



Original article

Predominant cognitive phenotypes in multiple sclerosis: Insights from patient-centered outcomes

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ARTICLE INFO

Keywords:

Multiple sclerosis
Cognitive phenotype
Cognitive impairment
Mood disorders
Latent class analysis

ABSTRACT

Background: Since combining information from different domains could be useful to increase prediction accuracy over and above what can be achieved at the level of single category of markers, this study aimed to identify distinct and predominant subtypes, i.e., cognitive phenotypes, in people with multiple sclerosis (PwMS) considering both cognitive impairment and mood disorders.

Methods: A latent class analysis (LCA) was applied on data from 872 PwMS who were tested with Montreal Cognitive Assessment (MoCA), Symbol Digit Modalities Test (SDMT) and Hospital Anxiety and Depression Scale (HADS). Furthermore, the distribution of demographic (i.e., age, gender, years of education) and clinical characteristics (i.e., disease duration, disease course, disability level) was examined amongst the identified phenotypes.

Results: Based on model fit and parsimony criteria, LCA identified four cognitive phenotypes: 1) only memory difficulties ($n = 247$; 28.3%); 2) minor memory and language deficits with mood disorders ($n = 185$; 21.2%); 3) moderate memory, language and attention impairments ($n = 164$; 18.8%); 4) severe memory, language, attention, information processing and executive functions difficulties ($n = 276$; 31.7%).

Conclusions: Since less is known about the progressive deterioration of cognition in PwMS, a taxonomy of distinct subtypes that consider information from different clustered domains (i.e., cognition and mood) represents both a challenge and opportunity for an advanced understanding of cognitive impairments and development of tailored cognitive treatments in MS.

1. Introduction

Cognitive impairment (CI) is one of the most debilitating and disturbing disorder in people with multiple sclerosis (PwMS), negatively affecting social and emotional functioning, employment status, and overall quality of life^{1–3}. CI can be present in 43–70% of adults and 30% of children with a pediatric form of MS⁴, and documented in all MS courses^{5–7}, with more severe deficits in progressive forms, both secondary progressive (SPMS) and primary progressive (PPMS), compared to relapsing-remitting MS (RRMS)⁸. Attention, information processing speed (IPS), learning and memory, and executive functions seem to be the most commonly affected cognitive domains^{3,9}. Although CI is well defined at group-level, a consistent inter-individual variability makes more intricate cognitive evaluation in MS¹⁰. This knowledge gap is due

to a general dichotomous approach when studying CI in MS: after administering a comprehensive neuropsychological battery of tests, individuals are then labeled as either “impaired” or “not-impaired” following several criteria (e.g., performance below 1.5 or 2 SD of the mean of normative values on 20–30% of test parameters; impairment in at least two cognitive domains; use of composite indices; or a combination of the previous strategies)⁸. For these reasons, a taxonomy that recognizes predominant subtypes, named cognitive phenotypes, could lead to an increased knowledge of CI and thus effective tailored treatments. However, an obstacle towards this classification is that most of the previous studies focused merely on CI, while overlooking other well-known and highly common disturbances of the disease that could tremendously impact quality of life of PwMS, as mood disorders (MD)^{11–13}. Depression and anxiety occur at much higher rates in PwMS than

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<https://doi.org/10.1016/j.msard.2021.102919>

Received 7 January 2021; Received in revised form 15 March 2021; Accepted 18 March 2021

Available online 21 March 2021

2211-0348/© 2021 The Authors.

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in general population^{14–16}. While depression has a prevalence of 30.5% to 31.7% in the MS population¹⁷, anxiety has been reported to be present in up to 22.1% of PwMS^{16,17}. MD can overlap with somatic (e.g., muscle tension, fatigability) and non-somatic (e.g., sustained attention, irritability) manifestations of the disease, increasing the possibility that the disorder and its causes go under-recognized and, consequently, untreated, impacting other clinical outcomes as well¹¹. In MS, CI have been found to preferably cluster with depression and anxiety, suggesting that these symptoms may be linked through shared etiological mechanisms (e.g., the cytokine-induced manifestation of sickness behavior or either a diffuse axonal damage across CNS)^{14,18}. Also, the association between CI and MD have been frequently reported to worse cognitive performances¹⁹.

