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A multifaceted approach to understand cognitive impairment in MS: exploring the nonlinearity of cognition

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5

**Cognition from a multi-
dimensional perspective**



5.1

Understanding the complex network of objectively assessed cognition and self-reported psychological symptoms in people with multiple sclerosis

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ABSTRACT

Background: Literature on the intricate relationship between self-reported and objectively assessed cognitive functioning suggests a discrepancy between self-reported cognitive complaints (SCC) and actual test performance.

Objectives: To investigate the interplay between patient-reported outcome measures (PROMs) and objective cognitive functioning using network analysis in people with multiple sclerosis (PwMS).

Methods: We collected PROMs on anxiety, depression, fatigue and SCC, and cognitive functioning across six domains ($n = 703$ PwMS; 71% female, mean age = 46.3 ± 11.2 years). We constructed cognitive symptom networks using Gaussian Graphical Models, in which the aforementioned variables were presented as nodes linked by regularized partial correlations. We compared global network strength between relevant subgroups.

Results: The networks primarily showed clustering of PROMs and cognitive domains into two separate modules, with weaker links connecting both modules. Global network strength was lower for PwMS with impaired information processing speed (IPS; indicating lower symptom interrelatedness) compared to those with preserved IPS (3.57 versus 4.51, $p = 0.001$), but not when comparing SCC subgroups ($p = 0.140$).

Conclusion: Cognitive symptom networks deepen our understanding of the discrepancy between self-reported and objectively assessed cognitive functioning. Lower symptom interrelatedness in PwMS with impaired IPS might suggest a nonlinear relation between PROMs and cognitive domains, which depends on the cognitive status.

INTRODUCTION

Cognitive impairment affects up to 65% of people with multiple sclerosis (PwMS), substantially impacting quality of life.¹ Slowed information processing speed (IPS) is highly prevalent and among the first cognitive impairments in PwMS,¹ possibly underlying other higher-level cognitive processes.² Cognitive impairment is assessed using patient-reported outcome measures (PROMs) and formal neuropsychological testing,¹ but prior research underlines a discordance between these methods, known as the subjective-objective discrepancy.³⁻⁵ Psychological factors, such as fatigue and depression, which are more common in MS than in the general population,^{6, 7} may explain the discrepancy between self-reported cognitive complaints (SCC) and objective test results, as PwMS who report more cognitive complaints than can be confirmed by neuropsychological testing more often struggle with depression and fatigue.^{4, 5} Conversely, some PwMS might notice cognitive changes in daily life before they become evident in objective assessments.⁸ Together, this suggests that the relationship between PROMs and objective cognitive function may vary among PwMS.

Despite recommendations for multifaceted cognitive screening in clinical care,⁹ an integrative approach to understanding these interrelated factors, rather than relying on univariate analyses, remains largely unexplored. To better understand the relationship between PROMs, including anxiety, depression, fatigue and SCC, and objectively assessed cognitive functioning, we explored symptom network analysis. This analysis examines the interactions among multiple symptoms rather than focusing on individual symptoms.¹⁰ In a network, nodes can represent PROMS or cognitive domains and edges represent associations between these at the group-level.¹⁰ While network analysis has been applied to study self-reported symptoms in cancer and psychiatric disease,^{11, 12} its application in MS remains understudied.

This study aimed to utilize network analysis to uncover correlational patterns of interrelatedness between objective cognitive functioning and PROMs in MS, to elucidate the subjective-objective discrepancy. We hypothesized that the relationship among these symptoms would differ between PwMS with and without cognitive impairments and those with and without SCC. To test this, we compared networks distinguishing between self-reported symptoms (i.e., SCC) and between objectively assessed impairment in IPS, the most common impairment in PwMS. Our objectives were to: 1) compute cognitive symptom networks in PwMS; 2) compare these networks between subgroups with less and more SCC; and 3) compare these networks between subgroups with and without IPS impairment. Through these comparisons, we sought to determine whether symptoms are more tightly interconnected in different subgroups of PwMS. Understanding these patterns could enhance clinical understanding, therapeutic interventions, and symptom management strategies, given the significant impact of cognitive impairment on quality of life and daily functioning.

MATERIALS AND METHODS

Participants

This study retrospectively evaluated cross-sectional data from eight observational studies performed between 2008 and 2023 at Amsterdam UMC location VUmc. The Medical Ethics Review Committee of Amsterdam UMC granted ethical approval, and all PwMS provided written informed consent. Table 1 summarizes cohort details and inclusion criteria, with previous publications listed in Supplementary Table 1. Participants were included if they met criteria for clinically definite MS or clinically isolated syndrome, completed PROMs, and underwent a neuropsychological assessment. PwMS with missing data were excluded ($n = 209$). If PwMS participated in multiple studies or visits ($n = 43$), only the first visit was included, resulting in a total of 703 PwMS eligible for analysis.

Demographic and clinical characteristics were collected. Level of education was assessed according to the Verhage classification,¹³ and physical disability was assessed using the Expanded Disability Status Scale (EDSS).¹⁴

Table 1. Overview of the included cohorts, with their in- and exclusion criteria.

	<i>n</i> (% of total)	Inclusion criteria	Exclusion criteria
Cohorts			
1. Attention METC-number: 2014.377	86 (12.2)	• MS diagnosis according to the 2010-McDonald criteria¹⁵ • 18-68 years of age • Ability to safely undergo an MRI examination • Screening for motor and visual skills	• History or presence of drug abuse • Neurological (other than MS) and psychiatric diseases • Relapse and/or steroid treatment 4 weeks prior to examination
2. Amsterdam MS cohort	188 (26.7)	• MS diagnosis according to the 2010-McDonald criteria¹⁵	• Neurological (other than MS) and psychiatric diseases
General MS cohort	61/188		
METC-number: 2002.140	(32.4)	• 18 years of age and older	• Relapse and/or steroid treatment 2 months prior to examination
(P02.1381L), 2004.009			
(P04.0142L)			
Longstanding MS cohort	127/188	• MS diagnosis according to the 2010-McDonald criteria¹⁵ • 18 years of age and older • Minimum disease duration of 10 years from onset	• Neurological (other than MS) and psychiatric diseases • Relapse and/or steroid treatment 6 weeks prior to examination
METC-number: 2010.336	(67.6)		
3. Fingolimod	45 (6.4)	• MS diagnosis according to the 2010-McDonald criteria¹⁵ • PwMS with RRMS	• Neurological (other than MS) and psychiatric diseases • Relapse and/or steroid treatment 4 weeks prior to examination
METC-number: 2014.418			

Table 1. Continued

	n (% of total)	Inclusion criteria	Exclusion criteria
		• 18-65 years of age • Ability to safely undergo an MRI examination • Screening for motor and visual skills	
4. GABA & glutamate METC-number: 2017.380	49 (7.0)	• MS diagnosis according to the 2017-McDonald criteria¹⁶ • PwMS with RRMS or SPMS • 18-65 years of age • Ability to safely undergo an MRI examination • Screening for motor and visual skills	• History or presence of drug abuse • Neurological (other than MS) and psychiatric diseases • Relapse and/or steroid treatment 4 weeks prior to examination
5. RemindMS ^a METC-number: 2017.009	99 (14.1)	• MS diagnosis according to the 2010-McDonald criteria¹⁵ • 18-65 years of age • Scoring ≥ 23 on the Multiple Sclerosis Neuropsychological Questionnaire – Patient version (MSNQ-P)	• History/presence of psychosis and/or suicidal ideation • Inability to speak Dutch • Previous experience with the similar interventions • Physical or cognitive disabilities/ comorbidities/ treatments likely to cause interference
6. SOMSCOG ^a METC-number: 2016.395	101 (14.4)	• MS diagnosis according to the 2017-McDonald criteria¹⁶	
7. Tecfidera METC-number: 2017.469	64 (9.1)	• MS diagnosis according to the 2017-McDonald criteria¹⁶ • PwMS with RRMS • 18-65 years of age • Ability to safely undergo an MRI examination • Screening for motor and visual skills	• History or presence of drug abuse • Neurological (other than MS) and psychiatric diseases • Relapse and/or steroid treatment 4 weeks prior to examination • Participation in other studies using cognitive or physical training programs
8. Temprano METC-number: 2020.021	71 (10.1)	• MS diagnosis according to the 2017-McDonald criteria, within one year¹⁶ • PwMS with RRMS • 18-65 years of age • Sufficient Dutch proficiency • Ability to safely undergo an MRI examination	• History or presence of drug abuse • Neurological (other than MS) and psychiatric diseases • Relapse and/or steroid treatment 4 weeks prior to examination • Participation in other studies using cognitive or physical training programs

^a Although the presence of an acute relapse was not an exclusion criteria for this study, no PwMS experienced a relapse when participating in the study. Abbreviations: MS = Multiple Sclerosis; RRMS = Relapsing-Remitting MS.

Patient-reported outcome measures

Anxiety and depression symptoms were measured with the Hospital Anxiety and Depression Scale (HADS),¹⁷ and fatigue with the Checklist Individual Strength-20 Revised (CIS), including the subscales: subjective fatigue (CIS-subjective), concentration (CIS-concentration), motivation (CIS-motivation) and activity (CIS-activity).¹⁸ All PROMs were scaled (mean = 0, standard deviation (SD) = 1) to allow for comparison between questionnaires, with higher scores indicating worse psychological functioning (listed in Supplementary Table 2).

SCC was assessed using multiple PROMs for different cohorts (the MS Neuropsychological Questionnaire-patient version (MSNQ),¹⁹ the Cognitive Failures Questionnaire (CFQ)²⁰ and the Subjective Cognitive Performance Questionnaire (SCPQ)).²¹ Based on the z-scores obtained from each PROM, we constructed a single SCC variable. For three cohorts, PwMS completed two SCC PROMs, resulting in two z-scores. In such a case, the SCC was computed as the average of the two z-scores. Supplementary Table 3 details an explanation of this procedure.

Neuropsychological assessment

Cognitive functioning was assessed using adapted versions of the Minimal Assessment of Cognitive Function In MS²² or the Brief Repeatable Battery of Neuropsychological Tests.²³ Cognitive test scores from different cohorts were combined into six cognitive domains: attention, inhibition, IPS, verbal fluency, verbal memory, and visuospatial memory (see Supplementary Table 2).

Due to the statistical methods used, cognitive test scores were normed with two different approaches. First, scores were adjusted for age, sex, and education and transformed into domain-specific z-scores using normative data from Dutch healthy controls ($n = 407$).²⁴ These data were used to report the sample characteristics and to define subgroups with and without IPS impairment, indicated by a z-score ≤ -1.5 (third objective).²⁵

Second, domain z-scores were calculated based on the PwMS sample mean and SD. These cognitive domains were used as input for the networks and were not corrected for demographics. This is because PROMs data are generally not corrected for demographic characteristics, and for statistical consistency, the input variables in a network should undergo the same scoring procedure.²⁶

Subgroups

To explore the impact of SCC and IPS on the networks (objectives 2 and 3), we categorized PwMS into subgroups (see Figure 1).

SCC split. The entire sample was divided into tertiles based on SCC z-scores (see Figure 1.A). PwMS in the lower tertile for SCC (less complaints) constituted the “*less SCC*” subgroup ($n = 231$), and PwMS in the higher tertile were part of the “*more SCC*” subgroup (more complaints, $n = 235$).

IPS split. We split the entire dataset into an “*IPS impaired*” subgroup ($n = 240$) and an “*IPS preserved*” subgroup ($n = 463$, see Figure 1.B), using the z-scores based on normative data (described above, defining z-scores ≤ -1.5 as impaired).

Sensitivity analyses. We split the complete dataset into tertiles based on IPS z-scores from PwMS (rather than normative data, thereby mirroring the SCC split). We compared the networks of PwMS between the lower and higher IPS tertiles. The dataset was also dichotomized based on sex. These sensitivity analyses are outlined in the Supplementary Materials (see Appendix A and B).

