

A multifaceted approach to understand cognitive impairment in MS: exploring the nonlinearity of cognition Dam. M. van

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# Cognition from a multidimensional perspective



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 =  $46.3 \pm 11.2$  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.³ 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,<sup>9</sup> 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.<sup>10</sup> In a network, nodes can represent PROMS or cognitive domains and edges represent associations between these at the group-level.<sup>10</sup> While network analysis has been applied to study self-reported symptoms in cancer and psychiatric disease,<sup>11, 12</sup> 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,<sup>13</sup> and physical disability was assessed using the Expanded Disability Status Scale (EDSS).<sup>14</sup>

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

	n (% of total)	Inclusion criteria	Exclusion criteria
Cohorts			
1. Attention METC-number: 2014.377	86 (12.2)	<ul> <li>MS diagnosis according to the 2010-McDonald criteria<sup>15</sup></li> <li>18-68 years of age</li> <li>Ability to safely undergo an MRI examination</li> <li>Screening for motor and visual skills</li> </ul>	<ul> <li>History or presence of drug abuse</li> <li>Neurological (other than MS) and psychiatric diseases</li> <li>Relapse and/or steroid treatment 4 weeks prior to examination</li> </ul>
2. Amsterdam MS cohort General MS cohort METC-number: 2002.140 (P02.1381L), 2004.009 (P04.0142L) Longstanding MS cohort	188 (26.7) 61/188 (32.4)	<ul> <li>MS diagnosis according to the 2010-McDonald criteria<sup>15</sup></li> <li>18 years of age and older</li> </ul>	<ul> <li>Neurological (other than MS) and psychiatric diseases</li> <li>Relapse and/or steroid treatment 2 months prior to examination</li> </ul>
METC-number: 2010.336	127/188 (67.6)	<ul> <li>MS diagnosis according to the 2010-McDonald criteria<sup>15</sup></li> <li>18 years of age and older</li> <li>Minimum disease duration of 10 years from onset</li> </ul>	<ul> <li>Neurological (other than MS) and psychiatric diseases</li> <li>Relapse and/or steroid treatment 6 weeks prior to examination</li> </ul>
3. Fingolimod METC-number: 2014.418	45 (6.4)	<ul> <li>MS diagnosis according to the 2010-McDonald criteria<sup>15</sup></li> <li>PwMS with RRMS</li> </ul>	<ul> <li>Neurological (other than MS) and psychiatric diseases</li> <li>Relapse and/or steroid treatment 4 weeks prior to examination</li> </ul>

Table 1. Continued

	n (% of total)	Inclusion criteria	Exclusion criteria
		<ul> <li>18-65 years of age</li> <li>Ability to safely undergo an MRI examination</li> <li>Screening for motor and visual skills</li> </ul>	
4. GABA & glutamate METC-number: 2017.380	49 (7.0)	<ul> <li>MS diagnosis according to the 2017-McDonald criteria<sup>16</sup></li> <li>PwMS with RRMS or SPMS</li> <li>18-65 years of age</li> <li>Ability to safely undergo an MRI examination</li> <li>Screening for motor and visual skills</li> </ul>	<ul> <li>History or presence of drug abuse</li> <li>Neurological (other than MS) and psychiatric diseases</li> <li>Relapse and/or steroid treatment 4 weeks prior to examination</li> </ul>
5. RemindMS <sup>a</sup> METC-number: 2017.009	99 (14.1)	<ul> <li>MS diagnosis according to the 2010-McDonald criteria<sup>15</sup></li> <li>18-65 years of age</li> <li>Scoring ≥23 on the Multiple Sclerosis Neuropsychological Questionnaire – Patient version (MSNQ-P)</li> </ul>	<ul> <li>History/presence of psychosis and/or suicidal ideation</li> <li>Inability to speak Dutch</li> <li>Previous experience with the similar interventions</li> <li>Physical or cognitive disabilities/ comorbidities/ treatments likely to cause interference</li> </ul>
6. SOMSCOG <sup>a</sup> METC-number: 2016.395	101 (14.4)	<ul> <li>MS diagnosis according to the 2017-McDonald criteria<sup>16</sup></li> </ul>	
7. Tecfidera METC-number: 2017.469	64 (9.1)	<ul> <li>MS diagnosis according to the 2017-McDonald criteria<sup>16</sup></li> <li>PwMS with RRMS</li> <li>18-65 years of age</li> <li>Ability to safely undergo an MRI examination</li> <li>Screening for motor and visual skills</li> </ul>	<ul> <li>History or presence of drug abuse</li> <li>Neurological (other than MS) and psychiatric diseases</li> <li>Relapse and/or steroid treatment 4 weeks prior to examination</li> <li>Participation in other studies using cognitive or physical training programs</li> </ul>
8. Temprano METC-number: 2020.021	71 (10.1)	<ul> <li>MS diagnosis according to the 2017-McDonald criteria, within one year<sup>16</sup></li> <li>PwMS with RRMS</li> <li>18-65 years of age</li> <li>Sufficient Dutch proficiency</li> <li>Ability to safely undergo an MRI examination</li> </ul>	<ul> <li>History or presence of drug abuse</li> <li>Neurological (other than MS) and psychiatric diseases</li> <li>Relapse and/or steroid treatment 4 weeks prior to examination</li> <li>Participation in other studies using cognitive or physical training programs</li> </ul>

<sup>&</sup>lt;sup>a</sup> 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),<sup>17</sup> 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).<sup>18</sup> 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),<sup>19</sup> the Cognitive Failures Questionnaire (CFQ)<sup>20</sup> and the Subjective Cognitive Performance Questionnaire (SCPQ)).<sup>21</sup> 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 MS<sup>22</sup> or the Brief Repeatable Battery of Neuropsychological Tests.<sup>23</sup> 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).<sup>24</sup> These data were used to report the sample characteristics and to define subgroups with and without IPS impairment, indicated by a z-score  $\leq$  -1.5 (third objective).<sup>25</sup>

