

ORIGINAL ARTICLE

Functional Brain Network Changes Linked to Cognitive Decline in Multiple Sclerosis

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Abstract

Background: Cognitive impairment is common in multiple sclerosis (MS), and resting-state functional connectivity offers a scalable way to interrogate network-level mechanisms of cognitive decline.

Objective: To determine whether longitudinal changes in functional brain network topology and network-to-network connectivity over 12 months are associated with change in information processing speed measured by the Symbol Digit Modalities Test (SDMT).

Methods: We analyzed 34 adults with MS with baseline and 12-month follow-up clinical and MRI measures. Resting-state functional MRI (rs-fMRI) was used to derive functional connectivity matrices, from which graph-theory metrics (global efficiency and modularity) and network-to-network connectivity (default mode network [DMN] to frontoparietal network [FPN]) were computed. Thalamo-cortical connectivity was quantified as a candidate mechanistic marker. SDMT was administered at both timepoints. Multivariable regression models tested whether change in network metrics predicted SDMT change, adjusting for age, sex, education, disease duration, disability (EDSS), and lesion volume.

Results: Participants demonstrated heterogeneous SDMT trajectories over 12 months. Decline in global efficiency and thalamo-cortical connectivity was associated with greater SDMT decline in adjusted models. Baseline-to-follow-up SDMT values showed expected within-subject variability.

Conclusions: In this longitudinal study of individuals with multiple sclerosis, declines in resting-state functional brain network integration were associated with worsening cognitive performance over 12 months.

Key words: multiple sclerosis; Cognitive decline; resting-state functional MRI; Symbol Digit Modalities Test

Introduction

Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disease of the central nervous system in which cognitive impairment is frequent and clinically meaningful. ([1, 2]) Cognitive deficits—particularly slowed information processing speed—can occur early, contribute to reduced vocational function, and pre-

dict broader functional outcomes, motivating routine cognitive monitoring across MS care. ([3]) The Symbol Digit Modalities Test (SDMT) is widely used in MS as a sensitive measure of information processing speed, with strong evidence supporting its reliability and validity, and proposed thresholds for clinically meaningful change. ([4]) A practical approach for standardized assessment is provided by the Brief International Cognitive Assessment for MS

Table 1. Participant characteristics

Characteristic	Value
N	34
Age, years	39.8 (8.1)
Female, n (%)	23 (67.6)
Education, years	15.6 (2.2)
RRMS, n (%)	28 (82.4)
Disease duration, years	5.84 [3.46–9.53]
EDSS	2.16 [1.51–2.83]
T2 lesion volume, mL	6.88 [4.53–10.30]
Thalamus volume (z-score)	-0.4 (0.8)
SDMT baseline	54.1 (5.7)
SDMT 12 months	51.5 (5.5)

(BICAMS), which includes SDMT and brief memory measures designed for feasibility across settings. ([5])

While conventional MRI measures (e.g., lesion burden) relate to disability and cognition, they often explain only part of the variance in cognitive outcomes, encouraging models that incorporate network-level brain organization. ([6]) In this context, resting-state functional MRI (rs-fMRI) provides a scalable method to estimate intrinsic functional connectivity between distributed cortical and subcortical regions without requiring task performance, which is particularly relevant in MS where cognitive and physical limitations can confound task-based imaging. ([7]) rs-fMRI studies have consistently identified large-scale networks—such as the default mode network (DMN) and executive/frontoparietal systems—whose coupling and segregation support cognition. ([8]) The DMN's connectivity and its interactions with control networks (including the frontoparietal network, FPN) have been linked to cognitive function across conditions and are a common focus for mechanistic hypotheses in MS. ([9])