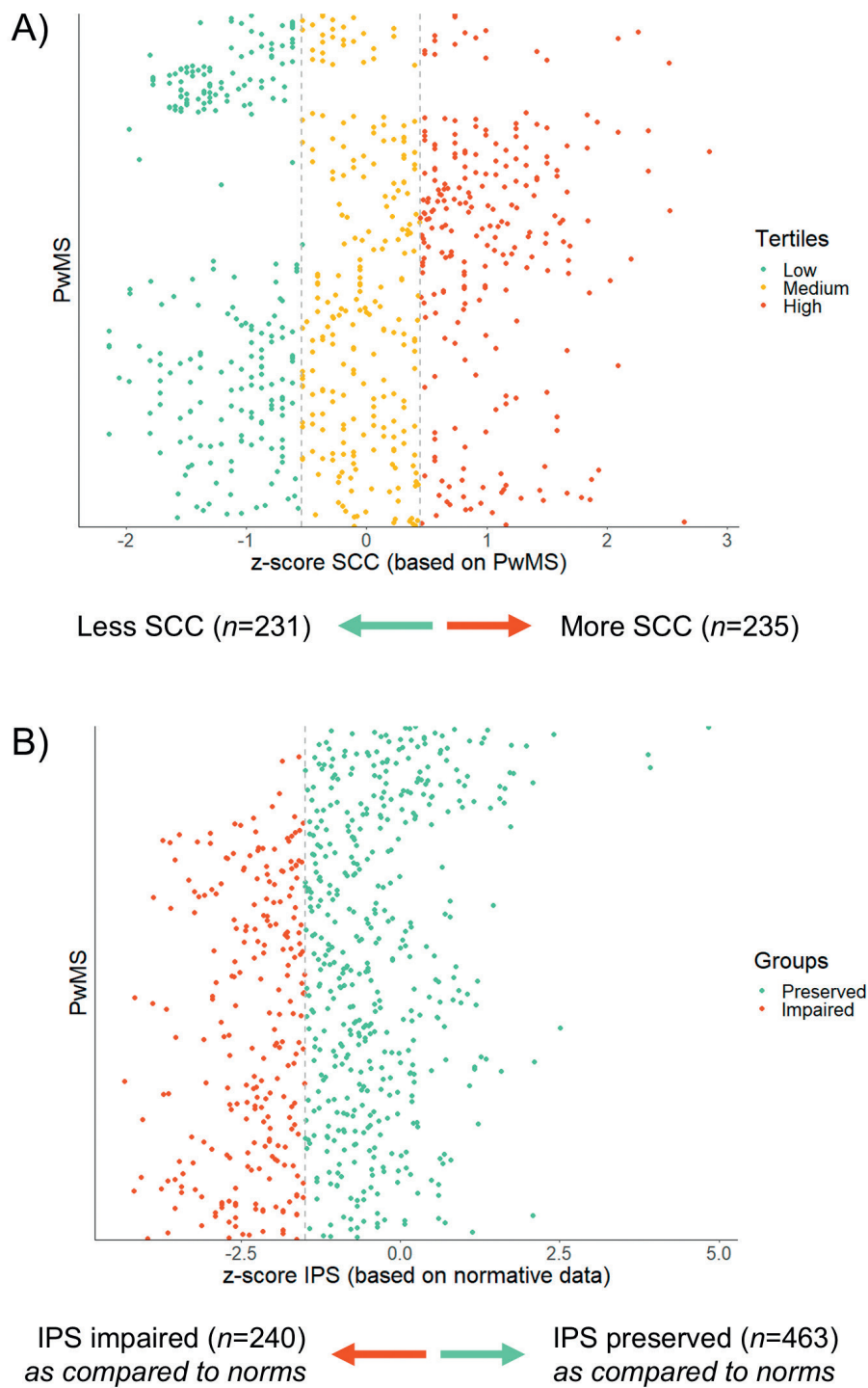


Figure 1. Constructing subgroups for network comparisons.

In panel A, the z-scores were computed based on the group itself (PwMS), with higher scores indicating more problems. Based on tertiles, we divided the total sample into a “less SCC” group and a “more SCC” group. For this split, the middle tertile was left out of the analysis. For panel B, z-scores were constructed based on normative data. Z-scores ≤ -1.5 were considered impaired. *Abbreviations: PwMS = People with MS; SCC = self-reported cognitive complaints; IPS = information processing speed.*

Statistical analyses

Network and statistical analyses were conducted in RStudio (version 4.2.1),²⁷ using the packages bootnet²⁶ and qgraph.²⁸ Normality of variables was checked by visually inspecting the histograms. Differences between subgroups were analyzed using independent samples *t*-tests for continuous variables and χ^2 -tests for categorical variables. An α -level of 0.05 was considered statistically significant. We followed the reporting guidelines for psychological network analyses in cross-sectional data.²⁹

Computing networks. We introduce cognitive symptom networks,^{12, 26} with nodes representing seven PROMs (sub)scales and six cognitive domains, connected by edges signifying regularized partial correlations between nodes at a group level.¹⁰ These z-scores of the cognitive domains were reversed to align with the PROMs (higher z-scores indicating worse cognitive performance). Detailed descriptions of the consecutive steps taken to construct the networks are included elsewhere.¹¹ In short, networks were computed with Gaussian graphical models based on Spearman’s partial correlation matrices. Networks were regularized with EBICglasso with a tuning parameter set at 0.25 due to the explorative nature of this study.²⁶ We present five networks: one comprising all PwMS with seven PROMs and six cognitive domains as nodes, and four subgroups networks based on SCC levels and IPS impairment. If a subgroup was dichotomized by SCC or IPS, the respective node was omitted from the network. We calculated node strength for each node per network, representing the sum of the edge weights connecting one node to others. If symptoms clustered within the network, these groups were called modules, representing symptoms that were more closely connected to each other.³⁰

Comparing networks. To understand whether network density was different between subgroups, we calculated the global strength of the networks (objectives 2 and 3).³¹ Global strength is the average node strength of a network, and provides a measure of overall interconnectedness of nodes. Global strength was compared between networks with permutation-based network comparison tests using 2000 iterations.³¹ If there was a significant difference in global strength between subgroups, we split the network into a PROMs and a cognitive domains network and compared these networks between subgroups.

Stability and accuracy. Given the high number of estimated parameters, the stability of node strengths and the accuracy of estimated edges were evaluated (see Supplementary Table 4).²⁶

RESULTS

Participants

The sample of 703 PwMS included 71.3% females, with a mean age of 46.3 ± 11.2 years (see Table 2). Most PwMS had relapsing-remitting MS (RRMS; 79.8%), a median disease duration of 8.2 years (interquartile range: 2.9-16.9), a median EDSS of 3.5 (range: 0.0-8.0), and 57.5% used disease modifying therapy (DMT). The domain-specific impairments were 34.1% for IPS, 23.6% for attention, 23.5% for inhibition, 16.9% for visuospatial memory, 16.4% for verbal memory and 12.7% for verbal fluency.

The SCC subgroups were similar regarding demographics and MS type. Compared to the “less SCC” subgroup, PwMS within the “more SCC” subgroup demonstrated a longer disease duration, higher EDSS, more frequent DMT use (range p -values = <0.001 -0.032), and worse scores on all PROMs and cognitive domains (range p -values = <0.001 -0.026), except for visuospatial memory ($p = 0.242$). Sex, educational level, DMT use, and the presence of severe fatigue were similar between the IPS subgroups (range p -values = 0.050-0.216). However, the “IPS impaired” subgroup scored worse on all other demographic, clinical, PROMs and cognitive domains (range p -values = <0.001 -0.021).

Table 2. Demographic, disease-related and psychological and cognitive characteristics of the total sample and per subgroups.

	Total sample		SCC split		IPS split	
	n = 703	% missing	Less SCC n = 231	More SCC n = 235	p-value	IPS preserved n = 463
Demographics						
Sex female, n (%)	501 (71.3%)	0.0%	163 (70.6%)	180 (76.6%)	.140	337 (72.8%)
Age years, median (SD)	46.3 (11.2)	0.0%	44.7 (11.0)	46.3 (10.6)	.099	44.8 (11.3)
Education Verhage ^a , median (IQR)	6.0 (5.0-6.0)	0.3%	6.0 (5.0-7.0)	6.0 (5.0-6.0)	.085	6.0 (5.0-6.0)
Clinical functioning						
MS type		1.9%			.153	
RRMS n (%)	561 (79.8%)		201 (87.0%)	183 (77.9%)		388 (83.8%)
SPMS n (%)	83 (11.8%)		18 (7.8%)	30 (12.8%)		36 (7.8%)
PPMS n (%)	42 (6.0%)		9 (3.9%)	14 (6.0%)		29 (6.3%)
CIS n (%)	4 (0.6%)		1 (0.4%)	2 (0.9%)		3 (0.6%)
Disease duration years, median (IQR)	8.2 (2.9-16.9)	2.4%	6.3 (1.0-13.4)	9.0 (3.8-18.0)	<.001*	6.5 (1.5-14.0)
EDSS ^b median (range)	3.5 (0.0-8.0)	1.0%	3.0 (0.0-7.5)	4.0 (1.0-8.0)	<.001*	3.0 (0.0-8.0)
DMT use yes, n (%)	404 (57.5%)	7.0%	154 (66.7%)	132 (56.2%)	.032*	282 (60.9%)
PROMS						
CIS20-R sub-scale mean (SD)	35.7 (12.1)	0.0%	29.6 (12.1)	40.9 (10.6)	<.001*	34.8 (12.4)
Severe fatigue ≥35, n (%)	398 (56.6%)		83 (35.9%)	176 (74.9%)	<.001*	250 (54.0%)
HADS-D score median (IQR)	4.0 (2.0-7.0)	0.0%	2.0 (1.0-5.0)	6.0 (4.0-9.0)	<.001*	3.0 (1.0-7.0)
Sig symptoms ≥8, n (%)	170 (24.2%)		34 (14.7%)	90 (38.3%)	<.001*	97 (21.0%)
HADS-A score median (IQR)	6.0 (4.0-8.0)	0.0%	5.0 (3.0-7.0)	8.0 (5.0-11.0)	<.001*	6.0 (4.0-8.0)
Sig symptoms ≥8, n (%)	238 (33.9%)		51 (22.1%)	118 (50.2%)	<.001*	143 (30.9%)
SCC mean (SD)	-0.05 (-0.06)	0.0%	-1.2 (-1.1)	1.03 (0.9)	<.001*	-0.2 (1.0)

Table 2. Continued

	Total sample		SCC split		IPS split	
	n = 703	% missing	Less SCC n = 231	More SCC n = 235	IPS preserved n = 463	IPS impaired n = 240
Cognitive domains (z-scores compared to normative data)						
Attention mean (SD)	-0.8 (1.2)	0.0%	-0.5 (1.2)	-1.1 (1.2)	-0.4 (1.0)	-1.6 (1.2)
Impaired ^c n (%)	166 (23.6%)		40 (17.3%)	78 (33.2%)	56 (12.1%)	110 (45.8%)
Inhibition mean (SD)	-0.6 (1.4)	0.1% ^d	-0.2 (1.3)	-1.1 (1.4)	-0.3 (1.2)	-1.2 (1.4)
Impaired ^c n (%)	165 (23.5%)		33 (14.3%)	76 (32.3%)	75 (16.2%)	90 (37.5%)
IPS mean (SD)	-1.0 (1.3)	0.0%	-0.6 (1.2)	-1.3 (1.2)	-0.3 (0.9)	-2.4 (0.7)
Impaired ^c n (%)	240 (34.1%)		52 (22.5%)	103 (43.8%)	0 (0.0%)	240 (100%)
Verbal fluency mean (SD)	-0.7 (0.7)	0.3% ^e	-0.7 (0.8)	-0.8 (0.8)	-0.6 (0.7)	-1.1 (0.7)
Impaired ^c n (%)	89 (12.7%)		21 (9.1%)	40 (17.0%)	32 (6.9%)	57 (23.8%)
Verbal memory mean (SD)	-0.5 (1.1)	0.3% ^e	-0.3 (1.0)	-0.7 (1.1)	-0.2 (0.9)	-1.1 (1.1)
Impaired ^c n (%)	115 (16.4%)		26 (11.3%)	45 (19.1%)	36 (7.8%)	79 (32.9%)
Visuospatial memory mean (SD)	-0.5 (1.1)	0.0%	-0.4 (1.1)	-0.5 (1.1)	-0.2 (1.0)	-0.9 (1.1)
Impaired ^c n (%)	119 (16.9%)		36 (15.6%)	39 (16.6%)	49 (10.6%)	70 (29.2%)

Significant at $p < 0.05$.^a Level of education is coded according to the Verhage classification. ^b Assessed by a certified examiner, either face-to-face or through validated telephone assessment. ^c Cognitive data in this table were corrected for age, sex and educational level based on a normative sample of Dutch healthy controls, and considered impaired if Z-score < -1.5 . ^d For 1 PwMS comparison to normative data was unsuccessful as transformation to normal distribution (log-transformation), needed for comparison to normative data was not possible (time on Card III was faster than the average on Card I and II). ^e Data for 2 PwMS was missing, as for comparison to normative data a correction with educational level was needed, and for these PwMS the level of education was not provided. Abbreviations: SD = Standard Deviation; IQR = Interquartile Range; RRMS = Relapsing-Remitting MS; SPMS = Secondary Progressive MS; PPMS = Primary Progressive MS; CIS = Clinically Isolated Syndrome; EDSS = Expanded Disability Status Scale; DMT = Disease Modifying Therapy; PROMS = Patient-Reported Outcome Measures; CIS20-R, Checklist Individual Strength-20 Revised; HADS-D, Hospital Anxiety and Depression Scale subscale Depression; HADS-A, Hospital Anxiety and Depression Scale subscale Anxiety; SCC = Self-reported Cognitive Complaints; IPS, Information Processing Speed; NA = Not Applicable.

