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RESEARCH

# Structure–function multilayer network integration and cognition in multiple sclerosis

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## ABSTRACT

People with multiple sclerosis (MS) often present with cognitive deficits that cannot fully be attributed to focal brain alterations. Whole-brain network changes show stronger relations, but MS network insights have mostly focused on either structural or functional (single-layer) networks, while recent work has shown the importance of multilayer frontoparietal network integration for cognition. Here, we explored the cognitive relevance of multilayer integration of the frontoparietal network in relapsing–remitting MS ($n$ = 780) using diffusion and resting-state fMRI. Cognitive relations were first assessed for nodal multilayer eigenvector centrality, averaged over frontoparietal network nodes as a measure of integration, and post hoc for mean eccentricity for both single layer and multilayers. Higher multilayer frontoparietal network centrality was associated with worse Symbol Digit Modalities Test (SDMT) performance ($\beta$ = −.117, $p$ = .005). Mean eccentricity of single-layer diffusion ($\beta$ = −.123, $p$ < .001) and multilayer networks ($\beta$ = .085, $p$ = .018) were associated with SDMT performance. However, results could not be replicated using a different anatomical parcellation. This study showed that cognition in MS is related to multilayer network parameters. Nevertheless, correlations were weak and atlas specific, suggesting that a binary structure–function multilayer network approach is not particularly relevant as a correlate of cognition in MS.

## AUTHOR SUMMARY

Cognitive dysfunction is common in people with multiple sclerosis (MS). Although network approaches have revealed associations between network topology and such cognitive deficits, they mostly focus on structural or functional networks in isolation. Recent work has shown the importance of multiplex networks, combining structural and functional network information into a single model, for cognition. Here, we leverage a large multicenter dataset ($n$ = 780) to explore the cognitive relevance of multiplex frontoparietal network integration in relapsing–remitting MS. We find evidence for a negative relation between multiplex frontoparietal network integration and cognitive performance. However, effect sizes are small and do not hold up to validation analyses, underscoring the importance of further exploring the complex interplay between structural and functional neuroimaging network dynamics and cognition.


## INTRODUCTION

People with multiple sclerosis (MS) often suffer from cognitive impairment (Chiaravalloti & DeLuca, 2008), impacting their quality of life (Campbell et al., 2017; Mitchell et al., 2005). Although the pathophysiology of MS centers around demyelination and hence the presence of focal white and gray matter (GM) lesions, lesion load does not necessarily explain cognitive dysfunction. This discrepancy is known as the clinico-radiological paradox (Barkhof, 2002) and has led to the search for more advanced imaging markers to better understand clinical symptoms and progression in MS.

In light of this, it has become common practice to view the brain as a complex network through the lens of graph theory (Barabási, 2016; Bullmore & Sporns, 2009). In this framework,

brain regions are represented as nodes, while the interactions between brain regions form the connections or edges between the nodes. These connections can be derived from structural white matter (WM) pathways obtained through diffusion magnetic resonance imaging (dMRI) or functional communication patterns derived from functional imaging modalities such as functional MRI (fMRI) or magnetoencephalography (MEG; Aertsen et al., 1989; Friston et al., 1993). Following the construction of a brain network using one of these modalities, its topological properties can be determined through numerous metrics. Broadly speaking, these metrics fall into one of two categories: network segregation or network integration. A balance between integrative and segregative organization is considered optimal for healthy brain functioning (Sporns, 2013; Wang et al., 2021).

Disturbances in this optimal network organization in MS may relate to clinical impairment and is hypothesized to center around a network collapse (Schoonheim et al., 2015). As structural damage accumulates, the network becomes less and less efficient until a critical point is reached, after which the network collapses and (cognitive) impairment emerges. Disruptions of network organization are well-established in MS, as evidenced by studies using dMRI, fMRI, and MEG (Chard et al., 2021; Fleischer et al., 2019). The relevance of variations in directionality and magnitude of these disturbances, however, is inconclusive within and across modalities, and as of yet, there is no consensus on a common network correlate of cognitive dysfunction in MS.

These mixed results in the field may at least in part be explained by the relatively simple way previous work has looked at the brain network, that is, by focusing on single-layer networks derived from a single modality. Such unimodal approaches disregard the crucial interplay between structure and different aspects of brain function in the brain network. For instance, we know that brain structure partly constrains functional dynamics but does not explain it fully (Honey et al., 2009; Park & Friston, 2013), suggesting a complex synergy between structure and function, which has not been evaluated extensively yet in MS. Indeed, a recent exploration looking at changes in the "core" of the network showed that incorporating information from both structure and function improved correlations with cognition (Pontillo et al., 2025).

Unimodal:
Composed of a single imaging modality (e.g., fMRI or diffusion MRI).

The multilayer network framework provides a novel solution to study the topology of the entire brain network by integrating structure and function in one model (Boccaletti et al., 2014; De Domenico et al., 2013; Kivelä et al., 2014). To do so, structural and functional single-layer networks are connected to each other through interlayer links. In its simplest form, the individual layers comprise the same set of brain regions, and interlayer links connect the same brain region across layers, reflecting that the same brain region participates in both structural and functional communication rather than being a measured connection. This enables network metrics to capture how structure and function jointly contribute to the global network organization.

Multilayer network:
Extension of the single-layer framework, allowing for integration of multiple networks in one network model.

Interlayer links:
Links connecting nodes between networks/layers in a multilayer framework.