Since combining information from different domains (i.e., cognition and mood) could help to increase prediction accuracy over and above what can be achieved at the level of single category of markers (i.e., cognition alone)²⁰, this study aimed to identify distinct and predominant cognitive phenotypes in PwMS considering both CI and MD using latent class analysis (LCA). The identified subtypes were then examined to establish whether they differ from each other according to demographic and clinical characteristics.

2. Methods

2.1. Participants

The dataset was acquired from a cohort of PwMS consecutively enrolled in the ongoing PROMOPRO-MS initiative²¹, a large, multi-center and prospective study, in which PwMS are evaluated periodically with various clinical scales and self-administered questionnaires to investigate several relevant domains (e.g., physical, cognitive, psychological, etc.). Participants were recruited among those followed by the Italian MS Society (AISM) Rehabilitation Services of Genoa, Padua and Vicenza. Following PROMOPRO-MS inclusion criteria (i.e., a definite diagnosis of MS and an age above 18 years), the current cohort included adult PwMS with RRMS and progressive MS (PMS), both SPMS and PPMS. Data collected between January 2014 and July 2020 were considered for study purpose. For each participant, only the first evaluation in time was included in the analyses.

All participants gave written informed consent prior to study entry in accordance with the revised Declaration of Helsinki²². The study was approved by the Regional Ethics Committee of Azienda Ospedaliera “San Martino”, Genoa, Italy.

2.2. Outcome measures

From PROMOPRO-MS database, we selected outcome measures which provided information about cognitive functioning, as Montreal Cognitive Assessment (MoCA)²³ and Symbol Digit Modalities Test (SDMT)²⁴. MoCA is a cognitive screening test scored on a 30-point scale with higher values corresponding to a better cognitive status. Cut-offs of the MoCA seven dimensions were used to isolate specific impaired domains²⁵: Visuospatial-Executive (< 4), Attention (< 6), Abstraction (< 1), Delayed Recall (< 4), Language (< 3), Naming (< 3), and Orientation (< 6). SDMT is a neuropsychological test used to assess IPS, with a score of ≤ 34 ²⁶ indicating the presence of IPS difficulties. This cut-off facilitates the application of the SDMT in clinical and research settings and allows Italian clinicians to use this neuropsychological tool with increased confidence. MoCA and SDMT have been chosen for their good psychometric properties^{24,27} and because they can be considered the best tools to quickly provide information about cognitive functioning in MS (about 10 and 5 min, respectively), thus reducing working load and preventing fatigability of participants.

MD were tested using Hospital Anxiety and Depression Scale (HADS)²⁸, a self-assessed questionnaire consisting of 14 multiple-choice (0–3 Likert scale) items probing the presence of depression (HADS-d

subscale) and anxiety (HADS-a subscale). A threshold score of 8 or above was found to be an accurate indicator for both depression and anxiety symptoms.

Furthermore, for each participant demographic (i.e., gender, age, years of education) and clinical (i.e., disease duration, disease course, and disability level as measured by the Expanded Disability Status Scale-EDSS²⁹) information were collected.

2.3. Statistical analysis

LCA was performed to identify distinct phenotypes based on the combination of the MoCA seven dimensions, SDMT, HADS-d and HADS-a of the study participants. LCA is a subset of structural equation modeling, which is used to detect mutually-exclusive homogeneous subgroups, named “latent classes”, regarding patterns of disease entities within a larger heterogeneous population³⁰. Since LCA required categorical responses, we used the cut-offs of the MoCA seven dimensions, SDMT, HADS-d and HADS-a to dichotomize the CI and MD domains into presence or absence of specific impairment.

In order to test the local independence assumption for LCA, we examined the magnitude of bivariate correlation using Spearman’s rho. Since small-to-moderate correlations were found (ranging from < 0.001 to 0.45), we assume that the assumption of local independence for LCA was adequately met³¹.