Cognitive symptom network

Figure 2 displays the cognitive symptom network of all 703 PwMS. The network comprised of 47 edges out of 78 possible edges (60.3%), connecting the 13 nodes. Visual inspection showed that PROMs and cognitive domain nodes primarily clustered into two modules, with weak links connecting these modules (see Figure 2.A, Supplementary Table 5). The nodes attention, CIS-concentration, HADS-D and SCC had the highest node strength, indicating strong connections to other nodes (see Figure 2.B). Each PROM and cognitive domain node was connected to at least one node from the other module. The strongest edges were present between SCC and CIS-concentration, HADS-D and HADS-A, attention and IPS, and CIS-activity and CIS-subjective (range edge weights = 0.586-0.340, see Supplementary Table 5). Stability checks indicated that node strength could be interpreted accurately (see Supplementary Figure 1).

Comparing networks based on SCC

Figures 3.1A and 3.1B depict the networks for the “less SCC” and “more SCC” subgroups, respectively. Global strength was not significantly different between these (4.21 versus 3.62, respectively, $p = 0.140$), indicating similar overall interconnectedness of the nodes in both networks. Supplementary Figures 2 and 3 show details on node strength, stability and edge accuracy.

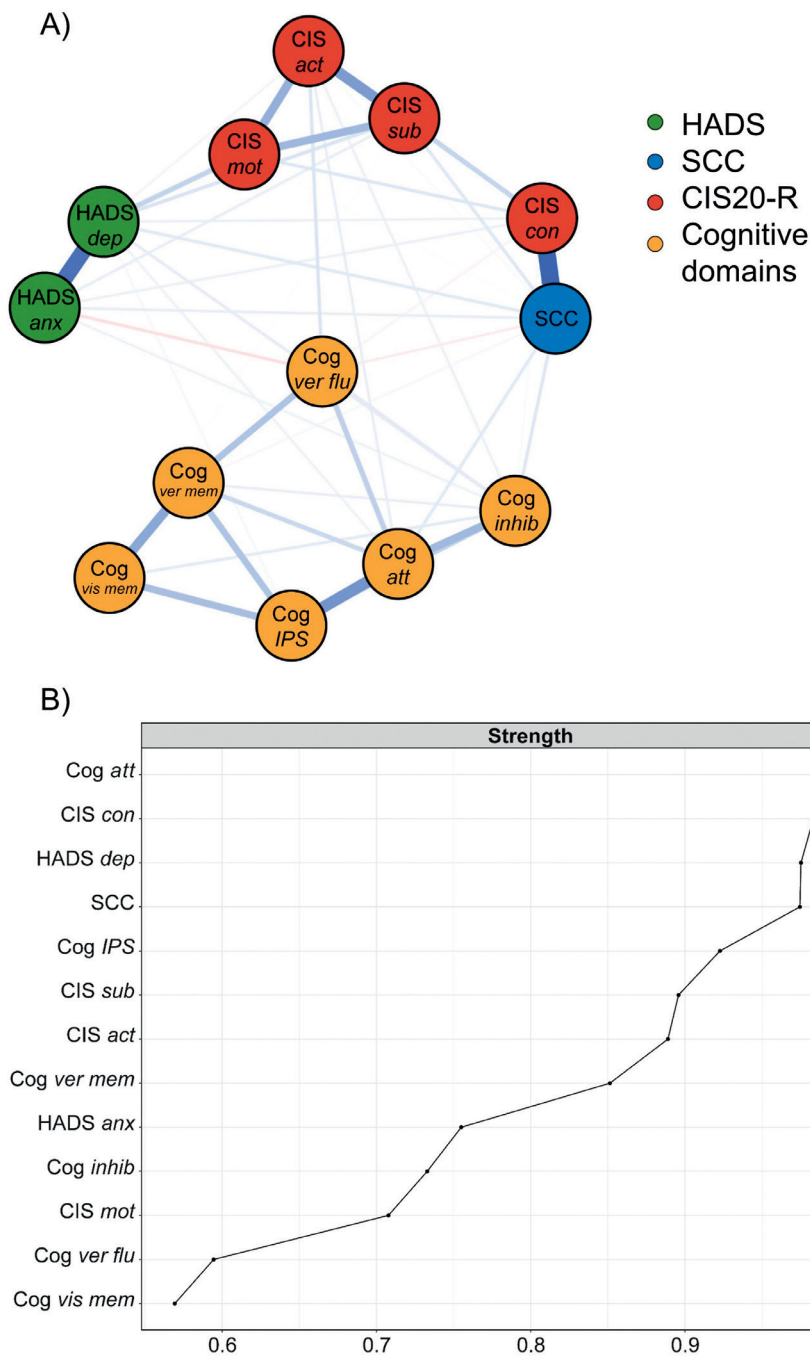


Figure 2. The overall cognitive symptom network in PwMS (panel A). The colors of the nodes refer to the corresponding PROMs or cognitive domains. A blue edge indicates a positive relationship between the two nodes and a red edge a negative relationship. Edges were undirected and weighted and in the presented figures, edge width corresponds to the

magnitude of the association. Node strength is depicted in panel B, with the cognitive domain “attention” showing the highest strength. Abbreviations: HADS = Hospital Anxiety and Depression Scale; SCC = self-reported cognitive complaints; CIS20-R = Checklist Individual Strength (CIS)-20 Revised; Cog = cognitive domain; att = attention; inhib = inhibition; IPS = information processing speed; ver flu = verbal fluency; ver mem = verbal memory; vis mem = visuospatial memory; HADS anx = HADS anxiety subscale; HADS dep = HADS depression subscale; CIS sub = CIS-subjective; CIS con = CIS-concentration; CIS mot = CIS-motivation; CIS act = CIS-activity.

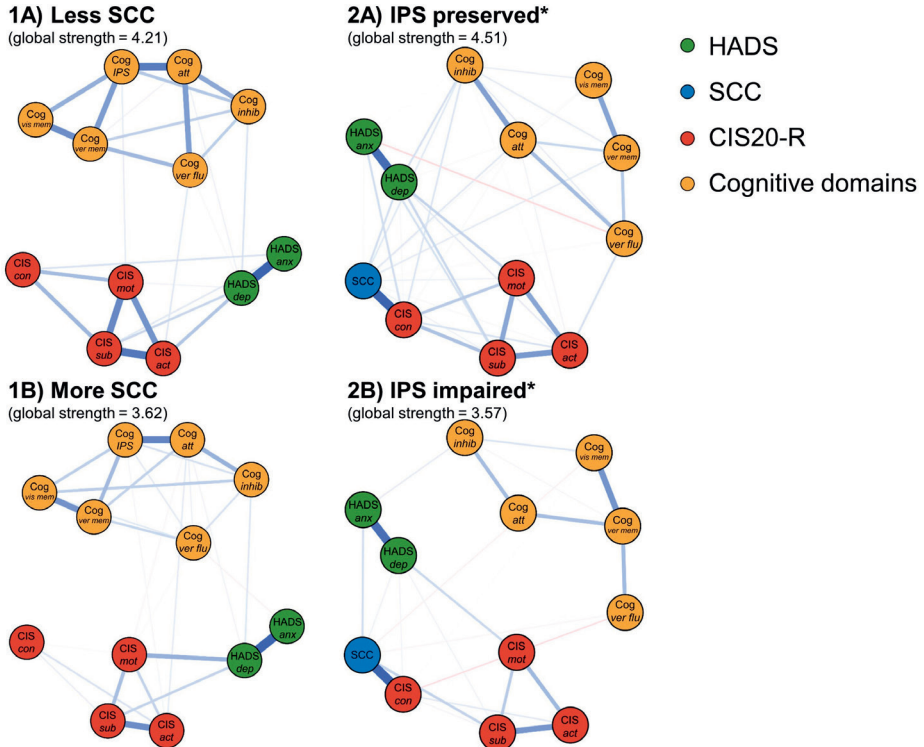


Figure 3. Comparisons of the cognitive symptom networks for the subgroups.

The networks for the SCC subgroups can be found in panels 1A and 1B. The networks for the IPS subgroups can be found in panels 2A and 2B. The colors of the nodes refer to the corresponding PROMs or cognitive domains. A blue line indicates a positive relationship between the two nodes, and a red line indicates a negative relationship. Edges were undirected and weighted, and in the presented figures, edge width corresponds to the magnitude of the association.* Global strength of the network is higher for the network of PwMS with preserved IPS, compared to impaired IPS ($p = 0.001$). Abbreviations: HADS = Hospital Anxiety and Depression Scale; SCC = self-reported cognitive complaints; CIS20-R = Checklist Individual Strength (CIS)-20 Revised; Cog = cognitive domain; att = attention; inhib = inhibition; IPS = information processing speed; ver flu = verbal fluency; ver mem = verbal memory; vis mem = visuospatial memory; HADS anx = HADS anxiety subscale; HADS dep = HADS depression subscale; CIS sub = CIS-subjective; CIS con = CIS-concentration; CIS mot = CIS-motivation; CIS act = CIS-activity.

Comparing networks based on IPS impairment

We found a lower global strength of the “IPS impaired” network compared to the “IPS preserved” network (3.57 versus 4.51, respectively, $p = 0.001$), indicating lower correlations among PROMs and cognitive domains in PwMS with impaired IPS (see Figures 3.2A and 3.2B). To further understand these results, we compared the global strength of separate cognitive and separate PROMs networks between the subgroups (see Figure 4), but no differences in global strength were found for these networks ($p = 0.080$, $p = 0.250$, respectively).

Since the difference in global strength was observed in the overall network only, not within the separate PROMs and cognitive networks, the difference in global strength of the networks between PwMS with and without IPS impairment may be due to weaker associations connecting PROMs and cognitive domains (although this was not specifically tested). Caution is warranted when interpreting the global strength of the PROMs network, as the nodes’ stability is below the preferred threshold (see Supplementary Figures 4-9).

In a post-hoc analysis of RRMS PwMS, we confirmed previous results: global strength of the “IPS preserved” network was 4.84 ($n = 391$) versus 3.03 for the “IPS impaired network” ($n = 170$; $p = 0.010$). No significant differences were found between groups for the separate cognitive ($p = 0.723$) or PROMs networks ($p = 0.495$).

Sensitivity analyses

No differences in global network strength were found between lower and higher IPS functioning ($p = 0.080$, see Supplementary Appendix A) or between females and males ($p = 0.470$, see Supplementary Appendix B).