Multilayer approaches have been validated previously, showing clinical relevance in schizophrenia (Brookes et al., 2016; De Domenico et al., 2016) as well as Alzheimer's disease (Guillon et al., 2017; Yu et al., 2017). In the healthy brain, we have previously used multilayer networks integrating structural MRI, fMRI, and MEG data to show a positive relation between integration of the frontoparietal network (FPN) and executive functioning, which is less pronounced when considering isolated single-layer networks (Breedt et al., 2023). We further validated the relevance of the FPN in the multilayer in a glioma population, observing this same positive correlation with cognition when integrating the different MEG frequency bands into a multilayer network (van Lingen et al., 2023). These findings suggest that such a multilayer

approach may be more sensitive than unimodal analyses to individual differences in cognition across different populations.

The aim of the present work was to investigate whether the positive relation between (multilayer) integration of the FPN and cognitive functioning also holds for MS and whether multilayer network correlates supersede their single-layer counterparts.

## METHODS

### *Participants*

For this study, we used a large cross-sectional dataset previously collected for a multimodal analysis of network dysfunction in MS (Pontillo et al., 2025) across 13 European centers part of the MAGNIMS (Magnetic Resonance Imaging in Multiple Sclerosis) consortium (https://www.magnims.eu/). The MAGNIMS study was reviewed and approved by each participating center's local ethical committee, and written informed consent was provided by each participant independently at each center.

A total of 1,517 participants were included in the study. Of these, as reported elsewhere (Pontillo et al., 2025), 33 were previously excluded due to suboptimal MRI quality or failures in image processing. The final dataset thus comprised 1,484 participants, of which 41 people with clinically isolated syndrome, 1,007 people with definite MS (according to the 2010 McDonald criteria), and 436 healthy controls (HCs). Of the people with MS (pwMS), 817 had relapsing–remitting (RR) MS, 121 had secondary progressive MS, and 69 had primary progressive MS. MRI and clinical data were collected in all patients; for HC, only MRI data were obtained. To minimize the effects of clinical heterogeneity, we focused only on the RRMS population in the present work (Brochet & Ruet, 2019; Leray et al., 2010).

### *Neuropsychological and Neurological Evaluation*

Clinical evaluation of pwMS was carried out around the time of MRI acquisition. To assess cognitive performance, the Symbol Digit Modalities Test (SDMT; Smith, 1973) was used. The SDMT is a neuropsychological test where the participant is asked to match symbols to digits ranging from 1 through 9 according to a provided key. Here, the spoken version of this test was used to circumvent the impact of motor impairment. Although traditionally seen as a measure of information processing speed in pwMS (Benedict et al., 2017), the SDMT also quantifies aspects of working memory (Leach et al., 2022; Leavitt, 2021) and executive functioning (Baggetta & Alexander, 2016). Importantly, the SDMT has been observed to be the most frequently impacted test in MS and is a sensitive marker of overall cognitive decline in pwMS (Benedict et al., 2017; Van Schependom et al., 2014). Country-specific normative data were used to convert raw SDMT scores to *z* scores by adjusting for gender, age, and education. To assess overall physical disability, the Expanded Disability Status Scale (EDSS; Kurtzke, 1983) was used.

### *MRI*

MRI data were obtained from all participants using 3 T MRI scanners, and included a 3D T1-weighted sequence, a T2-weighted fluid attenuated inversion recovery (FLAIR) sequence, and resting-state (rs)fMRI and (single- and multishell) dMRI acquisitions. Exact acquisition protocols differed across the centers. The details of the imaging protocols, as well as the exact preprocessing of the data, are described in detail previously (Pontillo et al., 2025) but summarized briefly below and in Supporting Information Table S4.

**Structural MRI.** T2-hyperintense lesions segmented on FLAIR images were used to fill in lesions on T1w images, so that total lesion volume (TLV) could be computed. T1w images were segmented into GM, WM, and CSF (cerebrospinal fluid) and were used to parcellate the brain into 100 cortical Schaefer atlas regions. This atlas integrates local gradient and global similarity approaches, and its parcels are assigned to seven canonical rs networks (Yeo et al., 2011), composed of the visual, somatomotor, limbic, dorsal attention, ventral attention, default mode, and control or frontoparietal networks. An additional 14 subcortical GM regions were segmented using FSL-FIRST and added to the parcellation, for a total of 114 regions.

**rsfMRI.** Preprocessing of rsfMRI data was done using fMRIPrep (20.2.6; Esteban et al., 2019) and included susceptibility-induced distortion correction based on available fieldmap sequences (phase-encoding polarity method, phase-difference B0 estimation) or a registration-based fieldmapless estimation, registration to the T1w image, slice-timing correction, head motion estimation, and confound estimation. Denoising consisted of removal of non-steady-state volumes, band-pass filtering (0.008–0.08 Hz), detrending, standardization and regression of mean WM and CSF signal, and nonaggressive Independent Component Analysis-based Automatic Removal of Motion Artifacts (ICA-AROMA) components. ICA-AROMA (Pruim et al., 2015) is a well-established method for identifying and removing motion artifacts (Ciric et al., 2017; Parkes et al., 2018). Though not its primary effect, it also partially removes a significant amount of noise from cardiac and respiratory sources, as does WM and CSF signal regression, which is an effective approach for removing nonneuronal physiological noise (Behzadi et al., 2007).

Time series were extracted from all atlas regions, and Pearson correlation coefficients between all pairs of time series were computed, Fisher *z*-transformed, and absolutized to obtain a 114 × 114 functional connectivity matrix.