Here, we evaluated models with two-, three- and four latent-classes and determined the optimal number of classes using the model-fit criteria of Bayesian Information Criterion (BIC), Akaike Information Criterion (AIC) and entropy³². Lower the values of BIC and AIC, better the model fit and parsimony; in addition, entropy with values closer to 1 (maximum value) indicates better classification utility. Consistently with recommendations by³³, selection of the best model hinges not only on individual fit indices, but also considering the clinical interpretability. After the subtype identification and participants’ assignment to their most likely class, the distribution of the demographic (i.e., age, gender, years of education) and clinical characteristics (i.e., disease duration, disease course, EDSS) was examined amongst the identified phenotypes. The differences between groups of clinical and demographic characteristics were compared by one-way ANOVA or χ^2 -test when appropriate. When group differences were observed, ANOVA with post hoc analyses (Tukey’s test) was applied. Furthermore, in order to investigate whether and to what extent each phenotype resembles with the overall MS population, t-tests and Chi square were run to compare variables of each single subtype to overall cohort. All the analyses were conducted with Stata Statistical Software (release 15; StataCorp, 2017).

3. Results

Data from 872 PwMS were collected (female = 569; mean age = 54.1 ± 12.6) (see Table 1 for a summary of demographic and clinical characteristics of PwMS). Due to missing data on outcome measures, 40 individuals were excluded from further analyses. Although gender and educational level did not differ between excluded and included participants, left out PwMS were older ($p = .039$), had a longer disease duration ($p = .0006$), higher EDSS ($p < .0001$) and more progressive disease course ($p = .001$). In any case, excluded data only constituted a small proportion of the overall sample (4.4%).

Here, LCA generated two-, three- and four-class models (see Table 2 for fit and parsimony indices of each model). AIC, BIC and entropy indicated that the four-class model was the best for both fit and parsimony. Besides the best combination of fit-statistics, the identified four-class model was the most parsimonious solution with the strongest theoretical and clinical distinction when compared to 2-class and 3-class solutions.

The four cognitive phenotype profiles are presented in Fig. 1. Phenotype 1 included (28.3%; $n = 247$) PwMS with only fewer delayed recall memory difficulties (panel A). Phenotype 2 (21.2%; $n = 185$)

Table 1Demographic and clinical sample characteristics ($N = 872$).

Gender, n (%)	Male	303 (34.8%)
	Female	569 (65.2%)
Age (in years), mean (SD)		54.1 (12.6)
Min-max		19–87
Years of education, mean (SD)		11.6 (4.0)
Disease duration, mean (SD)		19.3 (12.3)
Disease course, n (%)	RR	392 (45.3)
	SP	365 (42.1)
	PP	109 (12.6)
EDSS, mean (SD) score		5.0 (2.0)
Median (IQR)		5.5 (3.5–6.5)
MoCA, mean (SD) score		23.3 (4.3)
Median (IQR)		24 (21–26.5)
SDMT, mean (SD) score		35.3 (15.1)
Median (IQR)		35.5 (24.5–46.0)
HADS-d, mean (SD) score		5.3 (3.6)
Median (IQR)		5 (2–7)
HADS-a, mean (SD) score		6.8 (4.4)
Median (IQR)		6 (3–10)

Note. SD = standard deviation; RR = relapsing-remitting; SP = secondary progressive; PP = primary progressive; EDSS = Expanded Disability Status Scale; IQR = interquartile range; MoCA = Montreal Cognitive Assessment; SDMT = Symbol Digit Modalities Test; HADS-d = Hospital Anxiety and Depression Scale (depression subscale); HADS-a = Hospital Anxiety and Depression Scale (anxiety subscale). Disease course information for six participants was missing.

Table 2

Fit indices of the models in LCA.