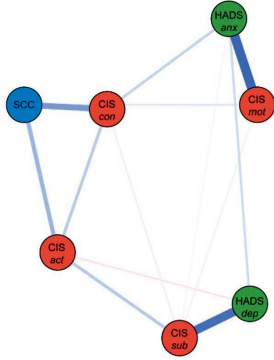
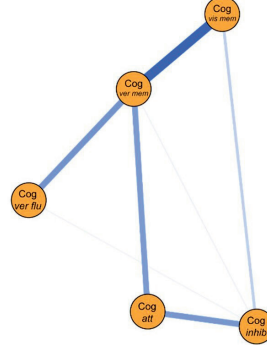
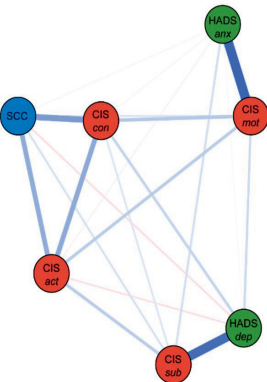
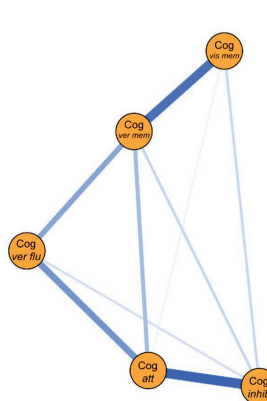
A) IPS preserved*PROMS network (global strength = 3.22)***B) IPS preserved***Cognitive domains network (global strength = 1.41)***C) IPS impaired***PROMS network (global strength = 2.77)***D) IPS impaired***Cognitive domains network (global strength = 1.26)*

Figure 4. Comparisons of the PROMs and objective cognitive modules for “IPS preserved” PwMS (panels A and B, respectively) and the “IPS impaired” PwMS (panels C and D, respectively). The colors of the nodes refer to the corresponding PROMs or cognitive domain (yellow). Nodes on depression and anxiety are depicted in green, nodes on fatigue in red, and SCC is depicted in blue. A blue edge indicates a positive relationship between the two nodes and a red edge a negative relationship. Edges were undirected and weighted and in the presented figures, edge width corresponds to the magnitude of the association. For each network, the global strength is indicated in the corresponding panel. *Abbreviations:* Cog = cognitive domain; att = attention; inhib = inhibition; ver flu = verbal fluency; ver mem = verbal memory; vis mem = visuospatial memory; HADS anx = Hospital Anxiety and Depression Scale anxiety subscale; HADS dep = Hospital Anxiety and Depression Scale depression subscale; CIS = Checklist Individual Strength-20 Revised; CIS sub = CIS-subjective; CIS con = CIS-concentration; CIS mot = CIS-motivation; CIS act = CIS-activity.

DISCUSSION

This study aimed to investigate the complex interplay between self-reported symptoms and objectively assessed cognitive functioning in PwMS by quantifying a cognitive symptom network based on PROMs (anxiety, depression, fatigue, and SCC) and cognitive domains. In this network, we observed clustering of nodes into two modules: a PROMs module and an objective cognitive module, connected by numerous weak edges. Particularly attention, fatigue (concentration-subscale), depression, and SCC were highly connected within the network. Second, we aimed to better understand the cognitive subjective-objective discrepancy in MS. Therefore, we studied how SCC and IPS impacted the networks, by comparing the global strength of the networks among subgroups. Networks for PwMS with different levels of SCC were similar. Interestingly, PwMS with IPS impairments demonstrated a lower global strength of the network compared to those with preserved IPS, indicating that PROMs and cognitive domains were less tightly interrelated for PwMS with impaired IPS.

Our first objective was to compute a cognitive symptom network and explore its potential for studying symptom interrelatedness in MS. The network showed distinct modules for PROMs and objectively assessed cognitive domains, supporting the expected subjective-objective discrepancy.^{4, 5} Specifically, SCC was mainly connected to other PROMs, a pattern also observed in networks of psychiatric populations.¹² Another study using network analysis in early RRMS, which also included physical and imaging outcomes, found self-reported fatigue to be more strongly associated with depression and physical disability compare to cognitive and imaging outcomes.³² In our network, we observed a central role for attention, fatigue (concentration subscale), depression, and SCC. Attention has been linked to symptom awareness and preoccupation,³³ potentially explaining its central role in our network. Furthermore, fatigue (concentration-subscale) and SCC specifically address self-reported aspects related to cognitive functioning, such as concentration and attention. This specificity makes their central role in this cognitive symptom network unsurprising. In addition, a meta-analysis demonstrated that heightened depressive symptomatology is strongly associated with increased cognitive difficulties.³⁴ The identified central nodes align with prior literature, supporting the viability of this multi-dimensional approach. While central nodes could help select intervention targets,¹⁰ understanding causal interconnections requires longitudinal study designs.³⁵ Nevertheless, the cross-sectional networks presented in our study still offer valuable insights into the co-occurrence of symptoms,³⁶ which is crucial for understanding complex and heterogeneous diseases like MS.

Second, we aimed to shed light on the subjective-objective cognitive discrepancy in PwMS. We found lower symptom interrelatedness for PwMS with impaired IPS compared to those with preserved IPS. In literature, self-reported cognitive

measures primarily correlate with depression and fatigue, instead of cognitive test scores.¹⁹ Similarly, a study found a stronger correlation between actual test performance and estimations about performance, as opposed to perceptions of daily cognitive functioning, with the latter not reaching statistical significance.³⁷ The subjective-objective discrepancy has gained renewed focus due to the growing importance of cognitive screening and monitoring tools for PwMS.¹ This discrepancy is often studied using univariate associations among these variables, constructing independent regression models for SCC or objective measures, or calculating/predicting discrepancy scores between SCC and objective cognitive functioning, categorizing PwMS as “under” or “over” estimators (facing statistical challenges such as multicollinearity when building prediction models).^{4, 5, 8} “Under” estimators (with more self-reported problems than cognitive deficits, leading them to underestimate their performance) comprised the largest proportions of PwMS (39-43%),^{4, 5} scoring higher on depression and fatigue compared to other groups,^{4, 5} with cognitive fatigue⁵ and estimated premorbid cognitive functioning⁸ being key predictors of these discrepancy scores. Our multi-dimensional approach suggests that the subjective-objective discrepancy becomes more pronounced with increasing objective IPS deficits, indicating a nonlinear relationship between subjective and objective outcomes. The finding of lower symptom interrelatedness with worse IPS is particularly intriguing, as one would expect greater levels of depression, anxiety and fatigue to go hand in hand with experiencing more cognitive deficits.¹

In clinical research settings, these insights should prompt a careful reevaluation of subjective and objective cognition, given the increasing challenge of accurately determining the specific (cognitive) deficits in PwMS based solely on self-reported information. Our findings confirm that symptomatology worsens for PwMS with impaired IPS (based on our sample characterization), but also reveal different patterns of symptom co-occurrence for PwMS with preserved and impaired IPS. It may be hypothesized that individuals with impaired IPS may have reduced accuracy in self-assessing their cognitive functioning due to broader deficits, affecting their ability to perceive and report accurately. The co-occurrence between psychological and cognitive symptoms appears more widespread in PwMS with impaired IPS. Speculatively, as cognitive deficits escalate, other symptoms tend to become more widespread. Therefore, it is crucial to carefully monitor the emerging symptoms individuals may experience.

A strength of this study is its relatively large sample, including retrospective data from eight different cohorts. However, this also posed challenges in constructing networks. For instance, only 125 progressive PwMS (17.8%) were included, preventing a network split based on MS type. Limited data on disease-specific information (such as lesion load or the use of specific DMTs) restricted our ability to investigate those variables within the network or between relevant groups, highlighting potential

avenues for future research. Combining multiple cohorts resulted in clustered data, a limitation that we addressed by applying bootstrapping procedures to ensure more robust estimates.²⁶ Furthermore, we were unable to include working memory or cognitive flexibility, which are acknowledged to be affected in MS.¹ For SCC, we had to utilize various questionnaires across different cohorts. This limitation is somewhat mitigated by existing literature demonstrating a large correlation between the MSNQ and the CFQ.¹⁹

In conclusion, we studied the interrelatedness between PROMs and objective cognitive domains in PwMS using network analysis. We found that, within the cognitive symptom network, PROMs and cognitive domains cluster separately but are still represented as one network. The finding of lower network interrelatedness for PwMS with impaired IPS, and not SCC, might suggest that the relation between subjectively and objectively measured symptoms does not follow a linear continuum but is dependent on the cognitive status of the PwMS. In PwMS with impaired IPS, patterns of psychological and cognitive symptoms are more widespread, contributing to the heterogeneity of clinical presentations as the disease progresses.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1. Overview of the included cohorts, with their corresponding references.

	<i>n</i> (% of total)
Cohorts	
1. Attention (1) METC-number: 2014.377	86 (12.2)
2. Amsterdam MS cohort (3-20) <i>General MS cohort</i> METC-number: 2002.140 (P02.1381L), 2004.009 (P04.0142L) <i>Longstanding MS cohort</i> METC-number: 2010.336	188 (26.7) 61/188 (32.4) 127/188 (67.6)
3. Fingolimod (21) METC-number: 2014.418	45 (6.4)
4. GABA & glutamate (22) METC-number: 2017.380	49 (7.0)
5. RemindMS (24, 25) METC-number: 2017.009	99 (14.1)
6. SOMSCOG (26, 27) METC-number: 2016.395	101 (14.4)
7. Tecfidera METC-number: 2017.469	64 (9.1)
8. Temprano METC-number: 2020.021	71 (10.1)

Abbreviations: MS = Multiple Sclerosis ; RRMS = Relapsing-Remitting MS.

Supplementary Table 2. Overview of the included tests per cognitive factor, the corresponding test scores and the number of cohorts (eight in total) that included the specific test in their design.

Test	Corresponding test scores and subscales	# of Cohorts
Patient-reported outcome measures		
Anxiety	• Hospital Anxiety and Depression Scale	8
Depression	• Hospital Anxiety and Depression Scale	8
Fatigue	• Checklist Individual Strength-20 Revised	8
	• Subscale subjective fatigue	
	• Subscale concentration	
	• Subscale motivation	
	• Subscale activity	
SCC	• Multiple Sclerosis Neuropsychological Questionnaire	4
	• Cognitive Failure Questionnaire	4
	• Subjective Cognitive Performance Questionnaire	3

Supplementary Table 2. Continued

	Test	Corresponding test scores and subscales	# of Cohorts
<i>Cognitive domains</i>			
Verbal memory	• California Verbal Learning Test – Version 2	• Direct recall • Delayed recall • Recognition	7
	• Selective Reminding Test	• Long-term storage 1 • Long-term retrieval sum • Short-term retrieval sum • Delayed recall	1
Visuospatial memory	• Location Learning Test	• Sum of displacement scores (five trials in total)	4
	• Brief Visuospatial Memory Test – Revised	• Direct recall • Delayed recall • Recognition	5
	• Spatial Recall Test	• Direct recall • Delayed recall	1
Information processing speed	• Symbol Digit Modalities Test	• Total of correct responses - reading subscale	4
	• Letter Digit Substitution Test	• Total of correct responses - reading subscale	6
Attention	• Stroop Color-Word Test	• Time to complete card I • Time to complete card II	8
Executive functioning – Inhibition	• Stroop Color-Word Test	• Time to complete card III – (Time to complete card I + card II)	8
Executive functioning – Verbal fluency	• Controlled Oral Word Association Test	• Trial 1 (letter D) • Trial 2 (letter A) • Trial 3 (letter T)	5
	• Word List Generation	• Trial 1 (animals) • Trial 2 (professions) • Trial 3 (m-words)	5

Supplementary Table 3. Background on self-reported cognitive complaints (SCC).

Procedure		Description						
Construction of the self-reported cognitive complaints (SCC) node		Included questionnaires: In our sample, SCC was measured with three different PROMS: the MSNQ, the CFQ, and the SCPQ. Availability: A total of 5 cohorts (i.e., Amsterdam MS cohort, GABA & Glutamate, SOMSCOG, Tecfidera and Temprano) had at least one of the abovementioned PROMS included (see the list on the distribution in the lower part of this Table). A total of 3 cohorts (i.e., Attention, Fingolimod and RemindMS) had two PROMS included, also listed in the panel below. Calculation of z-scores: Based on the available data per PROM, the mean and standard deviation (SD) of the PwMS was calculation, after which raw scores were transferred into z-scores. The specific sample size per PROM, along with the mean and SD is included below. This z-score was called the SCC node. In case a PwMS had filled-out two PROMS, and had therefore two z-scores, the average of the two z-scores was computed for the SCC. Check SCC node: We calculated the correlation between the final SCC-node (z-score) and the z-scores of the individual PROMS, as an indication of overlap. These results are included in the panel down blow. For the PwMS that had filled-out two PROMS, we also correlated both z-scores (and their corresponding sample size, as not all PwMS filled out the two PROMS).						
		Descriptives			Correlational analyses (using z-scores)			
	Cohorts	<i>n</i>	Mean raw score	SD raw score	SCC	MSNQ	CFQ	SCPQ
PROMS								
MSNQ	- Amsterdam MS cohort - RemindMS - SOMSCOG - Temprano	449	26.3	11.4	0.990	-	0.480 (n=99)	NA
CFQ	- Attention - Fingolimod - RemindMS - Tecfidera	292	37.3	21.3	0.967	-	-	0.839 (n=129)
SCPQ	- Attention - Fingolimod - GABA & glutamate	180	11.4	5.8	0.973	-	-	-

Abbreviations: SCC = Self-reported Cognitive Complaints; PROMS = Patient-Reported Outcome Measures; MSNQ = Multiple Sclerosis Neuropsychological Questionnaire; CFQ = Cognitive Failure Questionnaire; SCPQ = Subjective Cognitive Performance Questionnaire; PwMS = People with MS; NA = Not Available.

