Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. MRI Acquisition Protocol

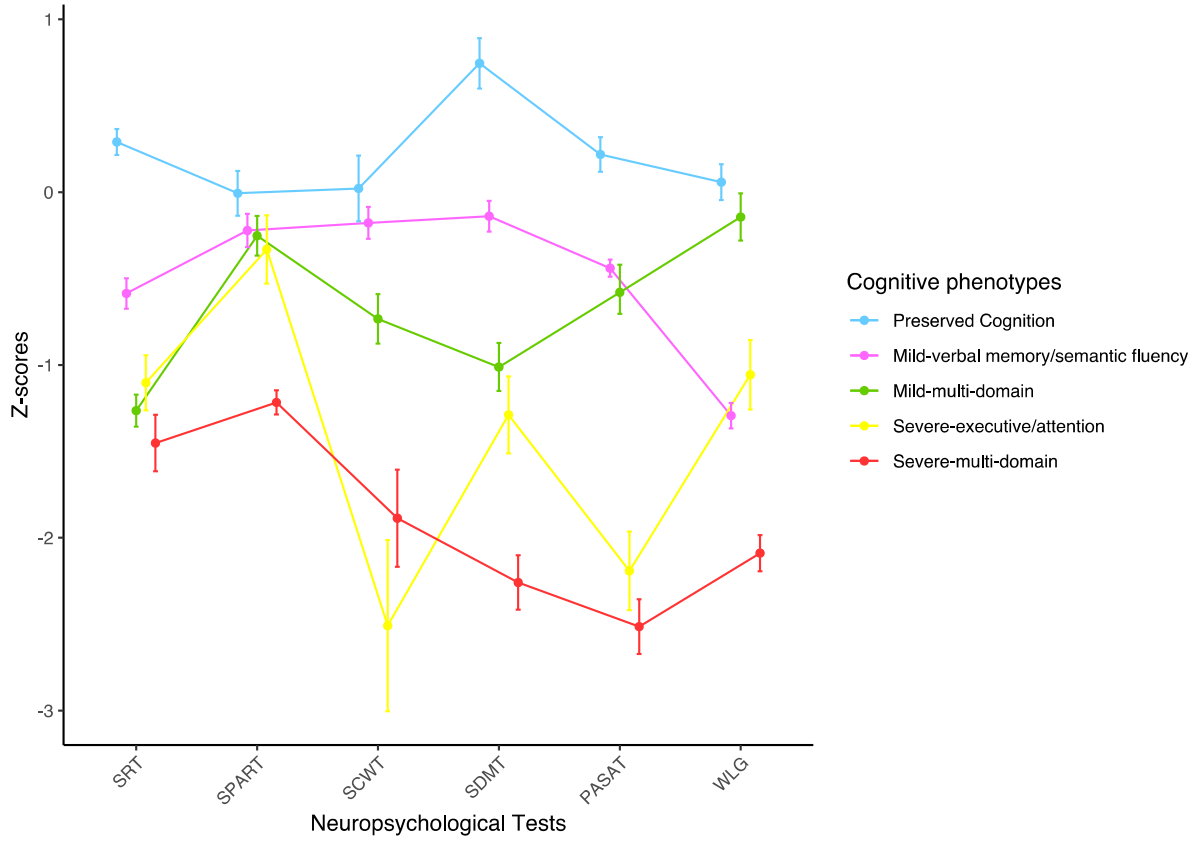
For both centers, a 3.0 Tesla Philips Intera MR scanner with 8-channel head coil (Philips Medical System, Best, The Netherlands) was used for MRI acquisition. The following MRI sequences of the brain were acquired from all subjects during a single session: a) 3DT1-weighted turbo field echo (repetition/echo time=25/4.6 ms; echo train length=1; flip angle=30°; matrix size=256x256; field-of-view=230x230mm^2; 220 contiguous, axial slices with voxel size=1x1x1 mm); b) dual-echo turbo spin echo yielding proton density (PD) and T2-weighted images (repetition/echo time=2599/16.80 ms, echo train length=6; flip angle=90º, matrix size=256x256, field-of-view=240x240 mm^2, 44 axial 3mm-thick slices). For all sequences, slices were positioned to run parallel to a line joining the most infero-anterior and infero-posterior margins of the corpus callosum.

eTable 1. Fit Indices of Latent Profile Analysis Models With 1 – 6 Profiles

Number of Classes	AIC	BIC	ICL	BLRT
1	23104	23242	-23242	-
2	22713	22993	-23382	0.009
3	22763	23187	-23893	0.009
4	22593	23159	-23768	0.009
5	22497	23206	-23903	0.009
6	22627	23479	-24227	0.089

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; ICL = Integrated Completed Likelihood, BLRT=Bootstrap Likelihood Ratio Test.

