	0.112
DSB	8 (2)*	8 (2)*	0.947	-0.12 (0.55)	-0.19 (0.73)	0.724
Processing Speed						
SDMT-Of	49.68 (11.08)	50.60 (13.09)	0.753	-0.54 (1.33)	-0.81 (1.26)	0.389
SNST	98.09 (21.02)	93.69 (22.13)	0.397	-0.17 (2.03)	-1.02 (2.29)	0.101
Executive Functions						
DSS	8 (1.5)*	8 (2.5)*	0.410	0.05 (0.62)	-0.17 (0.75)	0.188
XSA	32.80 (9.02)	30.11 (12.12)	0.240	-0.40 (0.97)	-0.62 (1.28)	0.424
Cognitive Reserve						
GAT	40.09 (5.63)	37.83 (5.83)	0.041	0.29 (1.10)*	-0.46 (1.34)*	0.072
CRIq	99.46 (7.11)	98.29 (9.41)	0.559	-0.26 (0.57)	-0.21 (0.87)	0.768
CRI-Edu	106.20 (9.22)	103.00 (12.24)	0.221	0.29 (0.71)	0.15 (0.81)	0.439
CRI-Work*	98 (12)	95 (13)	0.625	-0.38 (0.98)	-0.45 (1.31)	0.742
CRI-Leis*	93 (12.5)	93 (8.5)	0.832	-0.77 (1.13)	-0.64 (0.88)	0.356

The mean and standard deviation are presented for most variables, while * denotes the cases where the median and the interquartile range are presented. Significant differences between the groups ($p < 0.05$) are denoted with bold type. Abbreviations: MMSE: Mini-Mental State Exam; GVLТ: Greek Verbal Learning Test; BVMT-R: Brief Visuospatial Memory Test-Revised; AFO: Animals-Fruit-Objects; DSF: Digit Span Forward; DSB: Digit Span Backward; SDMT-Of: Symbol Digit Modalities Test-Oral Form; SNST: Stroop Neuropsychological Screening Test; DSS: Digit Span Sequencing; XSA: Chi-Sigma-Alpha; GAT: Greek Accentuation Test; CRIq: Cognitive Reserve Index questionnaire; CRI-Edu: CRI-Education subscale; CRI-Work: CRI-Working activity subscale; CRI-Leis: CRI-Leisure time subscale. Note: No significant differences between PwMS-CCT and PwMS-CON ($p > 0.05$), except for the raw score of GAT ($p < 0.05$).

Table 3. Responses to PROMs for the experimental (PwMS-CCT) and control (PwMS-CON) groups of PwMS.

	PwMS-CCT	PwMS-CON	p
PROMs			
Fatigue			
MFIS	36.11 (17.12)	30.94 (17.43)	0.215
MFIS-c	18.14 (8.72)	15.49 (9.52)	0.228
MFIS-p	17.49 (10.05)	15.46 (8.91)	0.375
Depression, Anxiety, Stress			
BDI*	4 (4.5)	3 (3.5)	0.109
DASS*	17 (17)	11 (12.5)	0.036
DASS-ds*	4 (9.5)	3 (5.5)	0.211
DASS-as*	5 (5)	2 (4.5)	0.021
DASS-ss*	6 (5.5)	5 (7)	0.061
Disease Impact			
MSIS-29	57.11 (18.80)	51.97 (15.48)	0.216
EQ-5D-5L-I*	0.91 (0.17)	0.91 (0.17)	0.901
EQ-5D-5L-VAS	72.77 (18.13)	73.09 (14.60)	0.937

The mean and standard deviation are presented for most variables, while * denotes the cases where the median and the interquartile range are presented. Significant differences between the groups ($p < 0.05$) are denoted with bold type. Abbreviations: PROMs: Patient-Reported Outcome Measures; MFIS: Modified Fatigue Impact Scale; MFIS-c: MFIS-Cognitive subscale; MFIS-p: MFIS-Physical Subscale; BDI-FS: Beck Depression Inventory-Fast Screen; DASS-21: Depression, Anxiety, Stress Scale-21 Items; DASS-21ds: DASS-21 Depression Subscale; DASS-as: DASS-21 Anxiety Subscale; DASS-ss: DASS-21 Stress Subscale; MSIS-29: Multiple Sclerosis Impact Scale-29 items; I: Index; VAS: Visual Analog Scale. Note: No significant differences between PwMS-CCT and PwMS-CON ($p > 0.05$), except for DASS and DASS-as ($p < 0.05$).

Table 4. Physical performance for the experimental (PwMS-CCT) and control (PwMS-CON) groups of PwMS.