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.<sup>26</sup>

#### Subgroups

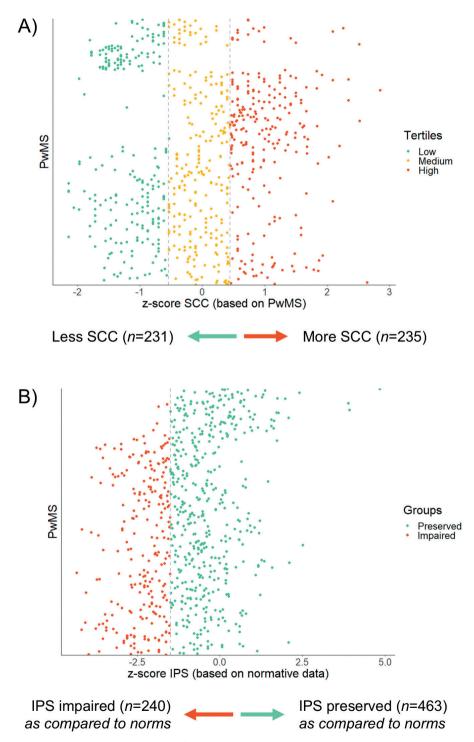
To explore the impact of SCC and IPS on the networks (objectives 2 and 3), we categorized PwMS into subgroups (see Figure 1).

5

**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  $\leq$  -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  $\leq$  -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 bootnet  $^{26}$  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  $\chi^2$ -tests for categorical variables. An  $\alpha$ -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.<sup>10</sup> 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.<sup>11</sup> 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.<sup>26</sup> 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.<sup>30</sup>

**Comparing networks.** To understand whether network density was different between subgroups, we calculated the global strength of the networks (objectives 2 and 3).<sup>31</sup> 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.<sup>31</sup> 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).<sup>26</sup>

#### **RESULTS**

#### **Participants**

The sample of 703 PwMS included 71.3% females, with a mean age of  $46.3 \pm 11.2$  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.

			•					
	n = 703	% missing	Less SCC n = 231	More SCC n = 235	p-value	IPS preserved n= 463	IPS impaired $n = 240$	p-value
Demographics								
Sex   female, <i>n</i> (%)	501 (71.3%)	%0.0	163 (70.6%)	180 (76.6%)	.140	337 (72.8%)	164 (68.3%)	.216
Age   years, median (SD)	46.3 (11.2)	%0.0	44.7 (11.0)	46.3 (10.6)	660.	44.8 (11.3)	49.1 (10.5)	<.001*
Education   Verhage <sup>a</sup> , 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)	6.0 (5.0-6.0)	.107
Clinical functioning								
MS type		1.9%			.153			<.001*
RRMS   <i>n</i> (%)	561 (79.8%)		201 (87.0%)	183 (77.9%)		388 (83.8%)	173 (72.1%)	
SPMS   <i>n</i> (%)	83 (11.8%)		18 (7.8%)	30 (12.8%)		36 (7.8%)	47 (19.6%)	
PPMS   <i>n</i> (%)	42 (6.0%)		9 (3.9%)	14 (6.0%)		29 (6.3%)	13 (5.4%)	
CIS   n (%)	4 (0.6%)		1 (0.4%)	2 (0.9%)		3 (0.6%)	1 (0.4%)	
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)	13.0 (5.9-19.9)	<.001*
EDSSb   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)	4.0 (1.0-8.0)	<.001*
DMT use   yes, <i>n</i> (%)	404 (57.5%)	7.0%	154 (66.7%)	132 (56.2%)	.032*	282 (60.9%)	122 (50.8%)	.050
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)	37.5 (11.3)	.004*
Severe fatigue   ≥35, <i>n</i> (%)	398 (56.6%)		83 (35.9%)	176 (74.9%)	<.001*	250 (54.0%)	148 (61.7%)	.052
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)	5.0 (3.0-8.0)	<.001*
Sig symptoms $  \ge 8$ , $n$ (%)	170 (24.2%)		34 (14.7%)	90 (38.3%)	<.001*	97 (21.0%)	73 (30.4%)	.005*
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)	6.0 (4.0-9.0)	<.001*
Sig symptoms $  \ge 8$ , $n$ (%)	238 (33.9%)		51 (22.1%)	118 (50.2%)	<.001*	143 (30.9%)	95 (39.6%)	.021*
SCC   mean (SD)	-0.05 (-0.06)	%0.0	-1.2 (-1.1)	1.03 (0.9)	<.001*	-0.2 (1.0)	0.2 (1.0)	<.001*