eFigure. Latent Profile Analysis Results



The figure represents the cognitive performance of each phenotype: points indicate mean z-scores obtained at each neuropsychological test and error bars reflect the 95% confidence interval. “Preserved cognition” phenotype is represented in cyan blue, “mild-verbal memory/semantic fluency” in purple, “mild-multi-domain” in green, “severe-attention/executive” in yellow and “severe-multi-domain” in red.
Abbreviations: SRT=Selective Reminding Test; SPART=Spatial Recall Test; SCWT=Stroop Color Word Test; SDMT=Symbol Digit Modalities Test; PASAT=Paced Auditory Serial Addition Test; WLG=Word List Generation.

eTable 2. Main Clinical and Demographic Features of Cognitive Phenotypes

Variables			*vs* Mild-verbal memory/semantic fluency		*vs* Mild-multi-domain		*vs* Severe-executive/attention		*vs* Severe-multi-domain	
		Mean (SD)	Effect size (95% CI)[a]	*p*	Effect size (95% CI)[a]	*p*	Effect size (95% CI)[a]	*p*	Effect size (95% CI)[a]	*p*
Age	Preserved Cognition	36.5 (9.8)	-0.16 (-0.33, -0.002)	.98	-0.56 (-0.75, -0.38)	<.001	-0.58 (-0.79, -0.37)	<.001	-0.72 (-0.91, -0.53)	<.001
	Mild-verbal memory/semantic fluency	38.2 (11.1)			-0.38 (-0.55, -0.21)	<.001	-0.41 (-0.60, -0.22)	<.001	-0.53 (- 0.71, -0.35)	<.001
	Mild-multi-domain	42.6 (11.2)					-0.04 (-0.23, 0.16)	>.99	-0.14 (-0.33, 0.04)	>.99
	Severe-executive/attention	42.9 (11.7)							-0.10 (-0.31, -0.09)	>.99
	Severe-multi-domain	44.0 (11.0)								
		Female/male	Effect size (95% CI)[b]	*p*	Effect size (95% CI)[b]	*p*	Effect size (95% CI)[b]	*p*	Effect size (95% CI)[b]	*p*
Sex	Preserved Cognition	155/80	0.01 (0.00, 0.08)	>.99	0.10 (0.00, 0.19)	.06	0.01 (0.00, 0.09)	>.99	0.01 (0.00, 0.09)	>.99
	Mild-verbal memory/semantic fluency	242/120			0.11 (0.03, 0.19)	.03	0.00 (0.00, 0.04)	>.99	0.00 (0.00, 0.01)	>.99
	Mild-multi-domain	133/103					0.11 (0.00, 0.21)	.05	0.11 (0.01, 0.20)	.04
	Severe-executive/attention	112/55							0.00 (0.00, 0.01)	>.99
	Severe-multi-domain	142/70								
		Median (range)	Effect size (95% CI)[c]	*p*	Effect size (95% CI)[c]	*p*	Effect size (95% CI)[c]	*p*	Effect size (95% CI)[c]	*p*
EDSS	Preserved Cognition	1.5 (0.0 – 7.0)	-0.25 (-0.34, -0.16)	<.001	-0.21 (-0.32, -0.11)	<.001	-0.17 (-0.29, -0.05)	.001	-0.39 (-0.49, -0.29)	<.001
	Mild-verbal memory/semantic fluency	2.0 (0.0 – 7.5)			-0.05 (-0.14, 0.05)	>.99	-0.02 (-0.14, 0.09)	>.99	-0.24 (-0.33, -0.14)	<.001
	Mild-multi-domain	2.0 (0.0 – 8.0)					0.06 (-0.05, 0.18)	>.99	-0.14 (-0.25, 0.03)	.001
	Severe-executive/attention	2.0 (0.0 – 8.0)							-0.17 (-0.29, -0.04)	.001