**Diffusion MRI.** Preprocessing of dMRI was performed using QSIPrep (0.14.3; Cieslak et al., 2021) and included denoising using MP-PCA, distortion correction using available sequences, head motion and eddy current correction, and resampling to the T1w image. A tissue response function was estimated using the Dhollander algorithm, and the fiber orientation distribution (FOD) for each voxel was determined using constrained spherical deconvolution and subsequently intensity-normalized using mtnormalize. Probabilistic anatomically constrained tractography based on WM FODs was used to generate 10 million streamlines and spherical-deconvolution-informed filtering of tractograms (SIFT2; Smith et al., 2015) was then performed to obtain weights for each streamline. A 114 × 114 structural connectivity matrix was obtained by summing the weights of all streamlines between each pair of atlas regions. To make the distribution of structural connectivity link weights more comparable to functional connectivity link weights, structural connectivity matrices were log10-transformed.

**Cross-site harmonization.** As data were acquired using different MRI systems and acquisition protocols in 13 centers across Europe, ComBat harmonization (Johnson et al., 2007) was used to correct structural and functional connectivity matrices and brain volumes for center-specific effects while maintaining biological associations with gender, age, and education.

### *Network Construction*

**Single-layer networks.** First, we used MATLAB (R2022b, Mathworks, Natick, MA, USA) to construct minimum spanning trees (MST) for the structural and functional single-layer networks for each subject by applying Kruskal's algorithm (Kruskal, 1956). Briefly, links were ranked in descending order (strongest to weakest) after which all the nodes in the network were

connected using only the strongest links without forming any loops, yielding a binarized subgraph of the original graph representing the strongest possible set of connections (assuming network weights are distinct). This subgraph is also referred to as the maximum spanning tree. The use of the MST prevents common issues stemming from differences in link density or connection strength across layers and between subjects (Stam et al., 2014; Tewarie et al., 2015). We used functions of the brain connectivity toolbox (2019.03.03, https://sites.google.com/site/bctnet/) to compute several single-layer network metrics for the functional and structural networks (see in the Methods section the Network Metrics section).

Multiplex network:
Special case of multilayer networks in which interlayer links are present only between a node's homologue across layers/networks.

Intralayer links:
Links connecting nodes within networks/layers in a multilayer framework.

**Multilayer networks.** For each subject, we then constructed a multiplex network, a special case of multilayer network, in which the structural and functional single-layer networks were modeled as two separate layers composed of the same set of $N = 114$ nodes (brain regions). In this framework, *intra*layer links represented the connectivity within a layer, while *inter*layer links connected each node (brain region) to itself across layers. These interlayer links did not encode connectivity strength between structural and functional layers; rather, they reflected the assumption that the same brain region participates in structural and functional networks simultaneously. Interlayer links were thus assigned a weight of 1, consistent with the binary intralayer links within the individual structural and functional MSTs.

Supra-adjacency matrix:
Extension of the adjacency matrix, encoding intralayer connections in diagonal blocks and interlayer connections in off-diagonal blocks.

A multiplex thus comprised L = 2 layers (one for rsfMRI and one for dMRI) where each layer consisted of an identical set of $N = 114$ nodes (the atlas regions) and $M = N - 1 = 113$ links. Multiplexes were represented as LxN by LxN supra-adjacency matrices where the diagonal NxN blocks encode intralayer connectivity and off-diagonal NxN blocks encode interlayer connectivity. These supra-adjacency matrices were exported to Python (3.6, Python Software Foundation, available at https://python.org/) where we used in-house scripts that implement the Python libraries NetworkX (2.3, https://github.com/networkx) and multiNetX (https://github.com/nkoub/multinetx) to compute several multilayer network metrics. All scripts used to analyze the data are openly available on our GitHub page at https://github.com/multinetlab-amsterdam. Figure 1 shows a schematic overview of the analysis pipeline.

### *Network Metrics*

**Main analysis.** To quantify the level of integration within the single-layer structural and functional networks as well as the multiplex networks, we used eigenvector centrality (EC). This is a centrality metric that takes into account not only the connections of a node itself but also that of its neighbors (Fornito et al., 2016). We previously showed significant associations between cognitive performance and EC of the FPN (*ECfpn*) in both a healthy (Breedt et al., 2023) as well

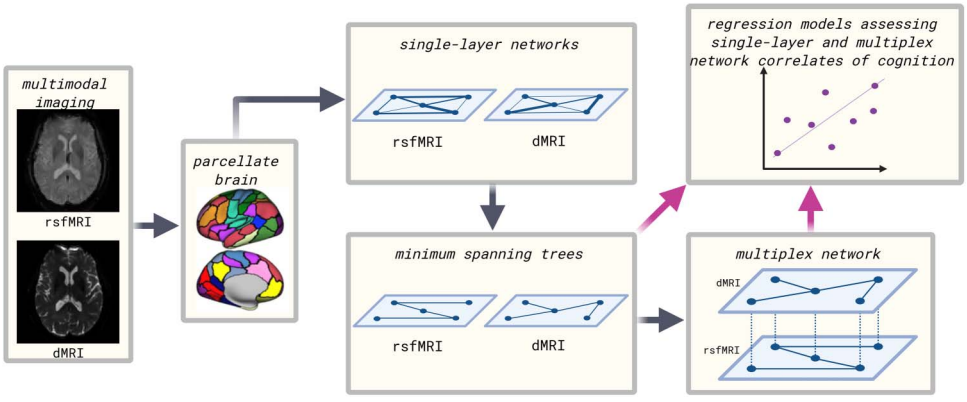


**Figure 1.** Flowchart of the analysis pipeline.

as a glioma population (van Lingen et al., 2023). Moreover, as EC is a spectral measure, it may be less sensitive to noise relative to other centrality metrics (Kardos et al., 2020). We computed nodal EC for the structural and functional single-layer networks and the multiplexes. For all three networks separately, EC values of nodes belonging to the FPN were extracted and averaged to obtain one value per subject representing *ECfpn*.