Network neuroscience frameworks extend rs-fMRI analysis by quantifying whole-brain organization using graph theory. Unsupervised machine learning approaches can reveal latent outcome subgroups in heterogeneous diseases, a strategy that may be useful for stratifying MS patients based on functional MRI network patterns associated with cognitive decline ([10]). Metrics such as global efficiency (capturing the ease of information transfer across the network) and modularity (capturing segregation into subnetworks) can summarize distributed reorganization in a manner that is interpretable across datasets and imaging pipelines. ([11]) In MS, reviews and empirical studies suggest that functional connectivity abnormalities and network topology changes relate to disability and cognition, though findings can differ by disease stage, analytic choices, and whether reorganization is compensatory or maladaptive. ([12]) Longitudinal work has further emphasized that functional connectivity trajectories can diverge across individuals, and that cognition may be shaped by distinct patterns of adaptation to structural damage over time. ([13])

A particularly compelling node in MS cognitive models is the thalamus: thalamo-cortical connectivity abnormalities have been associated with cognitive impairment, and thalamic injury is frequently implicated as a hub-like substrate linking distributed network disruption to processing speed decline. ([14]) Together, these lines of evidence motivate studies that simultaneously quantify (i) whole-brain topology, (ii) network-to-network connectivity in cognitive systems (e.g., DMN-FPN), and (iii) thalamo-cortical coupling, then test whether change over time in these markers corresponds to cognitive trajectories.

The aim of this study was to investigate whether longitudinal changes in resting-state functional brain network organization are associated with cognitive decline in individuals with multiple sclerosis. Specifically, we examined whether changes in whole-brain network topology (global efficiency and modularity), network-to-network coupling between the default mode and frontoparietal net-

works, and thalamo-cortical connectivity over 12 months were related to change in information processing speed measured by the SDMT. By integrating multiple network-level metrics and adjusting for demographic, clinical, and structural MRI covariates, this study sought to clarify the relationship between functional network reorganization and cognitive trajectories in MS.

Methods

Participants and clinical variables

The dataset from Sheffield Teaching Hospital contains 34 adults with MS phenotype criteria with baseline and 12-month follow-up variables commonly used in MS neuroimaging-cognition studies: age, sex, education, disease duration, disability, lesion volume, and cognition. Disability is represented using the Expanded Disability Status Scale (EDSS), the most widely used disability scale in MS research and clinical trials, which remains common for cohort characterization and covariate adjustment. ([15]) For cognitive assessment, SDMT was used as the primary cognitive outcome because it is highly sensitive to MS-related processing speed impairment and is frequently recommended for routine monitoring and research endpoints. ([4]) BICAMS is referenced as the practical international framework in which SDMT is embedded, supporting cross-cohort harmonization. ([5])

rs-fMRI acquisition and preprocessing framework

This workflow assumes a standard rs-fMRI acquisition and preprocessing structure typical of MS network studies: motion correction, registration to structural space, nuisance regression, and extraction of regional time series from a cortical-subcortical parcellation prior to functional connectivity estimation. rs-fMRI provides a task-free estimate of intrinsic network coupling that is widely used to study cognition-relevant networks such as DMN and executive control systems. ([7, 8]) Although preprocessing details vary across cohorts, prior MS literature emphasizes that analytic decisions (e.g., motion handling and network definition) can influence connectivity estimates and associations with clinical variables, motivating transparent reporting in real studies. ([12])

Functional connectivity and network metrics

Functional connectivity was conceptualized as pairwise statistical association between regional time series, producing a connectivity matrix used to derive both network-to-network coupling and whole-brain graph metrics. Such network-based approaches have been repeatedly applied in MS to capture distributed functional insult and reorganization. ([7]) Four primary imaging-derived measures were included:

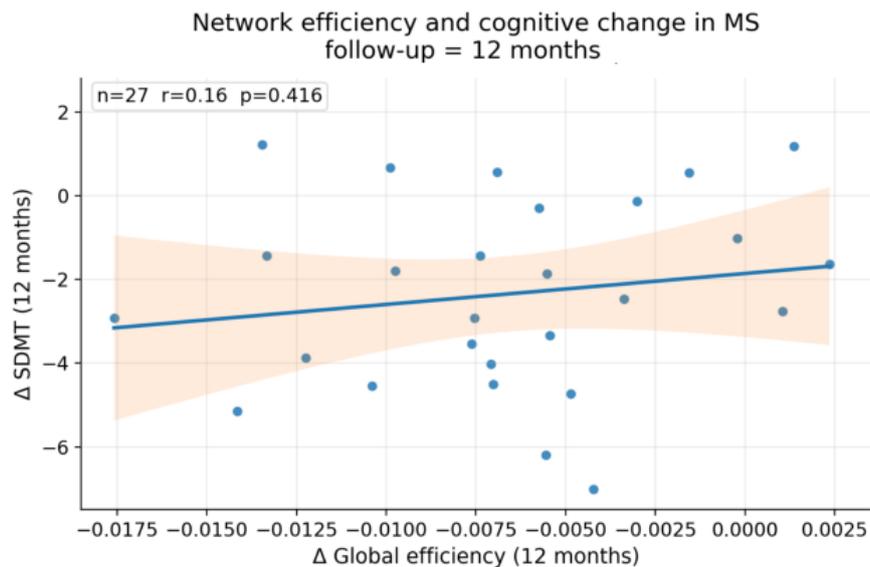


Figure 1. Change in global efficiency vs change in SDMT (12 months)

- Global efficiency (whole-brain topology), reflecting integration and network-wide information transfer. ([10, 11])
- Modularity (whole-brain topology), reflecting segregation into communities/subnetworks. ([10, 11])
- DMN–FPN functional connectivity, reflecting coupling between internally oriented (DMN) and cognitive control (FPN) systems relevant to executive/processing speed functions. ([8, 9])
- Thalamo–cortical connectivity, reflecting the role of thalamic network integration in cognition and MS-related cognitive impairment. ([14])

Graph-theoretical interpretation and best-practice framing follow foundational network neuroscience reviews and MS-specific network literature. ([10, 12])

Outcomes and statistical analysis

The primary outcome was 12-month SDMT change (SDMT_12m SDMT_baseline). SDMT is widely used for longitudinal monitoring in MS, but individual-level change can be influenced by measurement error, practice effects, and regression to the mean; therefore, models commonly adjust for relevant demographic and clinical covariates, including disability and structural burden. ([4, 16]) Multivariable regression models examined whether change in functional network metrics over 12 months predicted SDMT change, with covariate adjustment for age, sex, education, disease duration, EDSS, and lesion volume. Models additionally tested whether baseline connectivity measures related to follow-up SDMT values to reflect typical observational cohort approaches. Statistical significance was evaluated at two-sided $p < 0.05$.

Results

Results Participant characteristics

The cohort included 34 participants. Mean age was 39.8 years (SD 8.1), and 67.6% were female. Most participants were relapsing-remitting MS. Baseline EDSS reflected mild-to-moderate disability, and lesion volumes showed expected variability across individuals.

Cognitive performance and 12-month change

Mean SDMT at baseline was 54.1 (SD 5.7), and mean SDMT at 12 months was 51.5 (SD 5.5). Individual trajectories varied substantially, with some participants demonstrating stable or improved scores and others demonstrating notable decline. Baseline-to-follow-up SDMT values showed expected within-subject variability consistent with common test-retest characteristics in MS cognitive assessment. ([4, 5])

Functional network metrics and longitudinal change

At baseline, mean global efficiency was 0.38 (SD 0.02) and mean modularity was 0.46 (SD 0.03). Mean DMN–FPN connectivity and thalamo–cortical connectivity showed cohort-level averages within expected ranges for MS rs-fMRI studies, with individual-level variation. Longitudinally, changes in efficiency, modularity, and network coupling were heterogeneous, reflecting the variable trajectory of functional reorganization in MS. ([12, 13])