	Severe-multi-domain	3.0 (0.0 – 8.5)								
Disease duration		Mean (SD)	Effect size (95% CI)[a]	*p*	Effect size (95% CI)[a]	*p*	Effect size (95% CI)[a]	*p*	Effect size (95% CI)[a]	*p*
	Preserved Cognition	8.0 (7.3)	-0.04 (-0.31,0.24)	>.99	-0.56 (-0.84, -0.27)	<.001	-0.48 (-0.77, -0.20)	<.001	-0.90 (-0.61, -0.32)	<.001
	Mild-verbal memory/semantic fluency	8.3 (7.6)			-0.81 (-0.52, -0.23)	<.001	-0.73 (-0.45, -0.16)	<.001	-0.87 (-0.58, -0.29)	<.001
	Mild-multi-domain	12.8 (9.6)					0.07 (-0.21, 0.35)	.95	-0.05 (-0.33, 0.22)	.97
	Severe-executive/attention	12.2 (9.5)							-0.13 (-0.41, 0.15)	.72
	Severe-multi-domain	13.3 (10.2)								
Age at onset		Mean (SD)	Effect size (95% CI)[a]	*p*	Effect size (95% CI)[a]	*p*	Effect size (95% CI)[a]	*p*	Effect size (95% CI)[a]	*p*
	Preserved Cognition	28.6 (8.8)	-0.14 (-0.41, 0.14)	>.99	-0.10 (-0.38, 0.17)	>.99	-0.20 (-0.48, 0.08)	.50	-0.21 (-0.49, 0.07)	.21
	Mild-verbal memory/semantic fluency	30.0 (10.0)			0.03 (-0.24, 0.31)	>.99	-0.06 (-0.34, 0.22)	>.99	-0.08 (-0.35, 0.20)	>.99
	Mild-multi-domain	29.6 (10.3)					-0.09 (-0.37, 0.18)	>.99	-0.11 (-0.39, 0.17)	>.99
	Severe-executive/attention	30.6 (10.0)							-0.02 (-0.29, 0.26)	>.99
	Severe-multi-domain	30.7 (10.6)								
Education		Mean (SD)	Effect size (95% CI)[a]	*p*	Effect size (95% CI)[a]	*p*	Effect size (95% CI)[a]	*p*	Effect size (95% CI)[a]	*p*
	Preserved Cognition	12.5 (3.4)	0.002 (-0.27, 0.28)	>.99	-0.16 (-0.44, 0.12)	.48	0.14 (-0.14, 0.41)	.71	0.05 (-0.23, 0.32)	.99
	Mild-verbal memory/semantic fluency	12.4 (3.3)			-0.16 (-0.44, 0.12)	.34	0.13 (-0.14, 0.41)	.65	0.04 (-0.23, 0.32)	.99
	Mild-multi-domain	12.6 (3.9)					0.30 (0.02, 0.58)	.04	0.21 (-0.07, 0.48)	.21
	Severe-executive/attention	11.5 (4.2)							-0.09 (-0.37, 0.19)	.91
	Severe-multi-domain	11.8 (3.9)								
FSS		Mean (SD)	Effect size (95% CI)[a]	*p*	Effect size (95% CI)[a]	*p*	Effect size (95% CI)[a]	*p*	Effect size (95% CI)[a]	*p*
	Preserved Cognition	14.2 (15.3)	0.18 (-0.10, 0.46)	.12	-0.17 (-0.45, 0.11)	.18	-0.48 (-0.76, -0.19)	.002	-0.08 (-0.36, 0.20)	.52
	Mild-verbal memory/semantic fluency	11.1 (15.5)			-0.35 (-0.63, -0.07)	.03	-0.66 (-0.95, -0.37)	<.001	-0.26 (-0.54, 0.02)	.22
	Mild-multi-domain	17.2 (18.5)					-0.30 (-0.59, 0.03)	.05	0.09 (-0.18, 0.37)	.50

	Severe-executive/attention	22.4 (19.4)							0.40 (0.12, 0.68)	.01
	Severe-multi-domain	15.5 (18.7)								
MADRS		Mean (SD)	Effect size (95% CI)[a]	*p*	Effect size (95% CI)[a]	*p*	Effect size (95% CI)[a]	*p*	Effect size (95% CI)[a]	*p*
	Preserved Cognition	7.7 (9.5)	-0.45 (-0.74, -0.17)	.04	-0.20 (-0.48, 0.08)	>.99	-0.01 (-0.28, 0.27)	>.99	-0.59 (-0.87, -0.30)	.01
	Mild-verbal memory/semantic fluency	11.9 (10.0)			0.25 (-0.03, 0.53)	>.99	0.44 (0.16, 0.73)	.08	-0.13 (-0.41, 0.14)	>.99
	Mild-multi-domain	10.0 (8.9)					0.20 (-0.08, 0.47)	>.99	-0.38 (-0.66, -0.10)	.36
	Severe-executive/attention	8.3 (5.5)							-0.58 (-0.87, 0.29)	.02
	Severe-multi-domain	13.8 (11.0)								
Cognitive phenotype distribution			**vs Late RRMS**		**vs SPMS**		**vs PPMS**			
		Preserved Cognition/ Mild-verbal memory/semantic fluency/ Mild-multi-domain/ Severe-executive/attention/ Severe-multi-domain	Effect size (95% CI)[b]	*p*	Effect size (95% CI)[b]	*p*	Effect size (95% CI)[b]	*p*		
	Early RRMS	101/149/55/44/49	0.16 (0.09, 0.22)	<.001	0.37 (0.27, 0.45)	<.001	0.17 (0.04, 0.25)	.01		
	Late RRMS	125/178/146/92/114			0.21 (0.13, 0.27)	<.001	0.11 (0.00, 0.16)	.09		
	SPMS	5/15/26/20/37					0.27 (0.03, 0.40)	.02		
	PPMS	4/20/9/11/12								

[a] Cohen's d effect size
[b] Cramer's V effect size
[c] Cliff's delta effect size
Abbreviations: EDSS=Expanded Disability Status Scale; SD=standard deviation; FSS=Fatigue Severity Scale; MADRS=Montgomery Asberg Depression Rating Scale.