N° class	Log likelihood	Residual df	AIC	BIC	Entropy
2	−4641.0	21	9324.1	9424.3	0.68
3	−4576.8	32	9217.6	9370.2	0.65
4	−4547.0	43	9180.0	9385.1	0.68

Note. BIC = Bayesian Information Criterion; AIC = Akaike Information Criterion; df = degrees of freedom; BIC and AIC with lower values indicate better model fit and parsimony; Entropy with values closer to 1 (the maximum value) indicates better classification utility. In bold the 4-class model identified as the best solution.

contained individuals with mild delayed recall and language deficits with accompanying MD (panel B). Phenotype 3 (18.8%; $n = 164$) represented participants with moderate impairments in delayed recall, language and attention, in absence of MD (panel C). Finally, Phenotype 4 (31.7%; $n = 276$) involved PwMS with more severe and widespread CI in delayed recall, language, attention, IPS and executive functions, without depression and anxiety (panel D).

Post-hoc analysis revealed similarities and differences in demographic and clinical characteristics amongst the four phenotypes (Table 3). In general, cognitive phenotypes 1 and 2 were the most similar to each other with respect to age, disease duration, disease course and EDSS ($p > .05$). However, in phenotype 1 individuals had higher level of education compared to other phenotypes (13.3; $p < .05$). While phenotype 2 included more female (78.4%) and individuals with RRMS (59.8%) than other subtypes ($p < .05$), phenotype 3 had higher percentage of male (44.5%), and participants with PPMS (16.1%). Finally, the phenotypes 4 included older (60.0%) and more clinically compromised PwMS (disease duration = 23.4; EDSS = 6.0; $p < 0.05$). These results were further confirmed when comparing variables of each single phenotype to overall cohort (please see Table 4).

4. Discussion

In MS, cognition is typically considered dichotomously, impaired or not-impaired, which leads to heterogeneous groups of patients with different profiles of widespread deficits¹⁰. Applying a different approach in which cognitive functioning is considered as a continuous variable could help to identify a taxonomy that recognizes distinct and predominant cognitive phenotypes. This would be the main candidate to advance understanding of CI and to better tailor cognitive interventions for PwMS.

When assessing CI, several confounders must be taken into account. Among them, MD (depression and anxiety) stand as the most important¹⁸; they even have been hypothesized to contribute to early manifestations of cognitive difficulties and to potentially be useful in the early diagnosis of CI²⁵. Thus, the aim of this study was to identify cognitive phenotypes among 872 PwMS using LCA, combining information from both CI and MD.