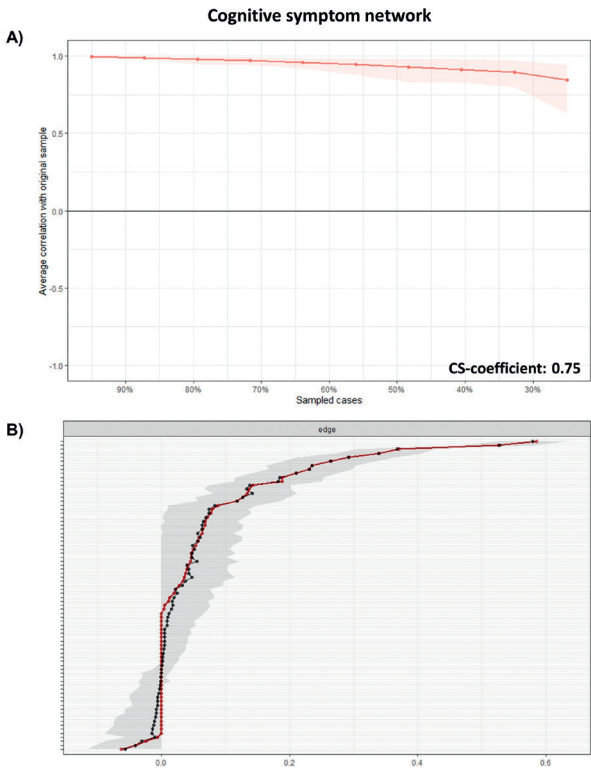
Supplementary Table 4. The applied bootstrapping procedure to quantify the stability and accuracy of the networks.

Procedure	Description
Stability of the nodes	To assess the stability of the strength of the nodes, we performed a case-dropping bootstrap with 1000 iterations (28). We computed correlation stability coefficients for each network as a measure of node stability. This measure should at least be ≥ 0.25 , and preferably ≥ 0.50 (28).
Accuracy of edge weights	To assess the accuracy of the edge estimates for each of the networks, we estimated 95% confidence intervals of the edge weights using nonparametric bootstrapping with 1,000 bootstrap samples (28). Larger confidence intervals indicate lower precision of the estimated edge weights.

Supplementary Table 5. Regularized partial correlation matrix of the full cognitive symptom network.

	Cog ver mem	Cog vis mem	Cog IPS	Cog ver flu	Cog att	Cog inhib	SCC	HADS anx	HADS dep	CIS sub	CIS con	CIS mot	CIS act
Cog ver mem		0.293	0.188	0.188	0.118	0.046	0.021	0	0	0	0	0	0
Cog vis mem			0.211	0.004	0	0.058	0	0	0	-0.006	0	0	0
Cog IPS				0	0.371	0.137	0	0	0.020	0	0	0	0
Cog ver flu					0.143	0.057	-0.041	-0.063	0	0	-0.024	0	0.077
Cog att						0.230	0.063	0	0.033	0	0	0	0.046
Cog inhib							0.068	0.036	0.054	0	0.011	0	0.038
SCC								0.049	0.064	0.068	0.585	0.005	0.013
HADS anx									0.526	0.045	0.039	0	0
HADS dep										0.126	0.041	0.134	0.027
CIS sub											0.126	0.235	0.340
CIS con												0.072	0.088
CIS mot													0.264
CIS act													

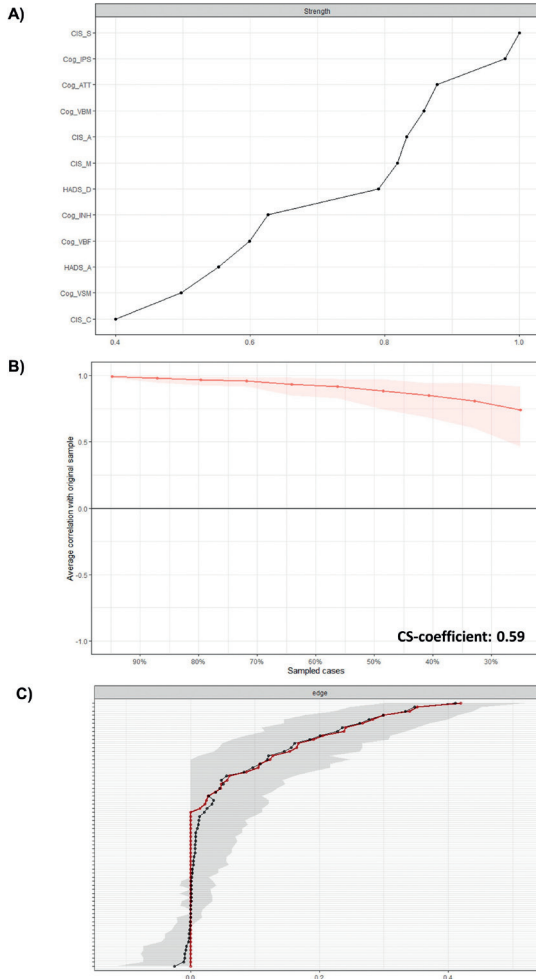
This is the regularized partial correlation matrix that is used as input for the visualization of the cognitive symptom network all PwMS ($n = 703$). Each number represents an edge and a zero indicates the absence of an edge. Blue indicates a positive relation and red a negative relation. Abbreviations: PwMS = People with MS; HADS = Hospital Anxiety and Depression Scale; SCC = Self-reported Cognitive Complaints; CIS20-R = Checklist Individual Strength (CIS) -20 Revised; Cog = Cognitive function; att = attention; inhib = inhibition; IPS = Information Processing Speed; ver flu = verbal fluency; ver mem = verbal memory; vis mem = visuospatial memory; HADS anx = HADS anxiety subscale; HADS dep = HADS depression subscale; CIS sub = CIS-subjective; CIS con = CIS-concentration; CIS mot = CIS-motivation; CIS act = CIS-activity.



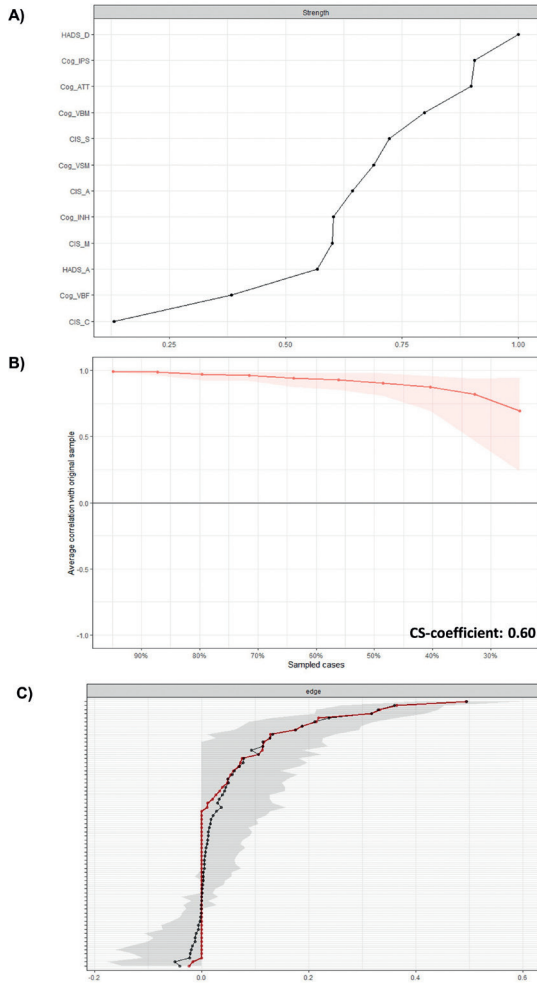
Supplementary Figure 1. The stability of the nodes and the accuracy of the edge weights for the overall cognitive symptom network ($n = 703$).

A) Case-dropping bootstrap, with on the x-axis the percentage of sampled cases dropped with decreases by 10% each time, and on the y-axis the average correlation of the centrality stability coefficient (CS-coefficient) with the original sample. B) Bootstrapped 95% confidence intervals of the edge weights, with on the y-axis all edges in the network ordered from the largest to smallest from top to bottom, and on the x-axis the confidence interval range. The red line represents the edge weights of the network, and the grey bars indicate the 95% confidence intervals around the edge weights. *Abbreviations: CS-coefficient = centrality stability coefficient.*

Cognitive symptom network
Less SCC subgroup

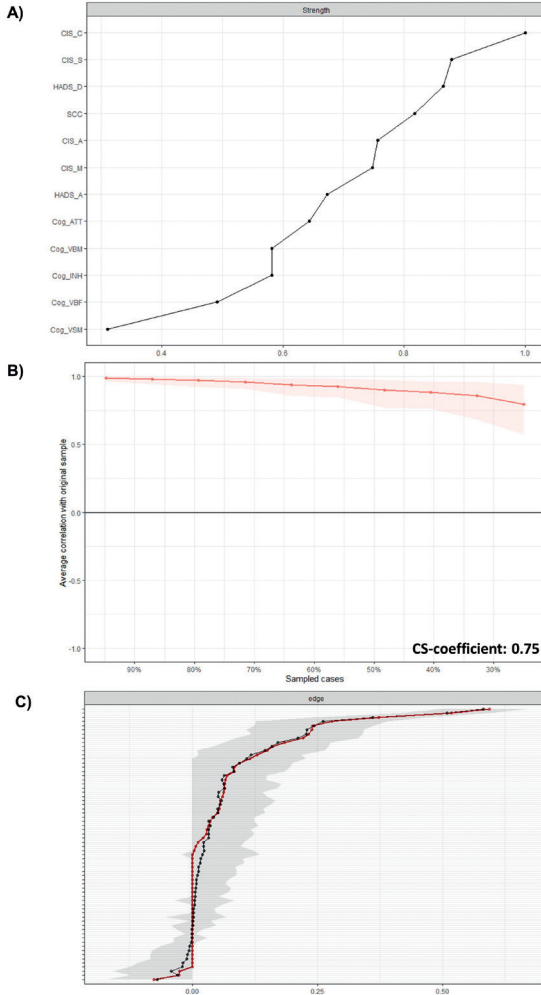


Supplementary Figure 2. The strength and the stability of the nodes and the accuracy of the edge weights for the cognitive symptom network within the 'less SCC' subgroup ($n = 231$). A) Node strength, with on the y-axis all 12 nodes, and the node strength on the x-axis. B) Case-dropping bootstrap, with on the x-axis the percentage of sampled cases dropped with decreases by 10% each time, and on the y-axis the average correlation of the centrality stability coefficient (CS-coefficient) with the original sample. C) Bootstrapped 95% confidence intervals of the edge weights, with on the y-axis all edges in the network ordered from the largest to smallest from top to bottom, and on the x-axis the confidence interval range. The red line represents the edge weights of the network, and the grey bars indicate the 95% confidence intervals around the edge weights. *Abbreviations:* HADS = Hospital Anxiety and Depression Scale; SCC = Self-reported Cognitive Complaints; CIS20-R = Checklist Individual Strength (CIS) -20 Revised; Cog = Cognitive domain; ATT = attention; INH = inhibition; IPS = information processing speed; VBF = verbal fluency; VBM = verbal memory; VSM = visuospatial memory; HADS_A = HADS anxiety subscale; HADS_D = HADS depression subscale; CIS_S = CIS-subjective; CIS_C = CIS-concentration; CIS_M = CIS-motivation; CIS_A = CIS-activity; CS-coefficient = centrality stability coefficient.