	PwMS-CCT	PwMS-CON	p
Physical performance			
Upper body status			
9HPT-D*	19.62 (8.66)	20.57 (7.46)	0.655
9HPT-ND*	22.06 (6.94)	20.78 (6.84)	0.456
HGS_D	27.04 (10.64)	29.31 (8.83)	0.336
HGS_ND	25.23 (8.40)	28.28 (9.04)	0.148
Ambulation			
T25fWT*	5.04 (1.88)	5.13 (2.32)	0.537
3mBWT*	3.70 (2.54)	3.82 (2.71)	0.967
Balance			
4SST*	9.28 (4.93)	9.99 (6.70)	0.823
SLS_Best*	18.08 (47.13)	36.68 (47.96)	0.330

The mean and standard deviation are presented for most variables, while * denotes the cases where the median and the interquartile range are presented. Significant differences between the groups ($p < 0.05$) are denoted with bold type. Abbreviations: 9HPT-D: 9-Hole Peg Test-Dominant; 9HPT-ND: 9-Hole Peg Test-Non-Dominant; HGS-D: Hand Grip Strength-Dominant; HGS-ND: Hand Grip Strength-Non-Dominant; T25fWT: Timed 25-feet Walking Test; 3mBWT: 3-meter Backwards Walking Test; 4SST: 4 Square Step Test; SLS-Best: Single Leg Stance-Best. Note: No significant differences between PwMS-CCT and PwMS-CON ($p > 0.05$).

Table 5. Demographics and disease-related information for PwMS and HC.

	PwMS (N=70)	HC (N=53)	p
Demographics			
Age (years)	40.96 (11.78)	38.04 (11.21)	0.169
Sex (women)	59 (84%)	37 (72.5%)	0.115
Education (years)*	16 (4)	18 (3)	<0.001
Disease-related characteristics			
MS type (RRMS/PMS)	51/19 (73/27 %)	–	–
EDSS*	3 (2)	–	–
Disease Duration (years)*	7 (12)	–	–
DMT (Yes/No/Unspecified)	57/8/5 (81/12/7%)	–	–

Sex and MS types are indicated as N (%). The mean and standard deviation are presented for most variables, while * denotes the cases where the median and the interquartile range are presented. Significant differences between the groups ($p < 0.05$) are denoted with bold type.

Abbreviations: RRMS: Relapsing-Remitting MS; PMS: Progressive MS; EDSS: Expanded Disability Status. Disease duration is defined as the time elapsed between the official diagnosis and the date of the first visit. Note: No significant differences between PwMS and HC ($p > 0.05$), except for years of education ($p < 0.05$).

Table 6. Cognitive performance for PwMS and HC.

Cognitive Performance	Raw scores			Standardised scores (z-scores)		
	PwMS	HC	p	PwM	HC	p
Overall Cognition						
MMSE*	29 (2)	30 (1)	<0.001	–	–	–
Memory						
GVLТ	53.98 (12.87)	62.47 (7.81)	<0.001	0.31 (0.77)	0.62 (0.74)	0.023
BVMT-R	23.69 (7.60)	27.73 (5.36)	0.005	-0.04 (1.57)*	0.30 (1.10)*	0.044
AFO	53.43 (17.50)	65.14 (10.39)	<0.001	-0.02 (1.04)	0.80 (0.97)	<0.001
Attention						
DSF*	8 (3)	10 (2)	<0.001	0.00 (1.25)	0.33 (1)	<0.001
DSB	8 (2)*	9 (2)*	<0.001	-0.16 (0.64)	0.48 (0.83)	<0.001
Processing Speed						
SDMT-Of	50.14 (12.04)	61.76 (11.82)	<0.001	-0.67 (1.57)	-0.015 (0.80)	0.002
SNST	95.88 (21.54)	120.65 (25.23)	<0.001	-0.60 (1.29)	2.16 (2.29)	<0.001
Executive Functions						
DSS	8 (1.75)*	10 (2.5)*	<0.001	0.00 (0.66)	0.33 (1)	<0.001
XSA	31.46 (10.69)	40.98 (9.73)	<0.001	-0.51 (1.30)	0.21 (0.77)	<0.001
Cognitive Reserve						
GAT	40.98 (5.80)	–	–	-0.05 (1.08)*	–	–
CRIq	98.87 (8.30)	107.33 (10.69)	<0.001	-0.23 (0.73)	0.13 (1.52)	<0.001
CRI-Edu	104.60 (10.88)	112.60 (12.53)	<0.001	0.22 (0.76)	0.47 (1.21)	0.052
CRI-Work*	95.5 (12.75)	103.00 (13.5)	0.006	-0.38 (1.03)	0.00 (0.67)	0.004
CRI-Leis*	93.00 (10.50)	99.50 (9.75)	<0.001	-0.66 (1.01)	0.00 (0.80)	<0.001