**Table 2.** Continued

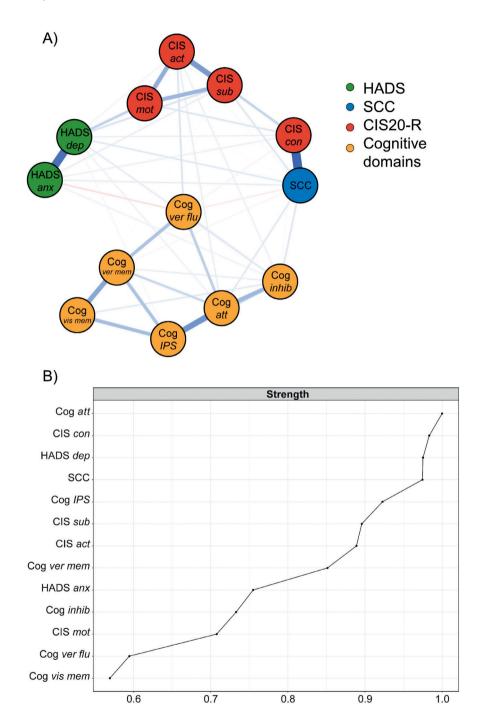
	lotal sample	е	SCC Split			IPS Split		
	n = 703	% missing Less SCC $n = 231$	Less SCC n = 231	More SCC <i>n</i> = 235	p-value	p-value IPS preserved IPS impaired $n=463$ $n=240$	IPS impaired $n = 240$	p-value
Cognitive domains (z-scores compared to normative data)	d to normative d	ata)						
Attention   mean (SD)	-0.8 (1.2)	%0:0	05 (1.2)	-1.1 (1.2)	<.001*	-0.4 (1.0)	-1.6 (1.2)	<.001*
Impaired $c \mid n$ (%)	166 (23.6%)		40 (17.3%)	78 (33.2%)	<.001*	56 (12.1%)	110 (45.8%)	<.001*
Inhibition   mean (SD)	-0.6 (1.4)	0.1% <sup>d</sup>	-0.2 (1.3)	-1.1 (1.4)	<.001*	-0.3 (1.2)	-1.2 (1.4)	<.001*
Impaired $c \mid n$ (%)	165 (23.5%)		33 (14.3%)	76 (32.3%)	<.001*	75 (16.2%)	90 (37.5%)	<.001*
IPS   mean (SD)	-1.0 (1.3)	%0:0	-0.6 (1.2)	-1.3 (1.2)	<.001*	-0.3 (0.9)	-2.4 (0.7)	<.001*
Impaired $c \mid n$ (%)	240 (34.1%)		52 (22.5%)	103 (43.8%)	<.001*	0 (0.0%)	240 (100%)	Ϋ́Z
Verbal fluency   mean (SD)	-0.7 (0.7)	0.3%	-0.7 (0.8)	-0.8 (0.8)	.026*	-0.6 (0.7)	-1.1 (0.7)	<.001*
Impaired <sup>c</sup>   <i>n</i> (%)	89 (12.7%)		21 (9.1%)	40 (17.0%)	.011*	32 (6.9%)	57 (23.8%)	<.001*
Verbal memory   mean (SD)	-0.5 (1.1)	0.3%€	-0.3 (1.0)	-0.7 (1.1)	<.001*	-0.2 (0.9)	-1.1 (1.1)	<.001*
Impaired $c \mid n$ (%)	115 (16.4%)		26 (11.3%)	45 (19.1%)	.017*	36 (7.8%)	79 (32.9%)	<.001*
Visuospatial memory   mean (SD)	-0.5 (1.1)	%0:0	-0.4 (1.1)	-0.5 (1.1)	.242	-0.2 (1.0)	-0.9 (1.1)	<.001*
Impaired $^{c} \mid n$ (%)	119 (16.9%)		36 (15.6%)	39 (16.6%)	.847	49 (10.6%)	70 (29.2%)	<.001*

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). Bata for 2 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 validated telephone assessment. <sup>c</sup> Cognitive data in this table were corrected for age, sex and educational level based on a normative sample of Dutch healthy 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 Measures; CIS20-R, Checklist Individual Strength-20 Revised; HADS-D, Hospital Anxiety and Depression Scale subscale Depression; HADS-A, Hospital Anxiety and Significant at p <0.05.³ Level of education is coded according to the Verhage classification. b Assessed by a certified examiner, either face-to-face or through Depression Scale subscale Anxiety; SCC = Self-reported Cognitive Complaints; IPS, Information Processing Speed; NA = Not Applicable.

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).

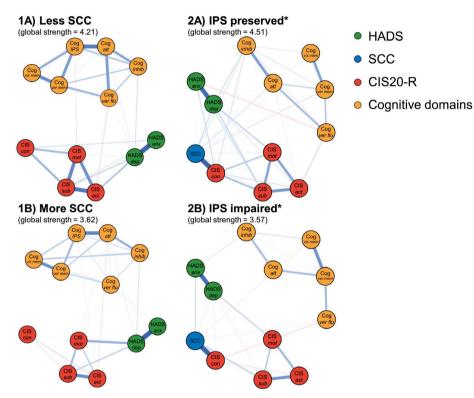
#### Comparing networks based on SCC

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

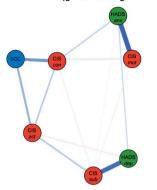
No differences in global network strength were found between lower and higher IPS functioning (p = 0.080, see Supplementary Appendix A) or between females and males (p = 0.470, see Supplementary Appendix B).

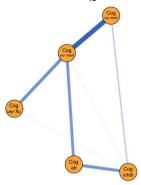
# A) IPS preserved

#### PROMS network (global strength = 3.22)

# B) IPS preserved

Cognitive domains network (global strength = 1.41)

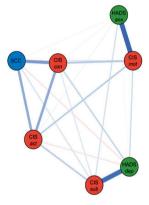




# C) IPS impaired

# D) IPS impaired

PROMS network (global strength = 2.77) Cognitive domains network (global strength = 1.26)



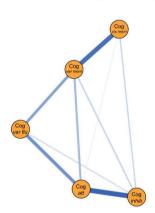


Figure 4. Comparisons of the PROMs and objective cognitive modules for "IPS preserved" PwMS (panels A and B, respectively) and the "IPS impaired" PwMS (panels C and D, respectively). The colors of the nodes refer to the corresponding PROMs or cognitive domain (yellow). Nodes on depression and anxiety 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 = CISconcentration; 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.<sup>4, 5</sup> Specifically, SCC was mainly connected to other PROMs, a pattern also observed in networks of psychiatric populations.<sup>12</sup> 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.<sup>32</sup> 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,<sup>33</sup> 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.<sup>19</sup> 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.<sup>37</sup> 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%),<sup>4,5</sup> scoring higher on depression and fatigue compared to other groups,<sup>4, 5</sup> with cognitive fatigue<sup>5</sup> and estimated premorbid cognitive functioning<sup>8</sup> 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. <sup>26</sup> Furthermore, we were unable to include working memory or cognitive flexibility, which are acknowledged to be affected in MS. <sup>1</sup> 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. <sup>19</sup>

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.