Cognitive symptom network**More SCC subgroup**

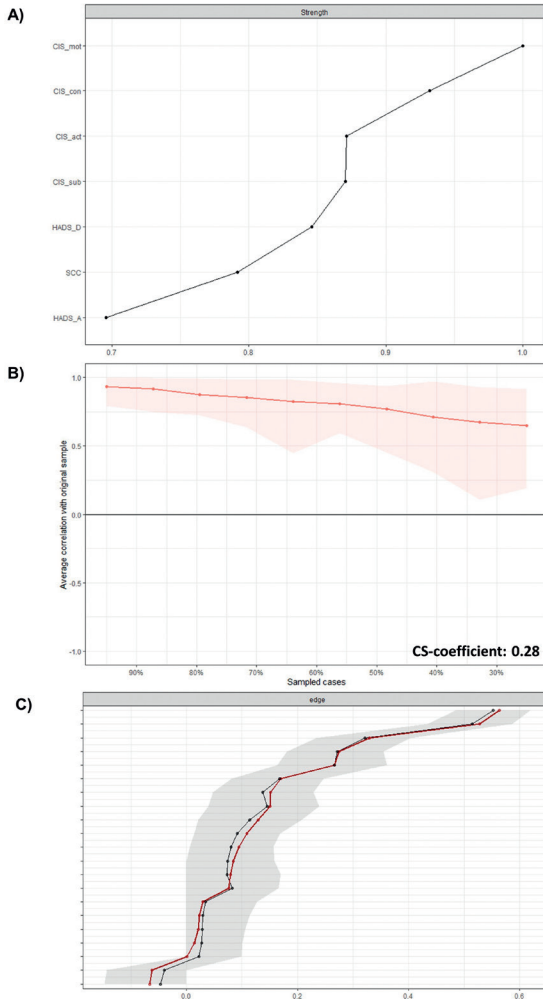
Supplementary Figure 3. The strength and the stability of the nodes and the accuracy of the edge weights for the cognitive symptom network within the ‘more SCC’ subgroup ($n = 235$).

A) Node strength, with on the y-axis all 12 nodes, and the node strength on the x-axis. B) Case-dropping bootstrap, with on the x-axis the percentage of sampled cases dropped with decreases by 10% each time, and on the y-axis the average correlation of the centrality stability coefficient (CS-coefficient) with the original sample. C) Bootstrapped 95% confidence intervals of the edge weights, with on the y-axis all edges in the network ordered from the largest to smallest from top to bottom, and on the x-axis the confidence interval range. The red line represents the edge weights of the network, and the grey bars indicate the 95% confidence intervals around the edge weights. Abbreviations: HADS = Hospital Anxiety and Depression Scale; SCC = Self-reported Cognitive Complaints; CIS20-R = Checklist Individual Strength (CIS) -20 Revised; Cog = Cognitive domain; ATT = attention; INH = inhibition; IPS = information processing speed; VBF = verbal fluency; VBM = verbal memory; VSM = visuospatial memory; HADS_A = HADS anxiety subscale; HADS_D = HADS depression subscale; CIS_S = CIS-subjective; CIS_C = CIS-concentration; CIS_M = CIS-motivation; CIS_A = CIS-activity; CS-coefficient = centrality stability coefficient.

Cognitive symptom network*IPS preserved subgroup*

Supplementary Figure 4. The strength and the stability of the nodes and the accuracy of the edge weights for the cognitive symptom network within the 'IPS preserved' subgroup ($n = 463$). A) Node strength, with on the y-axis all 12 nodes, and the node strength on the x-axis. B) Case-dropping bootstrap, with on the x-axis the percentage of sampled cases dropped with decreases by 10% each time, and on the y-axis the average correlation of the centrality stability coefficient (CS-coefficient) with the original sample. C) Bootstrapped 95% confidence intervals of the edge weights, with on the y-axis all edges in the network ordered from the largest to smallest from top to bottom, and on the x-axis the confidence interval range. The red line represents the edge weights of the network, and the grey bars indicate the 95% confidence intervals around the edge weights. *Abbreviations:* HADS = Hospital Anxiety and Depression Scale; SCC = Self-reported Cognitive Complaints; CIS20-R = Checklist Individual Strength (CIS) -20 Revised; Cog = Cognitive domain; ATT = attention; INH = inhibition; IPS = information processing speed; VBF = verbal fluency; VBM = verbal memory; VSM = visuospatial memory; HADS_A = HADS anxiety subscale; HADS_D = HADS depression subscale; CIS_S = CIS-subjective; CIS_C = CIS-concentration; CIS_M = CIS-motivation; CIS_A = CIS-activity; CS-coefficient = centrality stability coefficient.

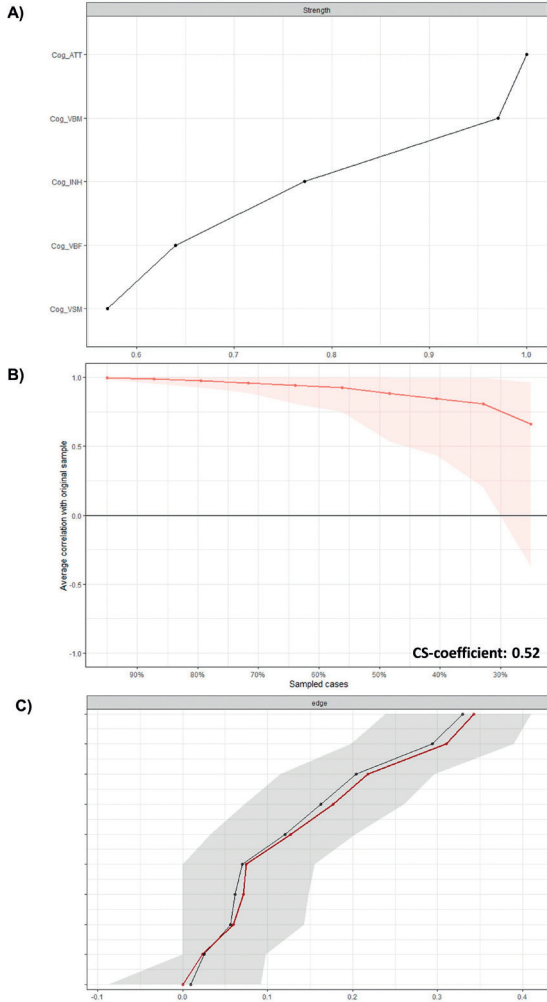
PROMS network
IPS preserved subgroup



Supplementary Figure 5. The strength and the stability of the nodes and the accuracy of the edge weights for the PROMS network within the 'IPS preserved' subgroup ($n = 463$).

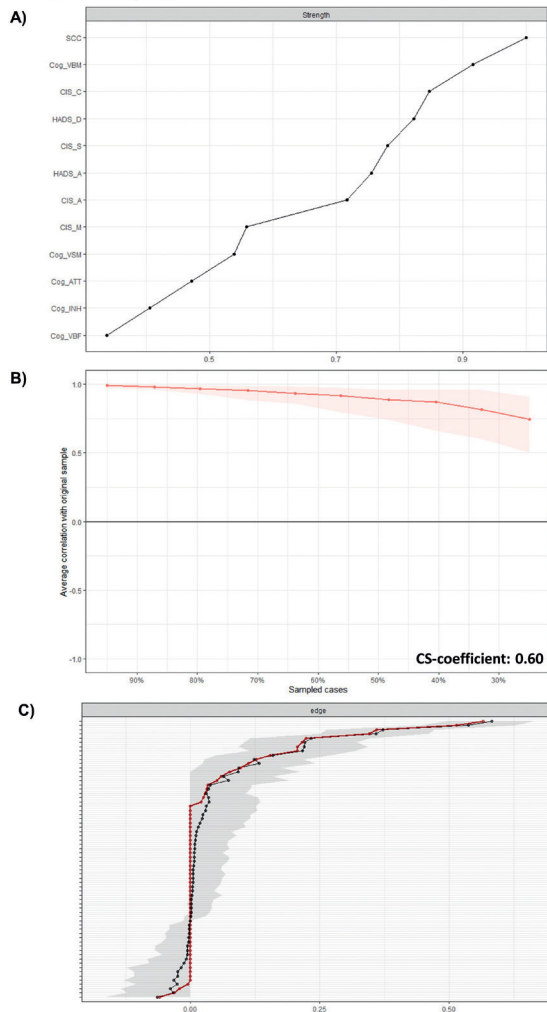
A) Node strength, with on the y-axis all 7 nodes, and the node strength on the x-axis. B) Case-dropping bootstrap, with on the x-axis the percentage of sampled cases dropped with decreases by 10% each time, and on the y-axis the average correlation of the centrality stability coefficient (CS-coefficient) with the original sample. C) Bootstrapped 95% confidence intervals of the edge weights, with on the y-axis all edges in the network ordered from the largest to smallest from top to bottom, and on the x-axis the confidence interval range. The red line represents the edge weights of the network, and the grey bars indicate the 95% confidence intervals around the edge weights. Abbreviations: HADS = Hospital Anxiety and Depression Scale; SCC = Self-reported Cognitive Complaints; CIS20-R = Checklist Individual Strength (CIS) -20 Revised; IPS = information processing speed; HADS_A = HADS anxiety subscale; HADS_D = HADS depression subscale; CIS_S = CIS-subjective; CIS_C = CIS-concentration; CIS_M = CIS-motivation; CIS_A = CIS-activity; CS-coefficient = centrality stability coefficient.

Cognitive domains network
IPS preserved subgroup



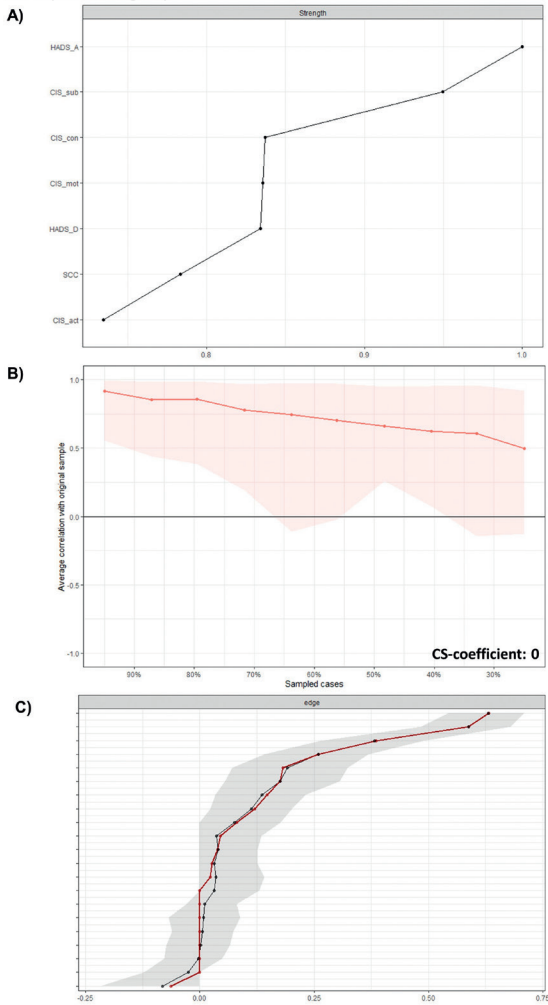
Supplementary Figure 6. The strength and the stability of the nodes and the accuracy of the edge weights for the cognitive domains network within the 'IPS preserved' subgroup ($n = 463$). A) Node strength, with on the y-axis all 5 nodes, and the node strength on the x-axis. B) Case-dropping bootstrap, with on the x-axis the percentage of sampled cases dropped with decreases by 10% each time, and on the y-axis the average correlation of the centrality stability coefficient (CS-coefficient) with the original sample. C) Bootstrapped 95% confidence intervals of the edge weights, with on the y-axis all edges in the network ordered from the largest to smallest from top to bottom, and on the x-axis the confidence interval range. The red line represents the edge weights of the network, and the grey bars indicate the 95% confidence intervals around the edge weights. Abbreviations: Cog = Cognitive domain; ATT = attention; INH = inhibition; IPS = information processing speed; VBF = verbal fluency; VBM = verbal memory; VSM = visuospatial memory; CS-coefficient = centrality stability coefficient.