All the four cognitive phenotypes showed memory dysfunction that

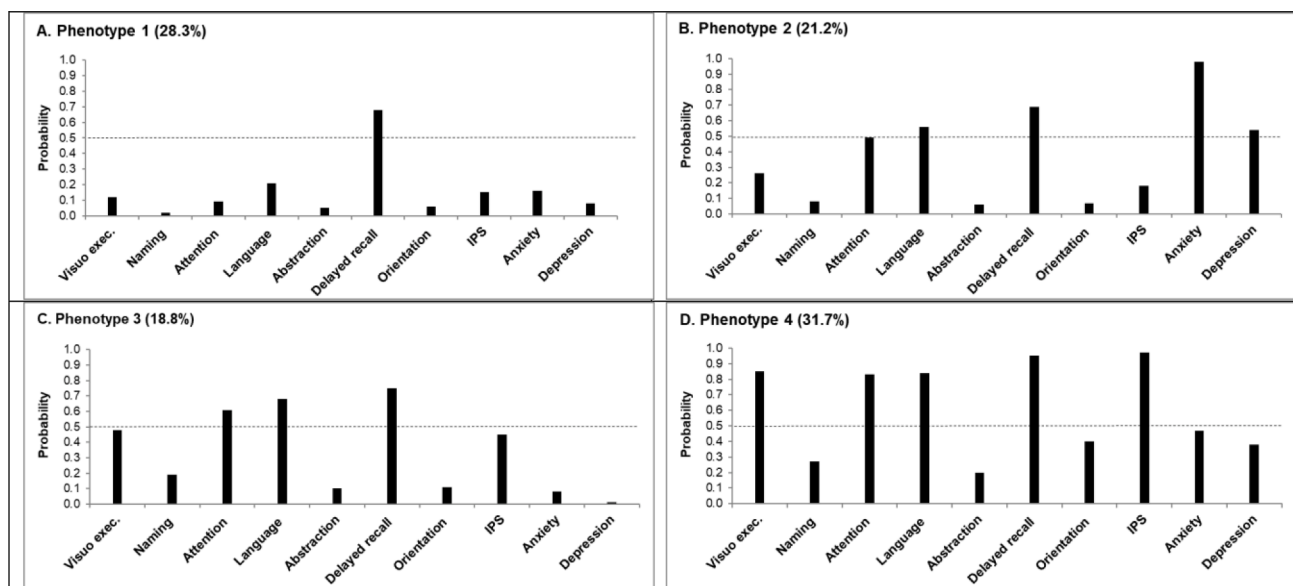


Fig. 1. Cognitive phenotypes based on the four-class model in LCA. The percentage in parenthesis indicates the proportion of participants in each phenotype. On x-axis, MoCA seven dimensions (visuo exec. = visuo executive, naming, attention, language, abstraction, delayed recall, orientation), SDMT (IPS = information processing speed) and HADS (anxiety and depression) outcomes included in LCA. On y-axis, probability of cognitive and mood deficits in each identified phenotype (0.5 indicated by dotted horizontal line).

Table 3

Summary of demographic and clinical characteristics by four phenotypes.

		Phenotype 1	Phenotype 2	Phenotype 3	Phenotype 4	p value	Significant post-hoc differences
Gender,%	F	62.8%	78.4%	55.5%	64.5%	.0001	a, d, e
	M	37.2%	21.6%	44.5%	35.5%		
Age, mean (SD)		50.0 (11.0)	50.5 (11.2)	54.3 (12.0)	60.0 (12.8)	< 0.0001	b, c, d, e, f
Years of education, mean (SD)		13.3 (3.4)	11.4 (3.4)	11.8 (4.1)	10.0 (4.0)	< 0.0001	a, b, c, e, f
Disease duration, mean (SD)		16.5 (10.1)	17.3 (11.5)	18.9 (12.0)	23.4 (13.7)	< 0.0001	c, e, f
Disease course,%	RR	57.5%	59.8%	40.1%	27.5%	< 0.0001	b, c, d, e
	SP	30.0%	33.2%	43.8%	58.2%		
	PP	12.5%	7.0%	16.1%	14.3%		
EDSS score, mean (SD)		4.2 (1.9)	4.6 (1.9)	5.1 (1.8)	6.0 (1.7)	< 0.0001	b, c, d, e, f

Note. F = female; M = male; SD = standard deviation; RR = relapsing-remitting; SP = secondary progressive; PP = primary progressive; EDSS = Expanded Disability Status Scale. Letters indicate significant post-hoc differences as follows: a = $p < .05$ between phenotype 1 and phenotype 2; b = $p < .05$ between phenotype 1 and phenotype 3; c = $p < .05$ between phenotype 1 and phenotype 4; d = $p < .05$ between phenotype 2 and phenotype 3; e = $p < .05$ between phenotype 2 and phenotype 4; f = $p < .05$ between phenotype 3 and phenotype 4.

Table 4

Comparison between each phenotype and overall MS cohort.

	Phenotype 1 vs all	Phenotype 2 vs all	Phenotype 3 vs all	Phenotype 4 vs all
Gender	$p = .330$	$p < .001$	$p = .004$	$p = .749$
Age	$p < .0001$	$p < .0001$	$p = .828$	$p < .0001$
Years of education	$p < .0001$	$p = .496$	$p = .508$	$p < .0001$
Disease duration	$p < .0001$	$p = .012$	$p = .584$	$p < .0001$
Disease course	$p < .001$	$p < .001$	$p = .202$	$p < .001$
EDSS score	$p < .0001$	$p = .0002$	$p = .429$	$p < .0001$

has been shown to be the most affected domain in MS, with a prevalence of 33–65%⁹. In the majority of cases, long-term memory (responsible for learning and recalling abilities) and working memory are the most disturbed³.

