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Original Research

Network analysis characterizes key associations between subjective fatigue and specific depressive symptoms in early relapsing-remitting multiple sclerosis

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YTC is responsible for study design, data analysis, writing and revision of the article. PKAK is responsible for study design, writing, revision, reviewing of the article. AC, DCG, RM, AK, MVH, CW, AS, NM, JOR, MAM, FJCA, PC, ADW are responsible for reviewing of the article. SC, PF is responsible for study design, data analysis, revision and reviewing of the article.

Highlights

- Fatigue severity in MS linked to a range of variables including depression
- Overlap between fatigue and tiredness as depressive symptom complicates interpretation
- Network analysis of large early RRMS cohort including structural MRI of brain
- No link between fatigue severity and cognitive performance, or included MRI metrics
- Fatigue linked to individual depressive symptoms in addition to tiredness

ABSTRACT

Background:

Fatigue is common and disabling in multiple sclerosis (MS), yet its mechanisms are poorly understood. In particular, overlap in measures of fatigue and depression complicates interpretation. We applied a multivariate network approach to quantify relationships between fatigue and other variables in early MS.

Methods:

Data were collected from patients with newly diagnosed immunotherapy-naïve relapsing-remitting MS at baseline and month 12 follow-up in FutureMS, a Scottish nationally representative cohort. Subjective fatigue was assessed by Fatigue Severity Scale. Detailed phenotyping included measures assessing each of physical disability, affective disorders, cognitive performance, sleep quality, and structural brain imaging. Network analysis was conducted to estimate partial correlations between variables. Baseline networks were compared between those with persistent and remitted fatigue at one-year follow up.

Results:

Data from 322 participants at baseline, and 323 at month 12, were included. At baseline, 154 patients (47.8%) reported clinically significant fatigue. In the network analysis, fatigue severity showed strongest connections with depression, followed by Expanded Disability Status Scale. Conversely, fatigue severity was not linked to objective cognitive performance or brain imaging variables. Even after controlling for measurement of "tiredness" in our measure of depression, four specific depressive symptoms remained linked to fatigue. Results were consistent at baseline and month 12. Overall network strength was not significantly different between groups with persistent and remitted fatigue (4.89 vs

2.90, p=0.11).

Conclusions:

Our findings support robust links between subjective fatigue and depression in early relapsing-remitting MS. Shared mechanisms between specific depressive symptoms and fatigue could be key targets of treatment and research in MS-related fatigue.

INTRODUCTION

Multiple sclerosis (MS) is an autoimmune-mediated neuroinflammatory and neurodegenerative condition which is a major cause of morbidity in young adults.[1] Fatigue is frequently described by people with MS (pwMS) as one of their most disabling symptoms,[2] with the estimated prevalence ranging from 38% to 83%.[2] Fatigue can be defined as "a subjective lack of physical and/or mental energy that is perceived by the individual or the care-giver to interfere with usual or desired activity".[3] Although fatigue is distinct from physical fatigability, depression, tiredness, and other phenomena which are frequently present in pwMS,[2] clearly differentiating subjective fatigue from these phenomena can be challenging.

Despite the high prevalence, treatment options for fatigue in pwMS are of limited effectiveness.[4] This in part reflects limited mechanistic understanding and an absence of clear biomarkers.[5–7] A fundamental challenge to the development of such mechanistic understanding is the overlap and interrelatedness with other common symptoms. Multiple factors have been linked to fatigue in pwMS, including physical disability,[7] obesity,[8] depression,[7] anxiety,[6] sleep disturbance,[9] subjective cognitive difficulty,[10] and brain imaging measures.[11] However, studies to date have highlighted inconsistency in many of these associations, partly due to different adjustment for confounders[12] and small sample sizes.[11] Links between fatigue and depression have been shown in many studies,[13] but the overlapping features between these two constructs have been incompletely addressed, which could compromise interpretation of this relationship.[14] Specifically, common research and clinical measures of depressive symptoms typically measure symptoms of tiredness, therefore leading to difficulty in interpreting correlations between sum scores of instruments measuring symptoms of depression, and of fatigue.[15] Analyses incorporating individual depressive symptoms would allow better understanding of shared mechanisms between fatigue and depression, at the level of individual depressive symptoms.

Given the clinical complexity, multivariate analysis that simultaneously evaluates physical, cognitive, affective, sleep, and imaging variables, is likely necessary to an improved understanding of the complex inter-relationships between these variables, and ultimately to advance understanding of pathogenic mechanisms.[11] Existing studies with sample size sufficient to allow multivariate analyses accounting for potential confounders, and overlapping symptoms between depression and fatigue, are lacking.