**Post hoc.** To further elucidate the single- and multiplex network correlates of cognition in pwMS, we also explored the mean network eccentricity. Eccentricity is a nodal measure obtained by computing the longest shortest path between a specific node and any other node in a network (West, 2001); mean eccentricity is a global measure reflecting the average distance information has to travel through a network. We computed mean eccentricity of the entire network for the structural and functional single-layer networks as well as the multiplex.

### *Statistical Analyses*

**Main analysis.** We tested our primary hypothesis on the relation between *ECfpn* and SDMT performance through a hierarchical multiple regression. Covariates (age and gender) were entered in block 1, single-layer functional and structural *ECfpn* were entered in block 2, and multiplex *ECfpn* was entered in block 3. Multicollinearity was checked for through observation of bivariate correlations between all independent variables as well as running collinearity diagnostics. All statistical analyses were performed in SPSS (version 28.0.1.1, IBM Corp., Armonk, NY, USA) using a two-tailed significance threshold of $p < .05$.

**Post hoc analyses.** To assess the association between mean eccentricity and the SDMT, an additional hierarchical multiple regression was run. Also, as visuomotor processing speed is an important component of the SDMT, we tested the association between EC of the relevant DAN and SDMT performance.

Furthermore, we previously showed an inverted-U relationship between age and multiplex centrality of the FPN in a healthy population when utilizing a multiplex network composed of dMRI, rsfMRI, and MEG (Breedt et al., 2023), indicating a nonlinear relation between multiplex parameters and age. To validate these findings in the current large HC population, we probed the biological relevance of *ECfpn* in a structure–function multiplex by running another hierarchical multiple regression. In this model, *ECfpn* was the dependent variable and age and the square of age were entered in the first and second block, respectively.

Next, to ensure the robustness of our findings, we repeated all analyses using an alternative 224-region brain parcellation: the 210 cortical regions of the Brainnetome atlas (BNA; Fan et al., 2016) combined with the 14 FSL-FIRST-derived subcortical GM regions. We used an earlier categorization (Vriend et al., 2018) of the BNA parcels into the seven canonical rs networks to determine FPN nodes for the computation of *ECfpn*. Additionally, to assess the robustness and generalizability of our regression models, we performed a Leave-Site-Out cross-validation (LSO-CV). For *ECfpn* and mean eccentricity, the full predictive model (including all predictors from the hierarchical regression) was trained on data from all but one site and then tested on the held-out site. This was repeated 13 times, so that every site had served as the test set once. We then conducted a Levene's test for homogeneity of variances on the residuals from these LSO-CVs to determine whether model performance was consistent across sites.

We performed a final additional validation step using another dataset, namely, the MuMo-Brain dataset consisting of 33 HCs where we previously observed an association between multiplex FPN integration and cognition as well as age (Breedt et al., 2023). See the Supporting Information for a brief description of this dataset. For these 33 HCs, we obtained structure–

function (dMRI/fMRI) multiplex networks constructed in identical manner as described in the current work and used regression models to again relate FPN integration of these multiplexes to cognition and age.

## RESULTS

### *Participants*

After exclusion of participants with missing data on any relevant variables, that is, SDMT performance, age, gender, or EDSS, a total of 780 people with RRMS remained. Information on age and gender was available for all 436 HCs. Characteristics of both samples are described in Table 1. Of all pwMS, 200 (25.6%) showed impairment of the SDMT at a $z$ score < −1.5. The median EDSS was 2.0 (interquartile range = 1.0–3.0).

**Table 1.** Demographics of the patients with RRMS as well as the HCs

| | pwRRMS | HC |
|---|---|---|
| *N* | 780 | 436 |
| Age (yr), mean (*SD*) | 41.51 (10.40) | 38.26 (11.77) |
| Sex (*n*), male/female | 244/536 | 186/250 |
| EDSS, median (range) | 2.0 (0.0–7.5) | |
| Disease duration (yr), mean (*SD*) | 10.67 (7.93) | |
| TLV (ml), median (IQR) | 3.02 (0.96–7.55) | |
| Scan site (*n*): | | |
| Amsterdam | 238 | 95 |
| Barcelona | 51 | 8 |
| Basel | 8 | 15 |
| Graz | 127 | 50 |
| London | 18 | 16 |
| Mainz | 40 | 55 |
| Milan | 29 | 35 |
| Naples | 30 | 52 |
| Oslo | 56 | 24 |
| Oxford | 16 | 17 |
| Siena | 73 | 30 |
| Vanvitelli | 51 | 18 |
| Verona | 43 | 21 |

pwRRMS = people with relapsing–remitting MS.