Cognitive symptom network
IPS impaired subgroup



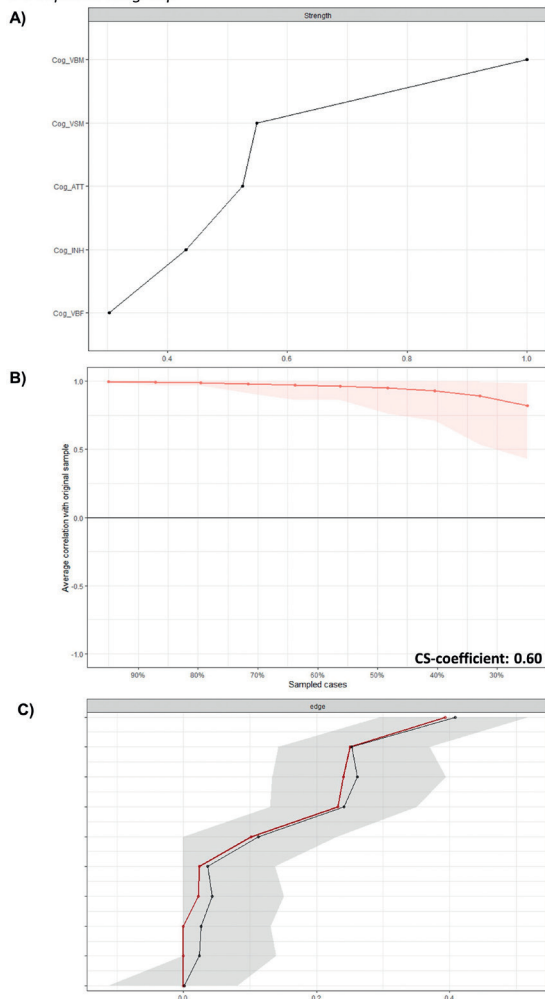
Supplementary Figure 7. The strength and the stability of the nodes and the accuracy of the edge weights for the cognitive symptom network within the 'IPS impaired' subgroup ($n = 240$). A) Node strength, with on the y-axis all 12 nodes, and the node strength on the x-axis. B) Case-dropping bootstrap, with on the x-axis the percentage of sampled cases dropped with decreases by 10% each time, and on the y-axis the average correlation of the centrality stability coefficient (CS-coefficient) with the original sample. C) Bootstrapped 95% confidence intervals of the edge weights, with on the y-axis all edges in the network ordered from the largest to smallest from top to bottom, and on the x-axis the confidence interval range. The red line represents the edge weights of the network, and the grey bars indicate the 95% confidence intervals around the edge weights. *Abbreviations:* HADS = Hospital Anxiety and Depression Scale; SCC = Self-reported Cognitive Complaints; CIS20-R = Checklist Individual Strength (CIS) -20 Revised; Cog = Cognitive domain; ATT = attention; INH = inhibition; IPS = information processing speed; VBF = verbal fluency; VBM = verbal memory; VSM = visuospatial memory; HADS_A = HADS anxiety subscale; HADS_D = HADS depression subscale; CIS_S = CIS-subjective; CIS_C = CIS-concentration; CIS_M = CIS-motivation; CIS_A = CIS-activity; CS-coefficient = centrality stability coefficient.

PROMS network
IPS impaired subgroup



Supplementary Figure 8. The strength and the stability of the nodes and the accuracy of the edge weights for the PROMS network within the 'IPS impaired' subgroup ($n = 240$).

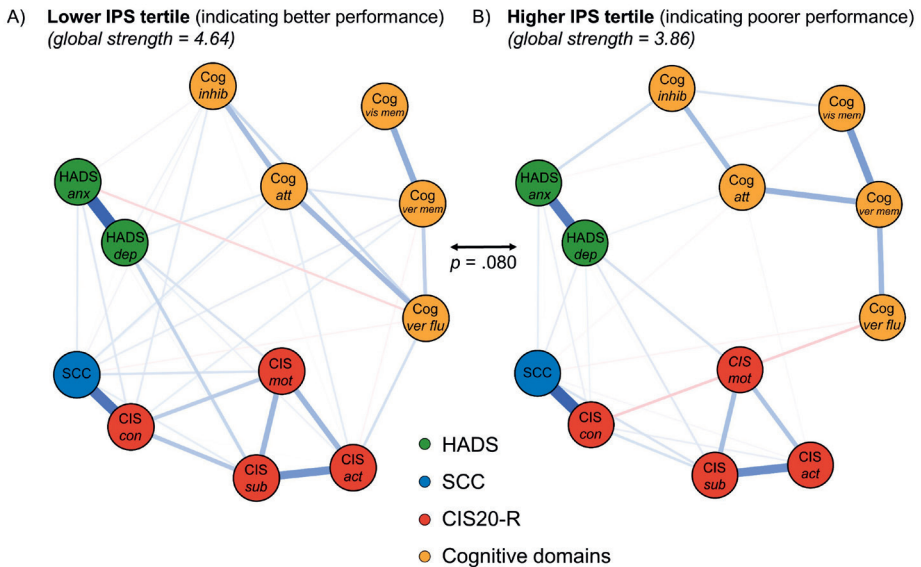
A) Node strength, with on the y-axis all 7 nodes, and the node strength on the x-axis. B) Case-dropping bootstrap, with on the x-axis the percentage of sampled cases dropped with decreases by 10% each time, and on the y-axis the average correlation of the centrality stability coefficient (CS-coefficient) with the original sample. C) Bootstrapped 95% confidence intervals of the edge weights, with on the y-axis all edges in the network ordered from the largest to smallest from top to bottom, and on the x-axis the confidence interval range. The red line represents the edge weights of the network, and the grey bars indicate the 95% confidence intervals around the edge weights. Abbreviations: HADS = Hospital Anxiety and Depression Scale; SCC = Self-reported Cognitive Complaints; CIS20-R = Checklist Individual Strength (CIS) -20 Revised; IPS = information processing speed; HADS_D = HADS depression subscale; CIS_S = CIS-subjective; CIS_C = CIS-concentration; CIS_M = CIS-motivation; CIS_A = CIS-activity; CS-coefficient = centrality stability coefficient.

Cognitive domains network*IPS impaired subgroup*

Supplementary Figure 9. The strength and the stability of the nodes and the accuracy of the edge weights for the cognitive domains network within the 'IPS impaired' subgroup ($n = 240$). A) Node strength, with on the y-axis all 5 nodes, and the node strength on the x-axis. B) Case-dropping bootstrap, with on the x-axis the percentage of sampled cases dropped with decreases by 10% each time, and on the y-axis the average correlation of the centrality stability coefficient (CS-coefficient) with the original sample. C) Bootstrapped 95% confidence intervals of the edge weights, with on the y-axis all edges in the network ordered from the largest to smallest from top to bottom, and on the x-axis the confidence interval range. The red line represents the edge weights of the network, and the grey bars indicate the 95% confidence intervals around the edge weights. Abbreviations: Cog = Cognitive domain; ATT = attention; INH = inhibition; IPS = information processing speed; VBF = verbal fluency; VBM = verbal memory; VSM = visuospatial memory; CS-coefficient = centrality stability coefficient.

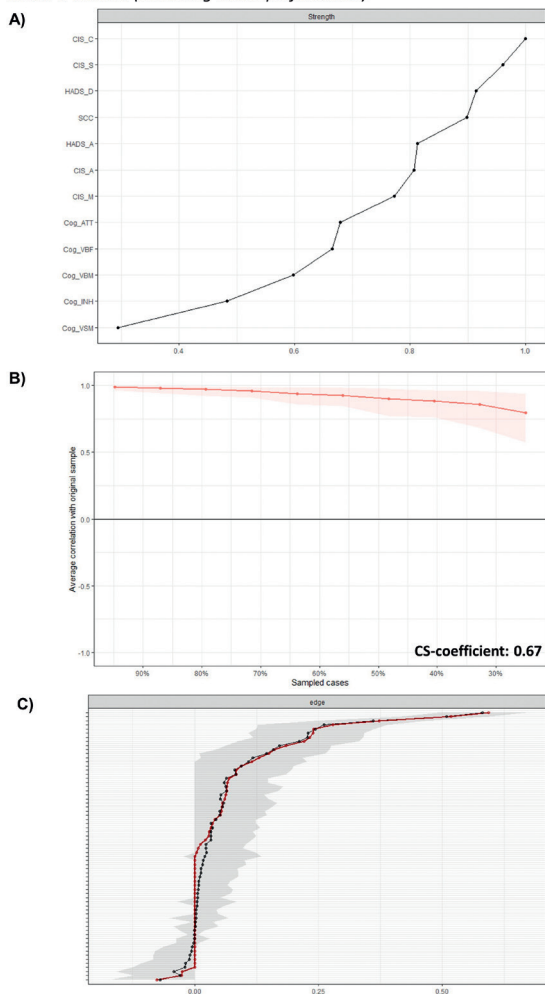
APPENDIX A – SPLIT BASED ON IPS FUNCTIONING IN PWMS

Importantly, not all PwMS in the 'higher IPS tertile' subgroup (indicating poorer performance) had an IPS impairment based on normative data ($n = 45$, 18.8%, $\chi^2 = 388.94$, $p < .001$). In the 'higher IPS tertile' subgroup (indicating worse performance), 40 PwMS (17.1%) exhibited no IPS impairment. The networks based on 'lower and higher IPS tertiles' are included in Supplementary Figure 10. Supplementary Figures 11 and 12 summarize the strength and stability of the nodes in these networks, as well as the accuracy of the edges. The global strength was not significantly different between the 'lower IPS tertile' and 'better IPS tertile' networks (global strength = 4.64 versus 3.86, respectively, $p = .080$).



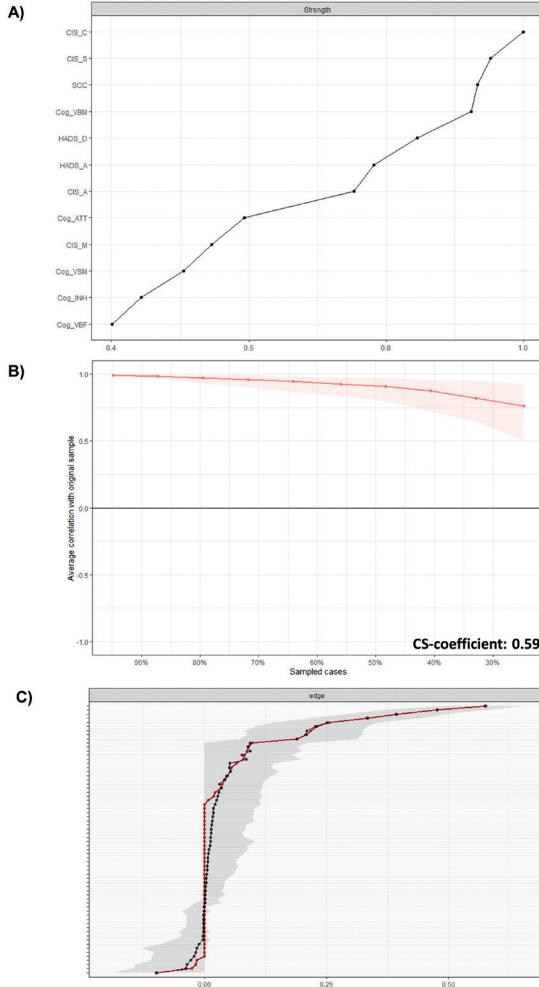
Supplementary Figure 10. The cognitive symptom networks in PwMS – split based on IPS functioning in PwMS.

A) The cognitive symptom network in PwMS in the 'lower IPS tertile' (indicating better performance on IPS, $n = 232$). B) The cognitive symptom network in PwMS in the 'higher IPS tertile' (indicating poorer performance on IPS, $n = 234$). The colors of the nodes refer to the corresponding PROMS or cognitive domains. A blue edge indicates a positive relationship between the two nodes and a red edge a negative relationship. Edges were undirected and weighted and in the presented figures, edge width corresponds to the magnitude of the association. *Abbreviations:* PwMS = People with MS; HADS = Hospital Anxiety and Depression Scale; SCC = Self-reported Cognitive Complaints; CIS20-R = Checklist Individual Strength (CIS)-20 Revised; Cog = Cognitive domain; att = attention; inh = inhibition; IPS = information processing speed; ver flu = verbal fluency; ver mem = verbal memory; vis mem = visuospatial memory; HADS anx = HADS anxiety subscale; HADS dep = HADS depression subscale; CIS sub = CIS-subjective; CIS con = CIS-concentration; CIS mot = CIS-motivation; CIS act = CIS-activity.