We therefore aimed to quantify the relationships between subjective fatigue and variables reflecting aspects of depressive symptoms, physical disability, cognitive performance, anxiety, sleep quality, and MRI brain imaging metrics. We employed mixed graphical model networks at study baseline and one-year follow up to examine and visualise the correlates of fatigue in pwMS. The use of network analysis allows for both the quantification and visualisation of relationships between fatigue and other network nodes, and between other nodes apart from fatigue. In addition, network centrality indices may be used to infer the relative influence of the included nodes in the estimated networks. Differences in network connectivity at baseline have previously been shown to differentiate subjects with persistent and remitting symptoms longitudinally.[16,17] To investigate any prognostic value of network structure on fatigue progression, symptom networks at baseline using subsamples of pwMS with persistent and remitted fatigue were compared.

SUBJECTS/MATERIALS AND METHODS

Participants

The study participants were drawn from FutureMS,[18] a nationally representative cohort of patients with newly diagnosed relapsing remitting MS (RRMS) in Scotland. This cohort was estimated to capture 45% of persons diagnosed with RRMS in Scotland during the study period[18] with data collected at baseline and 12 months follow up. Detailed phenotyping of all participants included a wide range of clinical measures and structural brain MRI data. Full details of the cohort[18] and the MRI brain acquisition and analysis[19] have been described elsewhere and are briefly summarized in Supplementary Materials. Current medication was obtained by participant report at both study visits.

Variable selection

Based on previous literature,[6–10,12] network variables were selected to include key clinical, cognitive and imaging metrics previously linked to subjective fatigue in pwMS. Clinical and patient-reported variables were - fatigue (Fatigue Severity Scale, FSS),[20] physical disability (Expanded Disability Status Scale, EDSS), upper limb dexterity (Nine Hole Peg Test, 9-HPT), walking speed (Timed 25 Foot Walk, T25FW) and Body Mass Index (BMI). Cognitive variables were - information processing speed (Symbol Digit Modality Test, SDMT), and working memory along with auditory information processing and attentional abilities (3 seconds-Paced Auditory Serial Addition Test, PASAT). Affective variables were - anxiety (Generalized Anxiety Disorder-7 instrument, GAD-7) and depression (Patient Heath Questionnaire-9, PHQ-9). Participant-reported sleep quality was measured by an item in the Multiple Sclerosis Impact Scale ("SLEEP").[18] Imaging variables were expressed as proportions of intracranial volume in native space, including whole-brain WMH volume, cortical grey matter volume ("cGM"), basal ganglia volume ("BG"), and thalamus volume ("THALA"). The PHQ-9 has been shown to be a suitable tool to screen for depression with adequate sensitivity and specificity in pwMS.[15] To control for possible overlap between one PHQ-9 item which assesses feelings of tiredness or reduced energy[21] and fatigue,[20] and explore the differential correlations between the remaining PHQ-9 items and fatigue, all nine individual PHQ-9 item scores were used in a secondary analysis.[22] (Table 1) These nine items are identical to the nine core criteria for major depressive disorder in the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5).[23] Because of data distribution, T25FW, 9-HPT and PASAT were transformed into Z-scores to increase comparability.[18]

Table 1. Description of items in the Patient Heath Questionnaire-9 (PHQ-9)

Item abbreviation	Description
PLEAS	Little interest or pleasure in doing things
DOWN	Feeling down, depressed, or hopeless
PHQ9-S	Trouble falling or staying asleep, or sleeping too much

TIRED	Feeling tired or having little energy
EAT	Poor appetite or overeating
FAIL	Feeling bad about yourself - or that you are a failure or have let yourself or your family down
CONCE	Trouble concentrating on things, such as reading the newspaper or watching television
MOVE	Moving or speaking so slowly that other people could have noticed; or the opposite, being so fidgety or restless that you have been moving around a lot more than usual
SELF	Thoughts that you would be better off dead, or of hurting yourself in some way

To aid interpretation of networks, we classified included variables into five domains as follows: "physical" (EDSS, 9-HPT, T25FW and BMI), "cognitive" (SDMT and PASAT), "affective" (GAD-7 and PHQ-9), "sleep" (SLEEP), "imaging" (WMH, cGM, BG and THALA), and fatigue (FSS). This classification was employed solely to aid interpretation of results and was not included during network estimation.

Statistical analysis

All analyses were done using R software (v 4.0.2) and R Studio V. 1.2.5042.[24]

Descriptive analysis of demographics and fatigue severity at baseline were conducted. Disease duration was defined as the interval between the patient-described first episode of demyelination, confirmed by clinicians, and the first study visit. Spearman correlations between FSS and the described variables were calculated at study baseline. Bonferroni correction of 13 comparisons was applied in analysis of bivariate Spearman correlations to control family-wise type 1 error rate (α=0.05). Interpretation of the strength of correlation according to Spearman correlation coefficient is defined in the eMethod section. For context and to aid data interpretation, clinical and imaging data at baseline and 12 months were compared.