Phenotype 1 included PwMS with memory difficulties (specifically delayed recall deficits). However, individuals in this subtype were cognitively preserved compared to others. This could be explained considering the cognitive reserve hypothesis, which shows that lifetime intellectual enrichment, commonly indexed by level of education, occupational complexity, engagement in stimulating leisure activities, attenuates the effect of disease burden on cognition³⁴. As consequence, a possible explanation is that PwMS with a higher level of education could be protected from the negative impact of disease on cognition³⁴. In phenotype 1, the rate of RRMS (57.5%) was higher than SPMS (30.0%) or PPMS (12.5%). As indicated by further evidence³⁵, individuals with RRMS performed better on cognitive tasks than PPMS and SPMS participants.

Phenotype 2 contained individuals with both CI (i.e., memory and language) and MD. At a cognitive level, this phenotype is similar to phenotype 1 except for the increasing trend of language impairments. Communication and language deficits in MS have been receiving more attention, due to their negative impact on quality of life, including emotional distress, anxiety and feelings of self-incompetence³⁶. Interestingly, in this phenotype the rate of RRMS was higher compared than other three subtypes (59.8%). This in line with evidence that confirmed PwMS with RRMS had higher anxiety and depression compared to those with SPMS or PPMS¹¹. At earlier stage of the disease, although a lower level of physical disability, PwMS could perceive that other functional domains started to be compromised. This may lead them to question their source and possible evolution, thus affecting mood and quality of life. Furthermore, phenotype 2 presented an high rate of female participants that were more anxious than male¹¹.

Phenotype 3 represented PwMS with greater impairments in memory, language and attention, but without MD. Here, the rate of progressive individuals (both SPMS and PPMS) was higher (59.9%). As the

disease progresses, CI tends to become more widespread and pronounced. Although cognitive deficits are present in all MS subtypes, they are prominent and more severe in progressive forms, maybe due to the extensive neurodegenerative brain process and cortical involvement⁷. Beyond memory and attention, our findings were in line with evidence that supported the hypothesis that other cognitive domains (e.g., language) may be typically affected in SPMS and PPMS³⁷.

Phenotype 4 involved PwMS with marked and widespread CI (i.e., memory, language, attention, IPS, executive functions) and a more severe clinical profile (i.e., older age, higher disability level and higher rate of PMS), but without MD. It is well known that aging in general population represents a risk factor for CI. Even in healthy individuals, aging is accompanying by a decrease in the integrity of white matter, and therefore myelin damage, which would be associated with CI³⁸. Thus, it is still challenging for clinicians and researchers to disentangle whether CI are by-product of age and/or indicators of pathological processes. This is also true for other major common indicators of MS (i.e., spasticity, fatigue, ataxia, visual disturbances, and bowel dysfunction) that present many similarities with elderly. We speculate that as age increases, comorbidities, and physiological and psychological changes associated with normal aging may accentuate the severity of MS and its impact on cognitive functions³⁹. Thus, older PwMS may be at a greater risk for significant cognitive disturbance⁷. In this phenotype the number of progressive patients was higher (PMS = 72.5% vs. RRMS = 27.5%). This was in line with a plethora of studies that demonstrated that CI has been shown to be more frequent and severe in patients with PMS compared to those with RRMS⁷. Although memory deficits were highly marked, IPS impairment was the most pronounced in this phenotype. In line with several evidence⁴⁰, this is considered one of the primary cognitive problem in MS³ and standardized tests of IPS are used to predict impairment in higher cognitive skills as executive functions that are crucial abilities for complex goal-directed behavior and adaptation to environmental changes or demands⁴¹.

Age of participants could be taken into account as possible explanation of the absence of depression and anxiety symptoms in phenotypes 3 and 4. Investigating the association between age and MD, several authors have found that MD tended to decrease across adulthood, suggesting that older people have learned increased emotional control so that they are better at dampening negative emotions and enhancing positive emotions¹¹. Another possible responsible factor for this result could be age bias in MD measurement. Older people are more likely to report sleep problems and fatigue compared to MD in general and this may indicate that MD could be not manifested exactly in the same way in younger and older people¹¹.