#### REFERENCES

- Benedict RHB, Amato MP, DeLuca J, Geurts JJG. Cognitive impairment in multiple sclerosis: clinical management, MRI, and therapeutic avenues. The Lancet Neurology 2020;19:860-871.
- Wojcik C, Fuchs TA, Tran H, et al. Staging and stratifying cognitive dysfunction in multiple sclerosis. Multiple Sclerosis Journal 2022;28:463-471.
- 3. Benedict RH, Zivadinov R. Predicting neuropsychological abnormalities in multiple sclerosis. Journal of the neurological sciences 2006;245:67-72.
- Hughes AJ, Bhattarai JJ, Paul S, Beier M. Depressive symptoms and fatigue as predictors of objective-subjective discrepancies in cognitive function in multiple sclerosis. Multiple sclerosis and related disorders 2019;30:192-197.
- Davenport L, Cogley C, Monaghan R, et al. Investigating the association of mood and fatigue with objective and subjective cognitive impairment in multiple sclerosis. Journal of Neuropsychology 2022;16:537-554.
- Boeschoten RE, Braamse AM, Beekman AT, et al. Prevalence of depression and anxiety in multiple sclerosis: a systematic review and meta-analysis. Journal of the neurological sciences 2017;372:331-341.
- Krupp L. Fatigue is intrinsic to multiple sclerosis (MS) and is the most commonly reported symptom of the disease. 2006: 367-368.
- 8. Stein C, O'Keeffe F, McManus C, et al. Premorbid cognitive functioning influences differences between self-reported cognitive difficulties and cognitive assessment in multiple sclerosis. Journal of Neuropsychology 2023.
- 9. Westergaard K, Skovgaard L, Magyari M, Kristiansen M. Patient perspectives on patient-reported outcomes in multiple sclerosis treatment trajectories: A qualitative study of why, what, and how? Multiple Sclerosis and Related Disorders 2022;58:103475.

- Borsboom D. A network theory of mental disorders. World psychiatry 2017;16:5-13.
- Röttgering JG, Varkevisser TMCK, Gorter M, et al. Symptom networks in glioma patients: understanding the multidimensionality of symptoms and quality of life. Journal of Cancer Survivorship 2023.
- Chavez-Baldini U, Nieman DH, Keestra A, et al. The relationship between cognitive functioning and psychopathology in patients with psychiatric disorders: a transdiagnostic network analysis. Psychological Medicine 2023;53:476-485.
- 13. Verhage F. Intelligentie en leeftijd: Onderzoek bij Nederlanders van twaalf tot zevenenzeventig jaar. : Assen: Van Gorcum, 1964.
- Lechner-Scott J, Kappos L, Hofman M, et al. Can the Expanded Disability Status Scale be assessed by telephone? Multiple Sclerosis Journal 2003;9:154-159.
- Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the Mc-Donald criteria. Annals of neurology 2011:69:292-302.
- Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. The Lancet Neurology 2018;17:162-173.
- Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta psychiatrica scandinavica 1983;67:361-370.
- Vercoulen JH, Swanink CM, Fennis JF, Galama JM, van der Meer JW, Bleijenberg G. Dimensional assessment of chronic fatigue syndrome. Journal of psychosomatic research 1994;38:383-392.
- Benedict RH, Munschauer F, Linn R, et al. Screening for multiple sclerosis cognitive impairment using a self-administered 15-item questionnaire. Multiple Sclerosis Journal 2003;9:95-101.

- Merckelbach H, Muris P, Nijman H, de Jong PJ. Self-reported cognitive failures and neurotic symptomatology. Personality and Individual Differences 1996;20:715-724.
- 21. Stewart AL, Ware J, Sherbourne CD, Wells KB. Psychological distress/ well-being and cognitive functioning measures. Measuring functioning and well-being: The medical outcomes study approach 1992:102-142.
- Benedict RH, Cookfair D, Gavett R, et al. Validity of the minimal assessment of cognitive function in multiple sclerosis (MACFIMS). Journal of the International Neuropsychological Society: JINS 2006:12:549.
- 23. Broeders TA, Douw L, Eijlers AJ, et al. A more unstable resting-state functional network in cognitively declining multiple sclerosis. Brain Communications 2022;4:fcac095.
- 24. van Dam M, de Jong BA, Willemse EA, et al. A multimodal marker for cognitive functioning in multiple sclerosis: the role of NfL, GFAP and conventional MRI in predicting cognitive functioning in a prospective clinical cohort. Journal of Neurology 2023:1-11.
- Fischer M, Kunkel A, Bublak P, et al. How reliable is the classification of cognitive impairment across different criteria in early and late stages of multiple sclerosis? Journal of the neurological sciences 2014;343:91-99.
- Epskamp S, Borsboom D, Fried EI. Estimating psychological networks and their accuracy: A tutorial paper. Behavior Research Methods 2018;50:195-212.
- 27. RStudio Team RIDEfR, RStudio, PBC, Boston, MA, 2020. .
- 28. Epskamp S, Cramer AO, Waldorp LJ, Schmittmann VD, Borsboom D. qgraph: Network visualizations of relationships in psychometric data. Journal of statistical software 2012;48:1-18.