Network estimation

Network analysis aims to identify partial correlations between nodes, and represents such correlations as edges. Network estimation was performed via Gaussian graphical models with Spearman's correlations. This method has been well-documented in previous publications.[25] Technical details were described in Supplementary Materials. Only participants with complete data of all included variables were included in network analysis. To quantify the importance of nodes in the network structure, centrality indices, including strength, closeness, betweenness and expected influence were calculated.

Robustness of networks

The robustness of networks was assessed through the methodology proposed by Epskamp et al.[26] using the R package "bootnet".[26] The precision of edge-weight estimates and central indices was obtained by implementing bootstrapping

methods with 1000 iterations. The stability of centrality indices, quantified by correlation stability (*CS*) coefficients, was estimated by case-dropping bootstrap.[26] *CS*-coefficients of 0.5 or higher suggest stable and interpretable results. Ranking of centrality indices where *CS*-coefficients are lower than 0.5 may be interpreted with caution.[26]

Post-hoc comparisons and sensitivity analysis

The links between fatigue severity and other variables in the networks were first identified, and then post-hoc analysis via network comparison test (NCT)[27] was performed to assess whether such links differed between baseline and month 12. A Holm-Bonferroni correction was employed to control for multiple testing. Significance level was set at alpha=0.05.

Sensitivity analysis was done by estimating separate networks as described above, stratifying on gender and whether patients had received any Disease Modifying Drugs (DMDs) from baseline to month 12.

Comparisons between networks associated with persistent versus remitted fatigue

Additionally, two networks were constructed, using baseline data, to compare participants who had persistent and remitting fatigue at one-year follow-up. The persistent-fatigue group was defined as pwMS who had FSS ≥ 36 at both baseline and month 12; while remitted group was defined as pwMS who had FSS ≥ 36 at baseline and FSS < 36 month 12.[20]

RESULTS

Baseline characteristics, fatigue severity and bivariate correlations

Among 440 participants enrolled in the FutureMS cohort, 322 participants (73.2%) at baseline and 323 participants (73.4%) at month 12, had complete data and were included in further analysis. There was no systematic difference in the demographic and clinical measures between participants included in our analysis and the complete cohort (Supplementary Table 1). Geographical and demographic characteristics of the cohort were shown in Table 2 and were comparable with those of patients with recently-diagnosed MS in Scotland as a whole, as confirmed by mandatory incidence register for MS in Scotland.[18,28] Median FSS was 34 (IQR 23 – 46, range 9 – 63), consistent with mild/moderate fatigue severity, and 154 participants (47.8%) reported significant fatigue (FSS ≥ 36).[20] Fatigue was neither significantly associated with participant sex (Female Median FSS 35, IQR 26 – 47; Male Median 33, IQR 19 – 44; Wilcoxon rank sum test with continuity correction p=0.08), nor correlated with age at study entry (Spearman's Rho = 0.07, p=0.21). Only one participant was prescribed Amantadine at both study visits, with one other participant commencing Amantadine between baseline and follow-up visits. No participant received Modafinil, Armodafinil, Methylphenidate, or Dextroamphetamine.

Table 2. Baseline characteristics of the study cohort (n=322)

Characteristics	Median (IQR)[a]
Age at study inclusion, years (mean, SD)	38.0 (10.2)
Sex Female (count, %)	241 (74.8)
Time from diagnosis to first study visit, days	60 (35 – 96)
Disease duration, years	1.8 (0.9 – 4.6)
EDSS at baseline	2 (1.5 – 3)

[a] If not otherwise specified, numbers are expressed as median (IQR).

Abbreviation: EDSS=Expanded Disability Status Scale, SD=Standard deviation

In initial bivariate analyses, including Bonferroni correction for multiple comparisons, FSS was correlated to a statistically significant degree with most of the included physical disability, cognitive and affective metrics. In all cases, increasing fatigue was associated with clinically adverse change in the correlated metric (Table 3). Specifically, FSS was correlated to a moderate degree with PHQ-9, EDSS, GAD-7 and sleep quality. Strengths of other statistically significant correlations were weak (see eMethod for interpretation of correlation strength).[29] FSS was not significantly correlated with the included imaging variables.