As recently stated by¹⁰, a taxonomy of cognitive phenotype has been indicated as a key future mission for the field of cognitive research in MS. Based on our results, the four cognitive phenotypes could be conceptualized as a continuum: from younger patients with a lower disability level, a RRMS disease course, fewer and restricted CI and with

accompanying MD (phenotype 1 and 2), to older patients with increasing and marked alteration of cognitive functioning (i.e., memory, language, attention, IPS, executive functions) combined with a more severe clinical profile (i.e., higher disability level and progressive forms) (phenotype 3 and 4).

The findings of this study may have several implications for clinical management and decision-making. Potentially, the four subtypes may be used in future studies to evaluate their utility in predicting the etiology, onset and progression of CI. A practical screen for identification of patients who might need a close monitoring of cognitive functioning could help clinicians in planning effective treatments tailored to subgroups of cognitively homogeneous patients^{42–45}. This categorization could be particularly relevant both in a phase of pre-habilitation for patients with only slight impaired profiles and also in transition to a more severe phenotype for those individuals who present an onward deterioration of cognitive functioning as the disease progresses throughout its course.

There are several limitations to consider in the present study. Due to the cross-sectional design of the study, it remains unknown to what extent the identified classes are stable over time. We decided to select only data from a single time point in order to catch a glimpse of MS cognitive phenotypes. Longitudinal work incorporating cognitive phenotypes may yield more informative predictive models of cognitive decline in MS⁴⁶. This issue is particularly important in MS because as disease progresses throughout its course, variables contributing to each cluster could be different.

LCA identifies subgroups based on categorical indicators, not dimensional scores. Thus, presence or absence of and number of classes was used herein to provide information about the overlapping nature of individual subtypes of CI and MD; this would be less clearly presented with dimensional severity scores.

Some other factors that may influence the identification of phenotypes were not included in the analysis. Since several studies in both non-depressed and depressed individuals have demonstrated that antidepressants have early beneficial effects on cognition that occur prior to improvements in mood and/or other non-cognitive symptom domain⁴⁷, integrating any information about past (or present) history of depression and treatment interventions (e.g., drugs, cognitive behavioural therapy or mindfulness based therapy) could improve predication accuracy of the taxonomy.

Furthermore, measures of brain atrophy are particularly sensitive in clarifying the relation between brain integrity and cognition^{3,7,48}. Future research on PwMS that evaluates cognitive abilities should include advanced MRI techniques to better characterize neural basis of each cognitive phenotype towards a biological validation of the taxonomy⁴⁸.

5. Conclusions

Latent variables have been widely embraced by the field of cognitive neuroscience as superior to single measures and should be adopted for future work in MS⁴⁶. Since less is known about the longitudinal progressive deterioration of cognitive skills in PwMS, a taxonomy of distinct subtypes that consider both CI and other relevant dimension that affect MS represents a challenge and a potential opportunity for an advanced understanding of CI and development of tailored treatments for cognition in PwMS.

CRedit authorship contribution statement

Jessica Podda: Conceptualization, Validation, Writing - original draft, Writing - review & editing, Visualization. **Michela Ponzio:** Conceptualization, Methodology, Formal analysis, Data curation. **Ludovico Pedullà:** Investigation, Writing - review & editing. **Margherita Monti Bragadin:** Resources. **Mario Alberto Battaglia:** Supervision. **Paola Zaratin:** Supervision, Writing - review & editing.

Giampaolo Brichetto: Writing - review & editing, Project administration, Funding acquisition. **Andrea Tacchino:** Conceptualization, Validation, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

None.

Acknowledgments

We would like to thank all the people with MS followed as outpatients at the Rehabilitation Service of Genoa of the Italian MS Society (AISM) for their participation to this research. A special thanks to Maria Madera and Giulia Bignone for their help in patients' enrollment.

Funding

This study has been supported by Italian MS Foundation (FISM/2013/S3—PROMOPRO-MS and FISM/2015/R3—DETECT-MS).

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