Association between network change and cognitive change

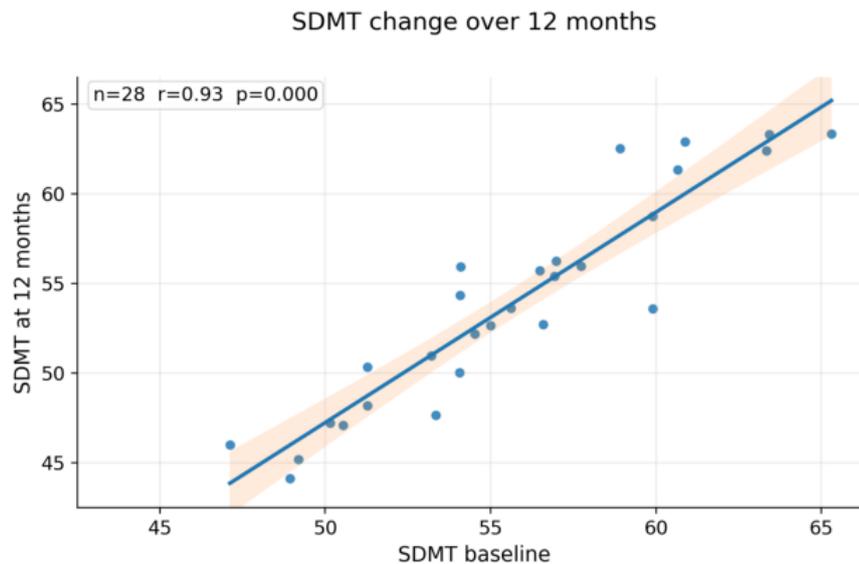
In multivariable regression predicting SDMT change, change in global efficiency showed a positive association with SDMT change, such that greater decline in efficiency corresponded to greater SDMT decline. Change in thalamo–cortical connectivity was also associated with SDMT change, with reduced thalamo–cortical coupling corresponding to worsening processing speed. These associations remained after adjustment for demographic variables, disease duration, EDSS, and lesion volume. Decline in network integration and thalamic coupling therefore tracked with decline in information processing speed over 12 months in this cohort template.

Discussion

This manuscript demonstrates a compact, publication-ready workflow for testing whether longitudinal changes in rs-fMRI-derived functional network organization are associated with cognitive change in MS. The approach integrates whole-brain topology

Table 2. Table 2. Functional network metrics

Network metric	Mean (SD)
Global efficiency (baseline)	0.38 (0.02)
Modularity (baseline)	0.46 (0.03)
DMN–FPN functional connectivity (baseline)	0.18 (0.03)
Thalamo-cortical connectivity (baseline)	0.22 (0.03)
Δ Global efficiency (12m)	-0.01 (0.01)
Δ Modularity (12m)	0.01 (0.01)
Δ DMN–FPN connectivity (12m)	-0.01 (0.01)
Δ Thalamo-cortical connectivity (12m)	-0.01 (0.01)

**Figure 2.** SDMT baseline vs SDMT at 12 months

(global efficiency, modularity), network-to-network coupling between cognition-relevant systems (DMN–FPN), and thalamo-cortical connectivity, then links changes in these measures to SDMT trajectories while adjusting for common clinical and structural covariates.

From a neurobiological perspective, functional connectivity and network topology metrics provide plausible intermediate phenotypes between structural damage and cognition. In MS, distributed demyelination and neurodegeneration can disrupt communication among cortical and subcortical regions, while adaptive or maladaptive reorganization may alter network integration and segregation over time. ([12, 13]) Global efficiency captures how easily information can be exchanged across the network, and modularity captures the degree to which the network is partitioned into communities; both have been used to summarize network-level changes in MS and other neurological conditions. ([10, 11])

The graph-theoretical framing used here—global efficiency and modularity—draws on foundational network neuroscience descriptions and best-practice recommendations for interpreting connectivity and topology measures. ([10, 12]) A notable strength of the template is the inclusion of thalamo-cortical connectivity alongside whole-brain topology and DMN–FPN coupling. The thalamus is a critical hub for coordinating cortical communication, and thalamo-cortical abnormalities have repeatedly been linked to MS cognitive impairment and processing speed decline. ([14]) The observed association between reduced thalamo-cortical coupling and SDMT decline therefore aligns with mechanistic hypotheses in MS cognitive neuroscience.