- 29. Burger J, Isvoranu A, Lunansky G, Haslbeck J, Epskamp S, Hoekstra R. Reporting standards for psychological network analyses in cross-sectional data. Psychological Methods 2020.
- Stam CJ. Modern network science of neurological disorders. Nature Reviews Neuroscience 2014;15:683-695.
- 31. van Borkulo CD, van Bork R, Boschloo L, et al. Comparing network structures on three aspects: A permutation test. Psychological Methods 2022:No Pagination Specified-No Pagination Specified.
- 32. Chang Y-T, Kearns PK, Carson A, et al. Network analysis characterizes key associations between subjective fatigue and specific depressive symptoms in early relapsing-remitting multiple sclerosis. Multiple Sclerosis and Related Disorders 2023;69:104429.
- 33. Solem S, Hagen R, Wang CE, et al. Metacognitions and mindful attention awareness in depression: A comparison of currently depressed, previously depressed and never depressed individuals. Clinical Psychology & Psychotherapy 2017;24:94-102.
- 34. Altieri M, Cerciello F, Gallo A, Santangelo G. The relationship between depression and cognitive performance in multiple sclerosis: a meta-analysis. The Clinical Neuropsychologist 2023:1-21.
- 35. Fried EI, Cramer AO. Moving forward: Challenges and directions for psychopathological network theory and methodology. Perspectives on Psychological Science 2017;12:999-1020.
- 36. Bos FM, Snippe E, de Vos S, et al. Can we jump from cross-sectional to dynamic interpretations of networks implications for the network perspective in psychiatry. Psychotherapy and psychosomatics 2017;86:175-177.
- Middleton LS, Denney DR, Lynch SG, Parmenter B. The relationship between perceived and objective cognitive functioning in multiple sclerosis. Archives of clinical neuropsychology 2006;21:487-494.

#### SUPPLEMENTARY MATERIALS

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

	n (% of total)
Cohorts	
1. Attention (1) METC-number: 2014.377	86 (12.2)
2. Amsterdam MS cohort (3-20) General MS cohort	188 (26.7) 61/188 (32.4)
METC-number: 2002.140 (P02.1381L), 2004.009 (P04.0142L) Longstanding MS cohort METC-number: 2010.336	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-reporte	ed outcome measures		
Anxiety	<ul> <li>Hospital Anxiety and Depression Scale</li> </ul>	Subscale anxiety	8
Depression	<ul> <li>Hospital Anxiety and Depression Scale</li> </ul>	Subscale depression	8
Fatigue	Checklist Individual Strength-20 Revised	<ul><li>Subscale subjective fatigue</li><li>Subscale concentration</li><li>Subscale motivation</li><li>Subscale activity</li></ul>	8
SCC	<ul> <li>Multiple Sclerosis         Neuropsychological Questionnaire     </li> </ul>	• Total score	4
	<ul> <li>Cognitive Failure Questionnaire</li> </ul>	<ul> <li>Total score</li> </ul>	4
	<ul> <li>Subjective Cognitive Performance Questionnaire</li> </ul>	• Total score	3

# Supplementary Table 2. Continued

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

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

Procedure		Desci	ription					
	n of the self-reported mplaints (SCC) node	Includ In our the M: Availa A tota Glutar one of the di cohor PROM Calcul Based deviat scores per PR z-score two PI the tw Check We ca (z-sco indica down also co	ed questic sample, SC SNQ, the C	orts (i.e. SCOG, Temention in the lo ention, Fi, also list scores: ilable dat the PWMs dishes commerced in the dishes commerced in the pwm scores ilable dat in the pwm score ilable dat in the pwm score ilable dat in the pwm score ilable dat ilable dat in the pwm score ilable dat ilable	easured whe SCPQ  , Amster ecfidera a led PRON wer part ingolimo ed in the la per PRON to z-scor mean an c node. In lirefore tw liputed for lation be less of the less result to that ha lirefore that lation be less of the less result to that ha lires (and that less (and that l	rdam MS and Temp MS include to of this Te d and Rer panel be  DM, the m alculation res. The sp d SD is inc case a Pw wo z-score or the SCC  etween the individu as are include d filled-out their corre	cohort, rano) had sed (see the able). A the mindMS) low.  ean and sed, after we sed for the able sed for the	GABA & dat least on otal of 3 had two standard hich raw mple size low. This filled-out rerage of CC-node S, as an he panel OMS, we
		Desci	riptives			ational a z-scores	-	
	Cohorts	n	Mean raw score	SD raw score	scc	MSNQ	CFQ	SCPQ
PROMS					,			
MSNQ	<ul><li>Amsterdam MS cohort</li><li>RemindMS</li><li>SOMSCOG</li><li>Temprano</li></ul>	449	26.3	11.4	0.990	-	0.480 ( <i>n</i> =99)	NA
CFQ	<ul><li>Attention</li><li>Fingolimod</li><li>RemindMS</li><li>Tecfidera</li></ul>	292	37.3	21.3	0.967	-	-	0.839 ( <i>n</i> =129)
SCPQ	<ul><li>Attention</li><li>Fingolimod</li><li>GABA &amp; glutamate</li></ul>	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.

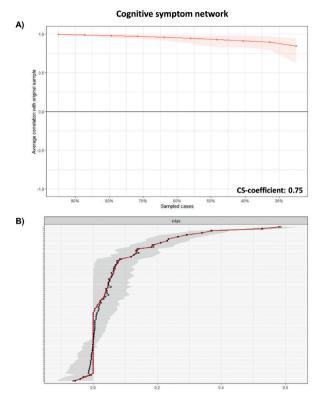
**Supplementary Table 4.** The applied bootstrapping procedure to quantify the stability and accuracy of the networks.