Cognitive symptom network*Lower IPS tertile (indicating better performance)*

Supplementary Figure 11. The strength and the stability of the nodes and the accuracy of the edge weights for the cognitive symptom network within the 'lower IPS tertile' subgroup (indicating better performance, $n = 232$).

A) Node strength, with on the y-axis all 12 nodes, and the node strength on the x-axis. B) Case-dropping bootstrap, with on the x-axis the percentage of sampled cases dropped with decreases by 10% each time, and on the y-axis the average correlation of the centrality stability coefficient (CS-coefficient) with the original sample. C) Bootstrapped 95% confidence intervals of the edge weights, with on the y-axis all edges in the network ordered from the largest to smallest from top to bottom, and on the x-axis the confidence interval range. The red line represents the edge weights of the network, and the grey bars indicate the 95% confidence intervals around the edge weights. Abbreviations: HADS = Hospital Anxiety and Depression Scale; SCC = Self-reported Cognitive Complaints; CIS20-R = Checklist Individual Strength (CIS) -20 Revised; Cog = Cognitive domain; ATT = attention; INH = inhibition; IPS = information processing speed; VBF = verbal fluency; VBM = verbal memory; VSM = visuospatial memory; HADS_A = HADS anxiety subscale; HADS_D = HADS depression subscale; CIS_S = CIS-subjective; CIS_C = CIS-concentration; CIS_M = CIS-motivation; CIS_A = CIS-activity; CS-coefficient = centrality stability coefficient.

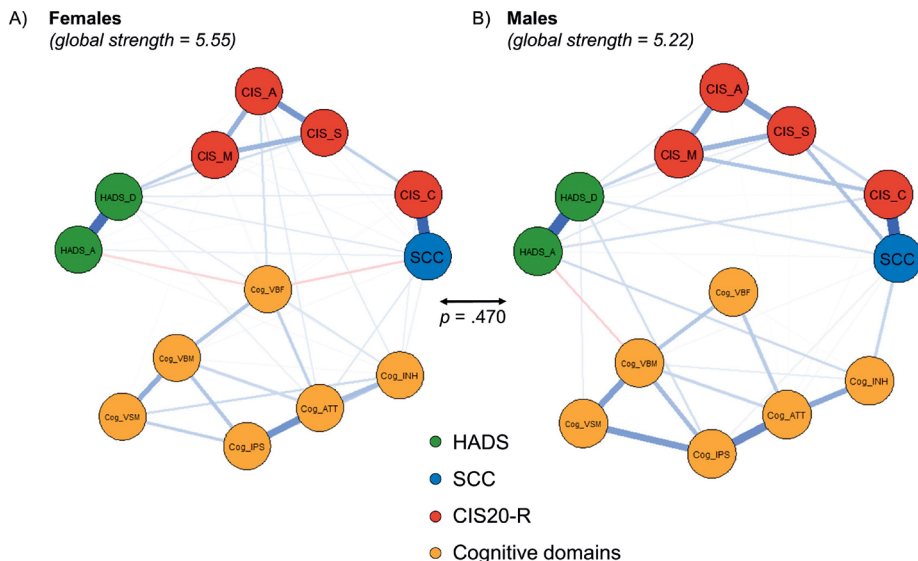
Cognitive symptom network*Higher IPS tertile (indicating poorer performance)*

Supplementary Figure 12. The strength and the stability of the nodes and the accuracy of the edge weights for the cognitive symptom network within the 'higher IPS tertile' subgroup (indicating poorer performance, $n = 234$).

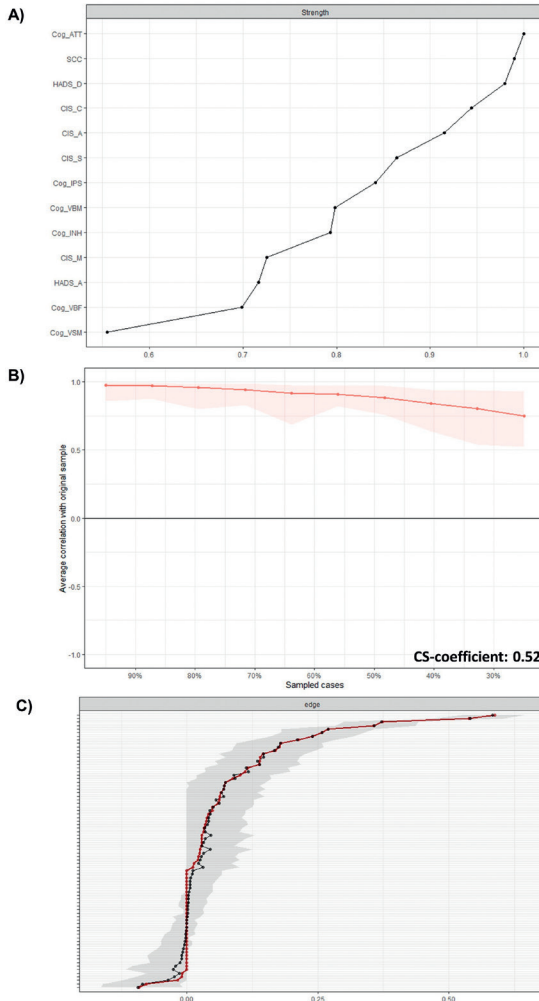
A) Node strength, with on the y-axis all 12 nodes, and the node strength on the x-axis. B) Case-dropping bootstrap, with on the x-axis the percentage of sampled cases dropped with decreases by 10% each time, and on the y-axis the average correlation of the centrality stability coefficient (CS-coefficient) with the original sample. C) Bootstrapped 95% confidence intervals of the edge weights, with on the y-axis all edges in the network ordered from the largest to smallest from top to bottom, and on the x-axis the confidence interval range. The red line represents the edge weights of the network, and the grey bars indicate the 95% confidence intervals around the edge weights. Abbreviations: HADS = Hospital Anxiety and Depression Scale; SCC = Self-reported Cognitive Complaints; CIS20-R = Checklist Individual Strength (CIS) -20 Revised; Cog = Cognitive domain; ATT = attention; INH = inhibition; IPS = information processing speed; VBF = verbal fluency; VBM = verbal memory; VSM = visuospatial memory; HADS_A = HADS anxiety subscale; HADS_D = HADS depression subscale; CIS_S = CIS-subjective; CIS_C = CIS-concentration; CIS_M = CIS-motivation; CIS_A = CIS-activity; CS-coefficient = centrality stability coefficient.

APPENDIX B – SPLIT BASED ON SEX

The networks based on sex are included in Supplementary Figure 13. Supplementary Figures 14 and 15 summarize the strength and stability of the nodes in these networks, as well as the accuracy of the edges. The global strength was not significantly different between the females and males networks (global strength = 5.55 versus 5.22, respectively, $p = .470$).

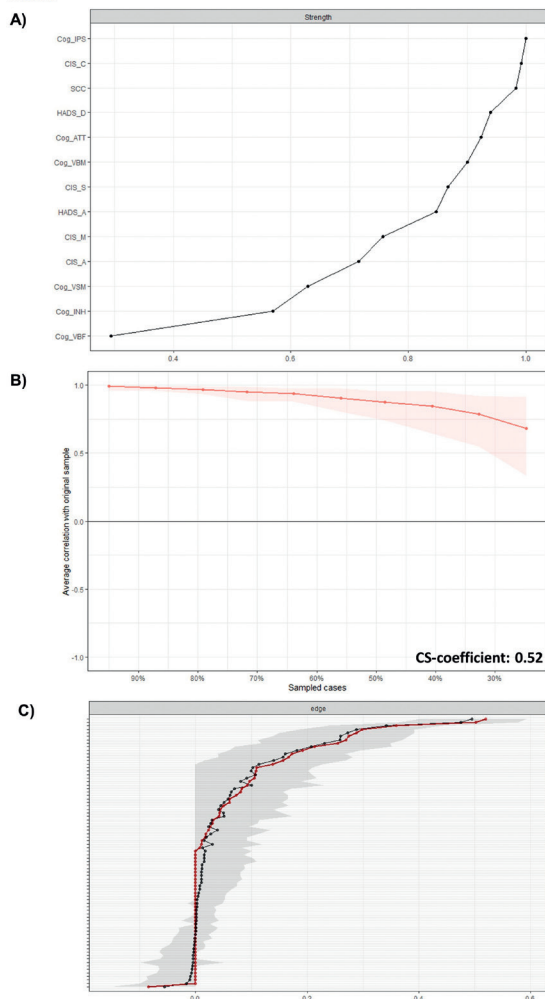


Supplementary Figure 13. The cognitive symptom networks in PwMS – split based on sex. A) The cognitive symptom network in females ($n = 501$). B) The cognitive symptom network in males ($n = 202$). The colors of the nodes refer to the corresponding PROMS or cognitive domains. A blue edge indicates a positive relationship between the two nodes and a red edge a negative relationship. Edges were undirected and weighted and in the presented figures, edge width corresponds to the magnitude of the association. Abbreviations: HADS = Hospital Anxiety and Depression Scale; SCC = Self-reported Cognitive Complaints; CIS20-R = Checklist Individual Strength (CIS) -20 Revised; Cog = Cognitive domain; ATT = attention; INH = inhibition; IPS = information processing speed; VBF = verbal fluency; VBM = verbal memory; VSM = visuospatial memory; HADS_A = HADS anxiety subscale; HADS_D = HADS depression subscale; CIS_S = CIS-subjective; CIS_C = CIS-concentration; CIS_M = CIS-motivation; CIS_A = CIS-activity; CS-coefficient = centrality stability coefficient.

Cognitive symptom network*Females*

Supplementary Figure 14. The strength and the stability of the nodes and the accuracy of the edge weights for the cognitive symptom network within females ($n = 501$).

A) Node strength, with on the y-axis all 13 nodes, and the node strength on the x-axis. B) Case-dropping bootstrap, with on the x-axis the percentage of sampled cases dropped with decreases by 10% each time, and on the y-axis the average correlation of the centrality stability coefficient (CS-coefficient) with the original sample. C) Bootstrapped 95% confidence intervals of the edge weights, with on the y-axis all edges in the network ordered from the largest to smallest from top to bottom, and on the x-axis the confidence interval range. The red line represents the edge weights of the network, and the grey bars indicate the 95% confidence intervals around the edge weights. Abbreviations: HADS = Hospital Anxiety and Depression Scale; SCC = Self-reported Cognitive Complaints; CIS20-R = Checklist Individual Strength (CIS) -20 Revised; Cog = Cognitive domain; ATT = attention; INH = inhibition; IPS = information processing speed; VBF = verbal fluency; VBM = verbal memory; VSM = visuospatial memory; HADS_A = HADS anxiety subscale; HADS_D = HADS depression subscale; CIS_S = CIS-subjective; CIS_C = CIS-concentration; CIS_M = CIS-motivation; CIS_A = CIS-activity; CS-coefficient = centrality stability coefficient.

Cognitive symptom network**Males**

Supplementary Figure 15. The strength and the stability of the nodes and the accuracy of the edge weights for the cognitive symptom network within males ($n = 202$).

A) Node strength, with on the y-axis all 13 nodes, and the node strength on the x-axis. B) Case-dropping bootstrap, with on the x-axis the percentage of sampled cases dropped with decreases by 10% each time, and on the y-axis the average correlation of the centrality stability coefficient (CS-coefficient) with the original sample. C) Bootstrapped 95% confidence intervals of the edge weights, with on the y-axis all edges in the network ordered from the largest to smallest from top to bottom, and on the x-axis the confidence interval range. The red line represents the edge weights of the network, and the grey bars indicate the 95% confidence intervals around the edge weights. Abbreviations: HADS = Hospital Anxiety and Depression Scale; SCC = Self-reported Cognitive Complaints; CIS20-R = Checklist Individual Strength (CIS) -20 Revised; Cog = Cognitive domain; ATT = attention; INH = inhibition; IPS = information processing speed; VBF = verbal fluency; VBM = verbal memory; VSM = visuospatial memory; HADS_A = HADS anxiety subscale; HADS_D = HADS depression subscale; CIS_S = CIS-subjective; CIS_C = CIS-concentration; CIS_M = CIS-motivation; CIS_A = CIS-activity; CS-coefficient = centrality stability coefficient.

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