### *Cognition and ECfpn: The Added Value of Multiplex Measures*

Our data showed that gender, age, and multiplex *ECfpn* were significantly associated with SDMT performance and that the full model of gender, age, single-layer structural and functional *ECfpn*, and multiplex *ECfpn* was statistically significant ($R^2$ = .054, adjusted $R^2$ = .048, $F$[5, 774] = 8.880, $p < .001$). However, single-layer structural and functional *ECfpn* did not significantly add to the model, and the model only explained 4.8% of variance in SDMT scores. Moreover, the level of integration of the FPN in the multiplex was not positively but negatively related to SDMT scores in pwMS ($\beta$ = −.117, $p$ = .005). See Table 2 and Figure 2.

To ensure these findings were not confounded by head motion, we performed two additional validation analyses. First, we reran the regression model including mean framewise displacement (FD) as a covariate. Second, we conducted a sensitivity analysis by excluding subjects with high motion (mean FD > 0.2 mm) before rerunning the model. These analyses revealed identical associations between multiplex *ECfpn* and SDMT ($\beta$ = −.117, $p$ = .005) compared with our initial findings, indicating that the results are robust to potential motion artifacts.

### *Post Hoc Evaluations: Network Eccentricity, Age, and Validation Analyses*

**Cognition and mean eccentricity in MS.** Mean eccentricity was associated with SDMT scores ($R^2$ = .065, adjusted $R^2$ = .059, $F$[5, 774] = 10.804, $p < .001$; see Supporting Information Table S1 and Figure 2). A shorter average longest path length in the single-layer structural network ($\beta$ = −.123, $p < .001$) but longer average path length in the multiplex network ($\beta$ = .085, $p$ = .018) related to better SDMT scores in pwMS. However, effects were small, explaining only 5.9% of the variance in SDMT scores.

**Table 2.** Hierarchical multiple regression predicting SDMT performance from single- and multiplex *ECfpn*

| | Model 1 | | Model 2 | | Model 3 | |
|---|---|---|---|---|---|---|
| Variable | B | $\beta$ | B | $\beta$ | B | $\beta$ |
| (Constant) | 0.419* | | 0.417* | | 0.560* | |
| Age | −0.023** | −0.179 | −0.023** | −0.180 | −0.023** | −0.180 |
| Sex | −0.323* | −0.112 | −0.319* | −0.111 | −0.332* | −0.116 |
| $EC_{fpn}$ single-layer structural network | | | −0.330 | −0.012 | 0.510 | 0.018 |
| $EC_{fpn}$ single-layer functional network | | | 0.365 | 0.021 | 1.359 | 0.079 |
| $EC_{fpn}$ multiplex | | | | | −1.552* | −0.117 |
| $R^2$ | 0.044 | | 0.045 | | 0.054 | |
| $F$ | 17.959** | | 9.080** | | 8.880** | |
| $\Delta R^2$ | 0.044 | | 0.001 | | 0.009 | |
| $\Delta F$ | 17.959** | | 0.236 | | 7.764* | |

*$p < .05$, **$p < .001$.

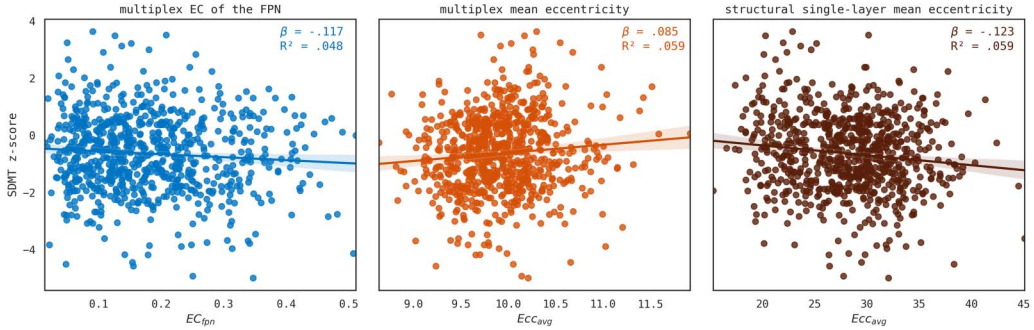


**Figure 2.** Network measures and SDMT performance in MS. Scatter plots including lines of best fit of significant associations between network correlates and SDMT performance. From left to right: multiplex *ECfpn*, mean eccentricity of the multiplex network, mean eccentricity of the single-layer structural network. $EC_{fpn}$ = eigenvector centrality of the FPN. $Ecc_{avg}$ = mean eccentricity.

Additional analyses to check for confounding effects of head motion, including separate regression models for the addition of mean FD as a covariate and the exclusion of patients with FD > 0.2 mm, revealed identical associations between single-layer ($\beta = -.123$, $p < .001$) and multiplex eccentricity ($\beta = .085$, $p = .018$) compared with our initial findings, indicating robustness to motion effects.

**Age and multiplex *ECfpn* in HC.** In contrast to our previously observed nonlinear relation between age and multiplex parameters in HC (see in the Methods section the Post Hoc Analyses section), a regression model in the current HC population revealed that multiplex *ECfpn* in a structure–function multiplex, in fact, did not follow the expected quadratic relationship with age ($p = .788$; see Supporting Information Table S1 and Figure 2).

**Validation analyses: BNA.** Although the full models assessing the relation between SDMT scores and *ECfpn* and mean eccentricity were significant ($p < .001$), in both models age and gender were the only significant predictors of executive functioning, see Supporting Information Table S2. The single- and multiplex network metrics added no significant value to the models.