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 $\geq$ 0.25, and preferably $\geq$ 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	Cog	SCC	HADS	HADS	CIS	CIS	CIS	CIS
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		-0.063	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													

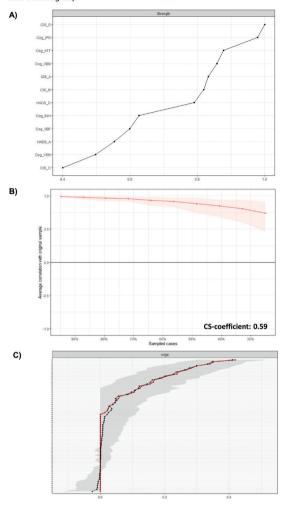
This is the regularized partial correlation matrix that is used as input for the visualization of the cognitive symptom network all PwMS (n = 703). Each number represents an edge and a zero indicates the absence of an edge. Blue indicates a positive relation and red a negative relation. Abbreviations: 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 anxiety subscale; HADS dep = HADS depression subscale; CIS sub = CIS-subjective; CIS con = CIS-concentration; CIS mot = CIS-motivation; CIS act = CISactivity.



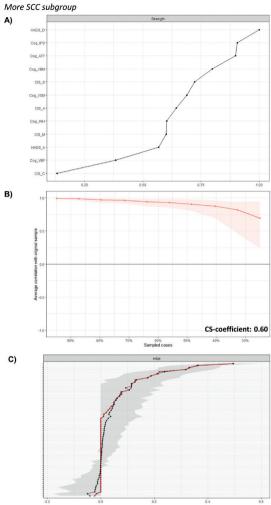
**Supplementary Figure 1.** The stability of the nodes and the accuracy of the edge weights for the overall cognitive symptom network (n = 703).

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.

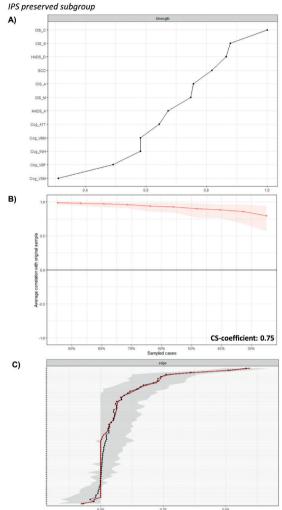
Less SCC subgroup



**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) Casedropping 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.



**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.

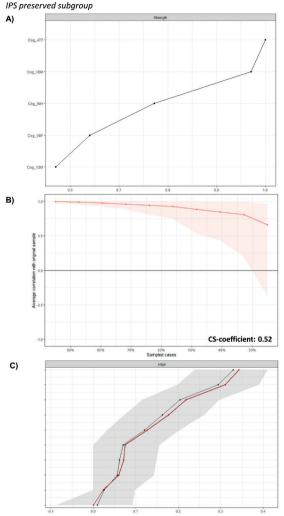


**Supplementary Figure 4.** The strength and the stability of the nodes and the accuracy of the edge weights for the cognitive symptom network within the 'IPS preserved' subgroup (n = 463). A) Node strength, with on the y-axis all 12 nodes, and the node strength on the x-axis. B) Casedropping bootstrap, 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 A) CIS\_c CIS\_a CIS\_st HADS I B) CS-coefficient: 0.28 C)

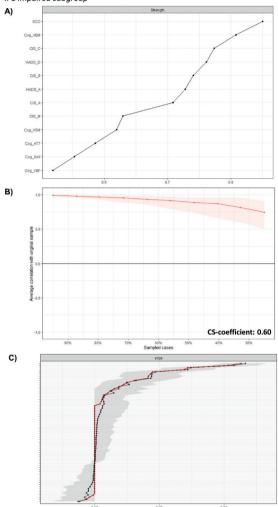
**Supplementary Figure 5.** The strength and the stability of the nodes and the accuracy of the edge weights for the PROMS network within the 'IPS preserved' subgroup (n = 463). A) Node strength, with on the y-axis all 7 nodes, and the node strength on the x-axis. B) Casedropping bootstrap, with on the 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



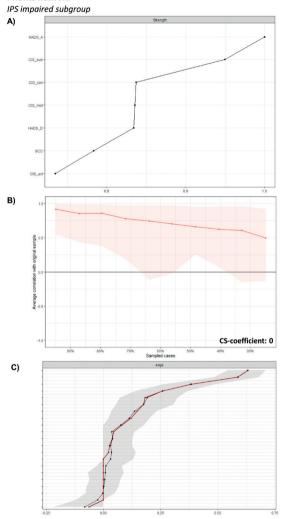
**Supplementary Figure 6.** The strength and the stability of the nodes and the accuracy of the edge weights for the cognitive domains network within the 'IPS preserved' subgroup (n = 463). A) Node strength, with on the y-axis all 5 nodes, and the node strength on the x-axis. B) Casedropping bootstrap, 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.





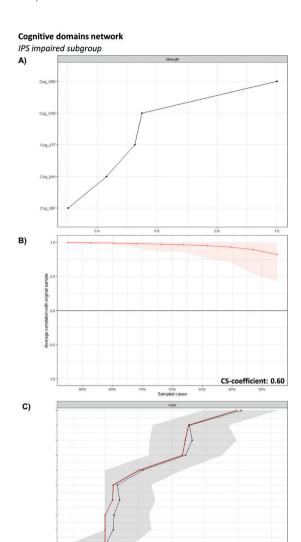
**Supplementary Figure 7.** The strength and the stability of the nodes and the accuracy of the edge weights for the cognitive symptom network within the 'IPS impaired' subgroup (n = 240). A) Node strength, with on the y-axis all 12 nodes, and the node strength on the x-axis. B) Casedropping bootstrap, 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.