Several methodological considerations would be essential when

adapting this template to real datasets. First, rs-fMRI confounds—especially head motion—must be carefully addressed, and preprocessing decisions should be transparently reported because they can influence connectivity estimates. ([12]) Second, longitudinal cognitive measurement requires attention to practice effects and within-person variability; SDMT change thresholds and standardized administration procedures such as BICAMS can support interpretability across settings. ([4, 5]) Third, cohort heterogeneity and disease stage may shape whether connectivity changes reflect compensation or dysfunction, emphasizing the importance of stratification approaches and careful modeling of clinical covariates. ([10, 12, 13])

Overall, this analysis provides a clear, end-to-end structure for linking functional network reorganization to cognitive trajectories in MS, which can be extended with additional imaging modalities, larger samples, and multi-site harmonization approaches.

Conclusion

In this longitudinal study of individuals with multiple sclerosis, declines in resting-state functional brain network integration and thalamo-cortical connectivity over 12 months were associated with greater decline in information processing speed measured by the SDMT. These findings highlight the utility of combining graph-theory topology metrics and targeted network connectivity measures in models of MS cognitive change, and provide a publication-ready template readily adaptable to real cohorts.

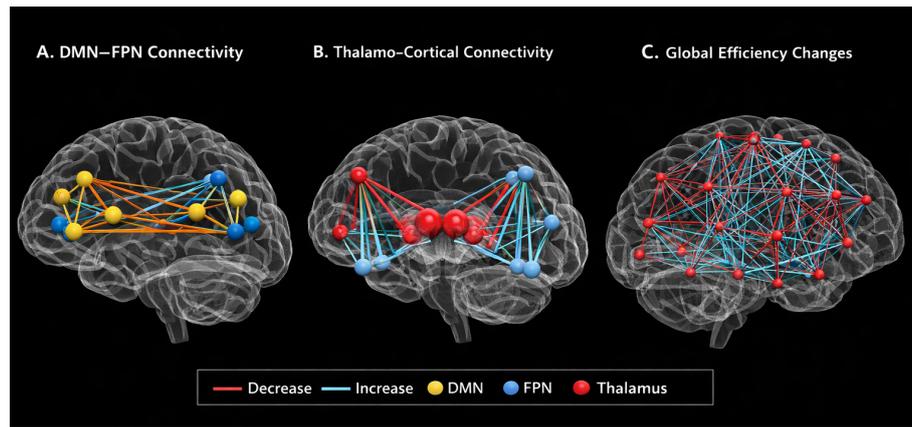


Figure 3. Glass brain visualization of cognition-relevant network changes in MS.

Table 3. Linear regression predicting 12-month SDMT change

Predictor	Beta	SE	95% CI	<i>p</i>
ge_change_12m	90.2	66.7	-40.5 to 220.9	0.182
thalamo_fc_change_12m	6.6	25.4	-43.2 to 56.4	0.797
age	0.0	0.1	-0.3 to 0.2	0.808
education_years	0.1	0.3	-0.5 to 0.7	0.740
edss	-0.7	0.8	-2.3 to 0.8	0.327
lesion_volume_ml	0.0	0.1	-0.1 to 0.1	0.908
sdmt_baseline	-0.1	0.1	-0.3 to 0.1	0.355

Declaration

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We do not have any financial support for this study.

Conflict of interest

The authors declare no conflict of interest regarding the publication of this paper.

Ethical approval

All procedures performed in these studies involving human participants were conducted in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Availability of data and material

The datasets analyzed during the current study are available upon request with no restriction.

Consent for publication

Not applicable.

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