For the association between age and multiplex *ECfpn*, results of the full model were nonsignificant ($p = .217$) and thus similar to the analysis using the Schaefer atlas. Neither age ($\beta = -.484$, $p = .177$) nor age squared ($\beta = .427$, $p = .235$) were significant predictors of multiplex *ECfpn*, indicating no relevant relation between a structure–function network correlate and age.

**Validation analyses: DAN.** Testing the relationship between SDMT performance and centrality of the DAN (*ECdan*) revealed that only gender and age significantly associated with SDMT performance. Although the full model was statistically significant ($R^2 = .048$, adjusted $R^2 = .042$, $F[5, 774] = 7.814$, $p < .001$), single-layer structural ($\beta = -.009$, $p = .806$) and functional *ECdan* ($\beta = .063$, $p = .101$) nor multiplex *ECdan* ($\beta = -.041$, $p = .315$) added significantly to the model.

**Validation analyses: LSO-CV.** The LSO-CV analyses revealed that the full model's predictive performance did not generalize to new sites for either *ECfpn* or mean eccentricity. Both yielded negative mean *R*-squared values across all 13 folds ($R^2 = -0.193$, $SD = 0.349$ for *ECfpn;* $R^2 = -0.169$, $SD = 0.317$ for mean eccentricity). Levene's tests on the residuals showed no significant differences in error variances across sites ($F = 1.328$, $p = .197$ for *ECfpn*; $F = 1.377$, $p = .171$ for mean eccentricity). This suggests that the models poor predictive performances were consistent across sites rather than driven by any one specific site.

**Validation analyses: MuMoBrain dataset.** In summary, our results showed a weak correlation between multiplex measures and SDMT performance that could not be replicated when using a different atlas. Interestingly, FPN integration of the MuMoBrain structure–function multiplex without MEG similarly showed no significant relation with cognition ($R^2$ = .065, adjusted $R^2$ = −.032, $F$[3, 29] = .673, $p$ = .576) nor age ($R^2$ = .031, adjusted $R^2$ = −.034, $F$[2, 30] = .478, $p$ = .625); see Supporting Information Table S3 and Supporting Information Figure S1; Supporting Information Figure S2 shows the significant associations present in the original multiplex with MEG.

## DISCUSSION

In this study, we aimed to investigate whether multiplex FPN parameters, integrating structural and fMRI data, were related to cognition in MS. This aim was chosen based on earlier observations of a positive relation with cognition in both HCs (Breedt et al., 2023) and glioma patients (van Lingen et al., 2023). However, in this dataset, we found a weak and negative relation between integration of the FPN in the multiplex network and SDMT performance in pwMS. These findings could not be replicated when using a different atlas. Additional validation analyses suggest that our findings may be affected by the absence of MEG in this dataset, in contrast to previous studies (Breedt et al., 2023; van Lingen et al., 2023).

We did not observe a consistent relation between multiplex parameters and SDMT performance in pwMS. Interestingly, a recent study in a largely overlapping dataset did show a relation with cognition for other measures, looking at hub-specific patterns of integration between structure and function; but this analysis used a less synergistic approach (Pontillo et al., 2025). That study used an additive multimodal approach, not directly considering the links between the structural and functional layers. Furthermore, the study also included an additional structural layer in the form of morphological covariance networks. The analysis could therefore have been driven by a predominance of structural layers. Moreover, morphological networks are based on the covariance of GM volumes between brain regions, and may thus also reflect the GM damage, which is a main hallmark of MS and relates to clinical outcomes (Geurts & Barkhof, 2008; Horakova et al., 2012). This was not included in our study, as our approach was based on the aforementioned HC and glioma studies, where morphological networks were also not present. Another reason for the absence of a significant relation with SDMT performance could reside in specific methodological choices we made. For instance, interlayer links were present only between identical node pairs across layers and were binarized (i.e., with a weight of 1) across the entire network. This approach fails to acknowledge the heterogeneity of (dMRI-fMRI) structure–function tethering across the cortex, which, moreover, shows low convergence in higher-order areas such as the FPN (Vázquez-Rodríguez et al., 2019). In neurodegenerative populations including pwMS, this structure–function coupling may be even more complex and more difficult to capture in a single measure (Koubiyr et al., 2021; Kulik et al., 2022). When integrating these modalities, it may therefore be crucial to take into account the coupling between structure and function, particularly in those parts of the brain where this relationship is inherently weak.

Both the negative relation we see between multiplex integration of the FPN and SDMT scores as well as the finding that higher average path length in the multiplex relates to better SDMT performance should be interpreted with caution, as effect sizes were small and did not survive validation analyses. While we may speculate that these results indicate a pathological network organization in MS where overload of hub nodes leads to network failure (Stam, 2024), such as the heightened centrality of hub nodes seen in cognitively impaired patients in previous MS studies (Eijlers et al., 2017, 2018; Meijer et al., 2017), our data do not provide

sufficient evidence to support this. This lack of a robust finding may instead further highlight the aforementioned methodological challenges of integrating brain structure and function, and future research replicating the relations between multiplex integration of the FPN and SDMT scores in pwMS is necessary.

We consistently find significant associations between SDMT performance and gender and age: Men performed slightly worse than women, and older age related to worse SDMT performance. While these findings might seem counterintuitive initially given that the SDMT scores have been corrected for demographic variables, normscoring corrects only for the normal variation in these scores that can be attributed to age and gender. It does not, however, correct for disease-specific variations. Indeed, men suffering from MS commonly present with more cognitive dysfunction than women (Beatty & Aupperle, 2002; Savettieri et al., 2004; Schoonheim et al., 2012). Similarly, longer disease duration, which correlates with and is difficult to disentangle from age, is linked to worse cognitive performance (Brochet & Ruet, 2019; Savettieri et al., 2004; Tremblay et al., 2020).