**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).

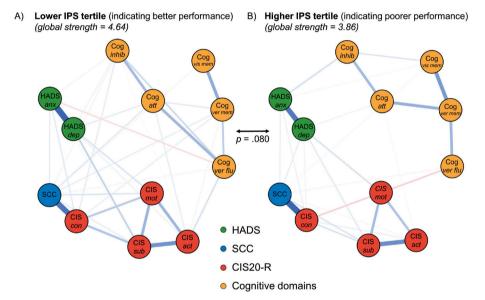
A) Node strength, with on the y-axis all 7 nodes, and the node strength on the x-axis. B) Casedropping bootstrap, with on the x-axis the percentage of sampled cases dropped with decreases by 10% each time, and on the y-axis the average correlation of the centrality stability coefficient (CS-coefficient) 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.



**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) Casedropping 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

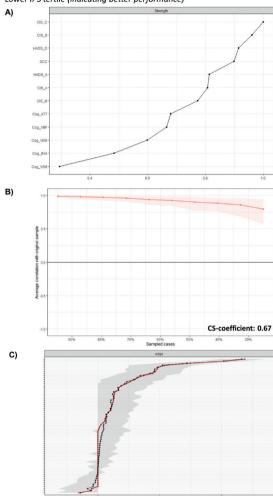
Importantly, not all PwMS in the 'higher IPS tertile' subgroup (indicating poorer performance) had an IPS impairment based on normative data (n = 45, 18.8%,  $\chi^2$  = 388.94, p <.001). In the 'higher IPS tertile' subgroup (indicating worse performance), 40 PwMS (17.1%) exhibited no IPS impairment. 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; 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.

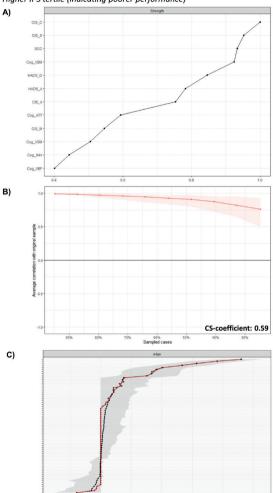
Lower IPS tertile (indicating better performance)



**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.



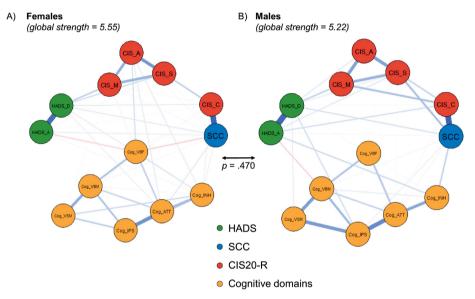


**Supplementary Figure 12.** The strength and the stability of the nodes and the accuracy of the edge weights for the cognitive symptom network within the 'higher IPS tertile' subgroup (indicating poorer performance, n = 234).

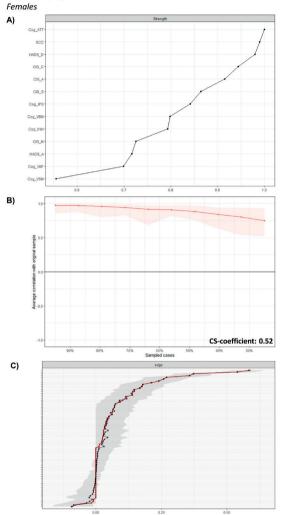
A) Node strength, with on the y-axis all 12 nodes, and the node strength on the x-axis. B) Casedropping bootstrap, with on the x-axis the percentage of sampled cases dropped with decreases by 10% each time, and on the y-axis the average correlation of the centrality stability coefficient (CS-coefficient) 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 in 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).

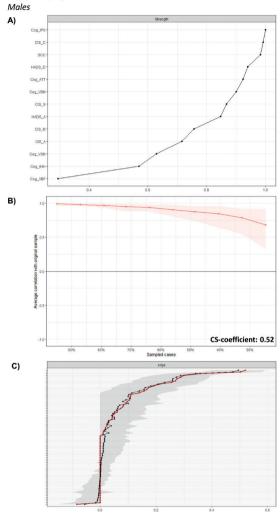


**Supplementary Figure 13.** The cognitive symptom networks in PwMS – split based on sex. A) The cognitive symptom network in females (n = 501). B) The cognitive symptom network in males (n = 202). The colors of the nodes refer to the corresponding PROMS or cognitive domains. A blue edge indicates a 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.



**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) Casedropping 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.



**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) Casedropping 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.

# SUPPLEMENTAL REFERENCES

- Prouskas SE, Schoonheim MM, Huiskamp M, Steenwijk MD, Gehring K, Barkhof F, et al. A randomized trial predicting response to cognitive rehabilitation in multiple sclerosis: Is there a window of opportunity? Multiple Sclerosis Journal. 2022;28(13):2124-36.
- Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the Mc-Donald criteria. Annals of neurology. 2011;69(2):292-302.
- 3. Schoonheim MM, Vigeveno RM, Lopes FCR, Pouwels PJ, Polman CH, Barkhof F, Geurts JJ. Sex-specific extent and severity of white matter damage in multiple sclerosis: Implications for cognitive decline. Human brain mapping. 2014;35(5):2348-58.
- 4. Steenwijk MD, Daams M, Pouwels PJ, Balk LJ, Tewarie PK, Killestein J, et al. What explains gray matter atrophy in long-standing multiple sclerosis? Radiology. 2014;272(3):832-42.
- 5. Schoonheim MM, Hulst HE, Brandt RB, Strik M, Wink AM, Uitdehaag BM, et al. Thalamus structure and function determine severity of cognitive impairment in multiple sclerosis. Neurology. 2015;84(8):776-83.
- Steenwijk MD, Daams M, Pouwels PJ, J. Balk L, Tewarie PK, Geurts JJ, et al. Unraveling the relationship between regional gray matter atrophy and pathology in connected white matter tracts in long-standing multiple sclerosis. Human brain mapping. 2015;36(5):1796-807.
- 7. Daams M, Steenwijk MD, Schoonheim MM, Wattjes MP, Balk LJ, Tewarie PK, et al. Multi-parametric structural magnetic resonance imaging in relation to cognitive dysfunction in long-standing multiple sclerosis. Multiple Sclerosis Journal. 2016;22(5):608-19.