The mean and standard deviation are presented for most variables, while * denotes the cases where the median and the interquartile range are presented. Significant differences between the groups ($p < 0.05$) are denoted with bold type. Abbreviations: MMSE: Mini-Mental State Exam; GVLТ: Greek Verbal Learning Test; BVMT-R: Brief Visuospatial Memory Test-Revised; AFO: Animals-Fruit-Objects; DSF: Digit Span Forward; DSB: Digit Span Backward; SDMT-Of: Symbol Digit Modalities Test-Oral Form; SNST: Stroop Neuropsychological Screening Test; DSS: Digit Span Sequencing; XSA: Chi-Sigma-Alpha; GAT: Greek Accentuation Test; CRIq: Cognitive Reserve Index questionnaire; CRI-Edu: CRI-Education subscale; CRI-Work: CRI-Working activity subscale; CRI-Leis: CRI-Leisure time subscale. Note: Significant differences between PwMS and HC for all relevant cognitive performance tests ($p < 0.05$), except for the standardised (z-score) CRI-Edu ($p > 0.05$).

Table 7. Responses to PROMs for PwMS and HC.

PROMs	PwMS	HC	p
Fatigue			
MFIS	33.53 (17.35)	24.86 (12.87)	0.006
MFIS-c	16.81 (9.16)	13.23 (7.56)	0.034
MFIS-p	16.47 (9.48)	12.09 (7.89)	0.013
Depression, Anxiety, Stress			
BDI*	3 (4)	1 (2.5)	<0.001
DASS*	14 (16.75)	8 (14)	0.036
DASS-ds*	3 (6.75)	2 (3.5)	0.055
DASS-as*	3 (4)	1 (4)	0.015
DASS-ss*	6 (6)	5 (6)	0.392
Disease Impact			
MSIS-29	54.54 (17.29)	–	–
EQ-5D-5L-I*	0.91 (0.17)	–	–
EQ-5D-5L-VAS	73.93 (16.34)	–	–

The mean and standard deviation are presented for most variables, while * denotes the cases where the median and the interquartile range are presented. Significant differences between the groups ($p < 0.05$) are denoted with bold type. Abbreviations: PROMs: Patient-Reported Outcome Measures; MFIS: Modified Fatigue Impact Scale; MFIS-c: MFIS-Cognitive subscale; MFIS-p: MFIS-Physical Subscale; BDI-FS: Beck Depression Inventory-Fast Screen; DASS-21: Depression, Anxiety, Stress Scale-21 Items; DASS-21ds: DASS-21 Depression Subscale; DASS-as: DASS-21 Anxiety Subscale; DASS-ss: DASS-21 Stress Subscale; MSIS-29: Multiple Sclerosis Impact Scale-29 items; I: Index; VAS: Visual Analog Scale. Note: Significant differences between PwMS and HC for all relevant PROMs ($p < 0.05$), except for DASS-ds and DASS-ss ($p > 0.05$).

Table 8. Physical performance for PwMS and HC.

	PwMS	HC	p
Physical performance			
Upper body status			
9HPT-D*	19.75 (7.56)	17.75 (2.78)	<0.001
9HPT-ND*	21.92 (7.29)	19.16 (2.42)	<0.001
HGS_D	28.18 (9.77)	35.25 (11.89)	0.004
HGS_ND	26.76 (8.09)	36.48 (12.20)	<0.001
Ambulation			
T25fWT*	5.12 (2.39)	3.99 (0.51)	<0.001
3mBWT*	3.82 (2.74)	2.49 (0.58)	<0.001
Balance			
4SST*	9.54 (6.26)	7.04 (1.30)	<0.001
SLS_Best*	20.15 (49.52)	60.59 (37.08)	<0.001

The mean and standard deviation are presented for most variables, while * denotes the cases where the median and the interquartile range are presented. Significant differences between the groups ($p<0.05$) are denoted with bold type. Abbreviations: 9HPT-D: 9-Hole Peg Test-Dominant; 9HPT-ND: 9-Hole Peg Test-Non-Dominant; HGS-D: Hand Grip Strength-Dominant; HGS-ND: Hand Grip Strength-Non-Dominant; T25fWT: Timed 25-feet Walking Test; 3mBWT: 3-meter Backwards Walking Test; 4SST: 4 Square Step Test; SLS-Best: Single Leg Stance-Best. Note: Significant differences between PwMS and HC for all physical performance tests ($p<0.05$).