Our study also aimed to validate previous findings in HC, namely, the previously observed nonlinear relation between multiplex FPN integration and age (Breedt et al., 2023). A U-shaped relation with age is ubiquitous in many other brain measures, such as whole-brain (Hedman et al., 2012) and WM volumes (Ge et al., 2002; Walhovd et al., 2005), but also network efficiency (Cao et al., 2014; Hwang et al., 2013; Onoda & Yamaguchi, 2013), all of which increase during early life and subsequently decline with older age. We did not observe such a relation with age in HC in the present MAGNIMS dataset. However, the previous HC dataset in which we did observe this relation included more functional modalities, that is, MEG, in the multiplex network (Breedt et al., 2023). Interestingly, this relation with age was no longer present after excluding MEG. We may speculate that this reflects the importance of different functional data in the multiplex context, and particularly for cognition. The specific relevance of MEG beyond fMRI could be explained by the fact that MEG can capture properties of faster neuronal oscillations, which may be particularly sensitive to cognitive functions (Marek & Dosenbach, 2018). Another consideration is the dominance of functional layers in the MuMoBrain study versus the present work: Our current multiplex was composed of 50% functional data, while the significant correlations between cognition and integration in both HCs and glioma patients were based on multiplexes that were composed of 88%–100% functional data. The fact that reanalysis of the MuMoBrain HC data without the additional functional MEG layers yielded no significant correlations with age and cognition further supports the potential relevance of incorporating additional functional modalities in multimodal explorations of cognition in MS and opens up interesting avenues for future research.

Several limitations of this work should be acknowledged. In our previous work, executive functioning was the main outcome of interest and was quantified through multiple relevant neuropsychological tests. In the present MS dataset, however, only a single assessment of more general cognitive performance (i.e., the SDMT) was available. Moreover, although the SDMT does capture aspects of executive functioning, it is most commonly regarded as a test of (visuomotor) information processing speed, and we should therefore interpret our results with caution. Additionally, given the multicenter nature of this dataset, intersite differences in test administration and normative populations used for *z* scoring of SDMT test performance should be noted, as should differences in specific MRI scanners and acquisition protocols; although we did use statistical harmonization techniques to minimize effects of the latter. Furthermore, the binarized multiplex we employed does not take into account link weights or interactions between different regions across modalities; future work may look to explore alternative methods. Finally, in order to reduce clinical heterogeneity, the present study investigated only

people with RRMS, while specific evaluations of changing relations between network measures and cognition across the disease span could be of subsequent interest.

To conclude, we observed network correlates of SDMT performance using a structure–function multiplex network approach in MS. However, observed effect sizes were negligible and results did not survive validation analyses, potentially highlighting the shortcomings of a binary structure–function multiplex composed of only dMRI and fMRI. Our study underscores the importance of further exploring the complex interplay between multimodal neuroimaging network dynamics and cognition, and future studies may consider additional (functional) modalities or alternative multiplex approaches to further elucidate these associations.

## SUPPORTING INFORMATION

Supporting information for this article is available at https://doi.org/10.1162/NETN.a.545.

## AUTHOR CONTRIBUTIONS

Lucas Christian Breedt: Conceptualization; Formal analysis; Methodology; Project administration; Software; Visualization; Writing – original draft; Writing – review & editing. Giuseppe Pontillo: Conceptualization; Data curation; Formal analysis; Funding acquisition; Methodology; Project administration; Software; Visualization; Writing – original draft; Writing – review & editing. Fernando Santos: Methodology; Software; Writing – review & editing. Chris Vriend: Conceptualization; Formal analysis; Methodology; Project administration; Supervision; Writing – original draft; Writing – review & editing. Ferran Prados: Investigation; Writing – review & editing. Alle Meije Wink: Investigation; Writing – review & editing. Alvino Bisecco: Investigation; Writing – review & editing. Alessandro Cagol: Investigation; Writing – review & editing. Massimiliano Calabrese: Investigation; Writing – review & editing. Marco Castellaro: Investigation; Writing – review & editing. Sara Collorone: Investigation; Writing – review & editing. Rosa Cortese: Investigation; Writing – review & editing. Nicola De Stefano: Investigation; Writing – review & editing. Christian Enzinger: Investigation; Writing – review & editing. Massimo Filippi: Investigation; Writing – review & editing. Michael Foster: Investigation; Writing – review & editing. Antonio Gallo: Investigation; Writing – review & editing. Gabriel Gonzalez-Escamilla: Investigation; Writing – review & editing. Cristina Granziera: Investigation; Writing – review & editing. Sergiu Groppa: Investigation; Writing – review & editing. Einar Høgestøl: Investigation; Writing – review & editing. Sara Llufriu: Investigation; Writing – review & editing. Eloy Martinez-Heras: Investigation; Writing – review & editing. Elisabeth Solana: Investigation; Writing – review & editing. Silvia Messina: Investigation; Writing – review & editing. Marcello Moccia: Investigation; Writing – review & editing. Gro Nygaard: Investigation; Writing – review & editing. Jacqueline Palace: Investigation; Writing – review & editing. Daniela Pinter: Investigation; Writing – review & editing. Mara Rocca: Investigation; Writing – review & editing. Ahmed Toosy: Investigation; Writing – review & editing. Paola Valsasina: Investigation; Writing – review & editing. Olga Ciccarelli: Investigation; Writing – review & editing. Eva Strijbis: Conceptualization; Writing – original draft; Writing – review & editing. Frederik Barkhof: Conceptualization; Writing – original draft; Writing – review & editing. Menno Schoonheim: Conceptualization; Formal analysis; Methodology; Project administration; Supervision; Writing – original draft; Writing – review & editing. Linda Douw: Conceptualization; Formal analysis; Methodology; Project administration; Supervision; Writing – original draft; Writing – review & editing.