- 8. Eijlers AJ, Meijer KA, Wassenaar TM, Steenwijk MD, Uitdehaag BM, Barkhof F, et al. Increased default-mode network centrality in cognitively impaired multiple sclerosis patients. Neurology. 2017;88(10):952-60.
- Meijer KA, Eijlers AJ, Douw L, Uitdehaag BM, Barkhof F, Geurts JJ, Schoonheim MM. Increased connectivity of hub networks and cognitive impairment in multiple sclerosis. Neurology. 2017;88(22):2107-14.
- Eijlers AJ, Meijer KA, van Geest Q, Geurts JJ, Schoonheim MM. Determinants of cognitive impairment in patients with multiple sclerosis with and without atrophy. Radiology. 2018;288(2):544-51.
- 11. Eijlers AJ, van Geest Q, Dekker I, Steenwijk MD, Meijer KA, Hulst HE, et al. Predicting cognitive decline in multiple sclerosis: a 5-year follow-up study. Brain. 2018;141(9):2605-18.
- Meijer K, Van Geest Q, Eijlers A, Geurts J, Schoonheim M, Hulst H. Is impaired information processing speed a matter of structural or functional damage in MS? NeuroImage: Clinical. 2018;20:844-50.
- Eijlers AJ, Wink AM, Meijer KA, Douw L, Geurts JJ, Schoonheim MM. Reduced network dynamics on functional MRI signals cognitive impairment in multiple sclerosis. Radiology. 2019;292(2):449-57.
- Nauta IM, Balk LJ, Sonder JM, Hulst HE, Uitdehaag BM, Fasotti L, de Jong BA. The clinical value of the patient-reported multiple sclerosis neuropsychological screening questionnaire. Multiple Sclerosis Journal. 2019;25(11):1543-6.
- Huiskamp M, Eijlers AJ, Broeders TA, Pasteuning J, Dekker I, Uitdehaag BM, et al. Longitudinal network changes and conversion to cognitive impairment in multiple sclerosis. Neurology. 2021;97(8):e794-e802.

- Schoonheim MM, Pinter D, Prouskas SE, Broeders TA, Pirpamer L, Khalil M, et al. Disability in multiple sclerosis is related to thalamic connectivity and cortical network atrophy. Multiple Sclerosis Journal. 2021:13524585211008743.
- Schoonheim MM, Douw L, Broeders TA, Eijlers AJ, Meijer KA, Geurts JJ. The cerebellum and its network: Disrupted static and dynamic functional connectivity patterns and cognitive impairment in multiple sclerosis. Multiple Sclerosis Journal. 2021;27(13):2031-9.
- Strik M, Chard DT, Dekker I, Meijer KA, Eijlers AJ, Pardini M, et al. Increased functional sensorimotor network efficiency relates to disability in multiple sclerosis. Multiple Sclerosis Journal. 2021;27(9):1364-73.
- Broeders TA, Douw L, Eijlers AJ, Dekker I, Uitdehaag BM, Barkhof F, et al. A more unstable resting-state functional network in cognitively declining multiple sclerosis. Brain Communications. 2022;4(2):fcac095.
- Kulik SD, Nauta IM, Tewarie P, Koubiyr I, van Dellen E, Ruet A, et al. Structure-function coupling as a correlate and potential biomarker of cognitive impairment in multiple sclerosis. Network Neuroscience. 2022;6(2):339-56.
- 21. Tijhuis FB, Broeders TAA, Santos FAN, Schoonheim MM, Killestein J, Leurs CE, et al. Dynamic functional connectivity as a neural correlate of fatigue in multiple sclerosis. NeuroImage: Clinical. 2021;29:102556.
- Huiskamp M, Yaqub M, van Lingen MR, Pouwels PJ, de Ruiter LR, Killestein J, et al. Cognitive performance in multiple sclerosis: what is the role of the gamma-aminobutyric acid system? Brain Communications. 2023;5(3):fcad140.
- Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. The Lancet Neurology. 2018;17(2):162-73.

- 24. Nauta IM, Bertens D, Fasotti L, Fieldhouse J, Uitdehaag BM, Kessels RP, et al. Cognitive rehabilitation and mindfulness reduce cognitive complaints in multiple sclerosis (REMIND-MS): a randomized controlled trial. Multiple Sclerosis and Related Disorders. 2023:104529.
- Nauta IM, Speckens AE, Kessels RP, Geurts JJ, de Groot V, Uitdehaag BM, et al. Cognitive rehabilitation and mindfulness in multiple sclerosis (RE-MIND-MS): a study protocol for a randomised controlled trial. BMC neurology. 2017;17(1):1-10.
- 26. van Dam M, de Jong BA, Willemse EA, Nauta IM, Huiskamp M, Klein M, et al. A multimodal marker for cognitive functioning in multiple sclerosis: the role of NfL, GFAP and conventional MRI in predicting cognitive functioning in a prospective clinical cohort. Journal of Neurology. 2023:1-11.
- Nauta I, Bertens D, van Dam M, Huiskamp M, Driessen S, Geurts J, et al. Performance validity in outpatients with multiple sclerosis and cognitive complaints. Multiple Sclerosis Journal.0(0):13524585211025780.
- Epskamp S, Borsboom D, Fried EI. Estimating psychological networks and their accuracy: A tutorial paper. Behavior Research Methods. 2018;50(1):195-212.