## CONFLICTS OF INTEREST

**F.B.:** Steering committee and iDMC member for Biogen, Merck, Roche, EISAI. Consultant for Roche, Biogen, Merck, IXICO, Jansen, Combinostics. Research agreements with Novartis, Merck, Biogen, GE, Roche. Cofounder and shareholder of Queen Square Analytics LTD. **A.B.** has received speaker honoraria and/or compensation for travel grant and consulting service from Biogen, Merck, Genzyme, Novartis, Alexion, Amgen, UCB, Coloplast, and Roche. **A.C.** is supported by EUROSTAR E!113682 HORIZON2020 and received speaker honoraria from Novartis and Roche. **M.C.** received speaker honoraria from Biogen, Bristol Myers Squibb, Celgene, Genzyme, Merck Serono, Novartis, and Roche and receives research support from the Progressive MS Alliance and Italian Minister of Health. **O.C.** is an NIHR Research Professor (RP-2017-08-ST2–004); acts as a consultant for Biogen, Merck, Novartis, Roche, and Teva; and has received research grant support from the MS Society of Great Britain and Northern Ireland, the NIHR UCLH Biomedical Research Centre, the Rosetree Trust, the National MS Society, and the NIHR-HTA. **S.C.** received travel support and speaker honoraria from Merck and is supported by Rosetrees Trust (MS632; PGL21/10079). **R.C.** was awarded a MAGNIMS-ECTRIMS fellowship in 2019; she received speaker honoraria/travel support from Roche, Merck Serono, UCB, Sanofi-Genzyme, Alexion, Novartis, and Janssen; and she received a research grant from the Italian Ministry of University and Research. **C.E.** received travel funding and speaker honoraria from Biogen Idec, Bayer Schering Pharma, Merck Serono, Novartis, Genzyme and Teva Pharmaceutical Industries Ltd./Sanofi-Aventis, Shire; received research support from Merck Serono, Biogen Idec, and Teva Pharmaceutical Industries Ltd./Sanofi-Aventis; and serves on scientific advisory boards for Bayer Schering Pharma, Biogen Idec, Merck Serono, Novartis, Genzyme, Roche, and Teva Pharmaceutical Industries Ltd./Sanofi- Aventis. **M.F.** is Editor-in-Chief of the Journal of Neurology, Associate Editor of Human Brain Mapping, Neurological Sciences, and Radiology; received compensation for consulting services from Alexion, Almirall, Biogen, Merck, Novartis, Roche, Sanofi; has speaking activities from Bayer, Biogen, Celgene, Chiesi Italia SpA, Eli Lilly, Genzyme, Janssen, Merck-Serono, Neopharmed Gentili, Novartis, Novo Nordisk, Roche, Sanofi, Takeda, and TEVA; has participation in Advisory Boards for Alexion, Biogen, Bristol-Myers Squibb, Merck, Novartis, Roche, Sanofi, Sanofi-Aventis, Sanofi-Genzyme, Takeda; and has scientific direction of educational events for Biogen, Merck, Roche, Celgene, Bristol-Myers Squibb, Lilly, Novartis, Sanofi-Genzyme. He receives research support from Biogen Idec, Merck-Serono, Novartis, Roche, the Italian Ministry of Health, the Italian Ministry of University and Research, and Fondazione Italiana Sclerosi Multipla. **M.A.F.** has received speaker honoraria from Merck. **C.G.**: The University Hospital Basel (USB) and the Research Center for Clinical neuroimmunology and Neuroscience (RC2NB), as the employers of Cristina Granziera, have received the following fees that were used exclusively for research support from Siemens, GeNeuro, Genzyme-Sanofi, Biogen, Roche. They also have received advisory board and consultancy fees from Actelion, Genzyme-Sanofi, Novartis, GeNeuro, Merck, Biogen, and Roche, as well as speaker fees from Genzyme-Sanofi, Novartis, GeNeuro, Merck, Biogen, and Roche. **E.A.H.** received honoraria for advisory board activity from Sanofi-Genzyme, and his department has received honoraria for lecturing from Biogen and Merck. **S.L.** received speaker honoraria from Sanofi, Biogen, Bristol Myers Squibb, Novartis, and Merck. **S.M.** received speaking honoraria from UCB and travel grants from Sanofi, Merck, Alexion, UCB, and Roche. **M.M.** received research funding from MUR PNRR Extended Partnership (MNESYS no. PE00000006, and DHEAL-COM no. PNC-E3–2022-23683267), ECTRIMS-MAGNIMS, UK MS Society, e Merck; salary as editorial board member from Neurology (AAN, MN, USA), and Multiple Sclerosis Journal (Sage, UK); and honoraria from Abbvie, Biogen, BMS Celgene, Ipsen, Jansen, Merck, Novartis,

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## DATA AVAILABILITY STATEMENT

The code used for the analyses in this study are available upon request; please contact L.D.

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