Table 3. Bivariate correlations of fatigue severity with physical, cognitive, affective, sleep and imaging variables at baseline (*n*=322)

Domain	Variable assessed	Spearmanôs Rho (95% CI)[a]	*p*
Physical disability	EDSS	0.46 (0.35 – 0.57)	<.001*
	zT25FW	-0.32 (-0.43 – -0.21)	<.001*
	BMI	0.12 (0.01 – 0.23)	0.033
	z9-HPT	-0.26 (-0.37 – -0.15)	<.001*
Cognitive performance	zPASAT	-0.14 (-0.25 – -0.03)	0.014
	SDMT	-0.23 (-0.34 – -0.12)	<.001*
Affective disorders	PHQ-9	0.64 (0.53 – 0.75)	<.001*
	GAD-7	0.46 (0.35 – 0.56)	<.001*
Sleep	MSIS-29-SLEEP	0.41 (0.31 – 0.52)	<.001*
Imaging[b]	WMH volume	0.002 (-0.11 – 0.11)	0.97
	Cortical grey matter volume	-0.08 (-0.19 – 0.03)	0.14
	Basal ganglia volume	0.05 (-0.06 – 0.16)	0.37
	Thalamus volume	-0.06 (-0.17 – 0.05)	0.25

As with FSS, higher values of measures of physical disability (EDSS & BMI), affective disorders, and sleep reflect raw test scores, and so correspond to worse performance/higher disability. The opposite is true of tests of zT25FW, z9-HPT and cognitive performance where lower values reflect worse performance on the test.

[a] denotes the bias-corrected and accelerated bootstrap intervals

[b] expressed as proportion of intracranial volume

* denotes statistical significance after Bonferroni correction: Threshold $p = 0.004$

Abbreviation: EDSS=Expanded Disability Status Scale; zT25FW=Z score of Timed 25 Foot Walk test; BMI=Body Mass Index; 9-HPT= Z score of Nine Hole Peg Test; zPASAT=Z score of Paced Auditory Serial Addition Test; SDMT=Symbol Digit Modality Test; PHQ-9=Patient Heath Questionnaire-9; GAD-7=Generalized Anxiety Disorder-7 instrument; MSIS-29-SLEEP=Multiple Sclerosis Impact Scale-problems sleeping; WMH=Whole-brain white matter hyperintensity

Network Analyses

Relevant sample characteristics

The characteristics of participants included in network analysis at baseline and month 12 are shown in Table 4. Over one year's follow-up, we observed statistically significant deterioration in EDSS, increase in WMH, and decreases in cGM, BG and Thalamic volume. Statistically significant improvement was seen in walking speed, upper limb dexterity, and cognitive performance measured by SDMT and PASAT. We noted reductions in self-reported depression and anxiety. There was no statistically significant difference in median fatigue severity at baseline and month 12.

Table 4 Comparison of clinical and imaging variables between baseline and month 12

Participants eligible for network analysis

	Baseline (*n* = 322)	Month 12 (*n* = 323)	*P*[a]
FSS	34 (23.3 – 45.8)	35 (19 – 50)	0.556
BMI	23.30 (26.05 – 30.27)	23.20 (26.70 – 31.20)	0.062
EDSS	2 (1.5 – 3)	2.5 (2 – 3)	<.001
zT25FW	0.22 (-0.35 – 0.59)	0.43 (-0.04 – 0.74)	<.001
z9-HPT	0.15 (-0.58 – 0.73)	0.39 (-0.38 – 1.00)	<.001
PHQ-9	6 (3 – 11)	4 (1 – 8.5)	<.001
GAD-7	4 (2 – 7)	3 (1 – 7)	<.001
SDMT	60.5 (54 – 68)	62 (54 – 69)	0.007
zPASAT	0.32 (-0.16 – 0.73)	0.53 (-0.06 – 0.87)	<.001
WMH[b]	0.65 (0.39 – 0.99)	0.80 (0.59 – 1.20)	<.001
cGM[b]	37.94 (36.24 – 39.77)	37.74 (36.16 – 39.47)	<.001
BG[b]	1.29 (1.20 – 1.40)	1.26 (1.18 – 1.37)	<.001
THALA[b]	0.91 (0.83 – 0.97)	0.90 (0.82 – 0.96)	<.001

Data presented above are median (IQR). All Z-scores transformed such that higher values reflect better performance on the test relative to the baseline cohort.

[a] *p*-values obtained from Wilcoxon signed-rank tests (317 pairs)

[b] expressed as percentage of intracranial volume (%)

Abbreviation: FSS=Fatigue Severity Scale; EDSS=Expanded Disability Status Scale; zT25FW= Z score of Timed 25 Foot Walk test; BMI=Body Mass Index; z9-HPT= Z score of Nine Hole Peg Test; zPASAT=Z score of Paced Auditory Serial Addition Test; SDMT=Symbol Digit Modality Test; PHQ-9=Patient Heath Questionnaire-9; GAD-7=Generalized Anxiety Disorder-7 instrument; SLEEP = Multiple Sclerosis Impact Scale-problems sleeping; WMH=Whole-brain white matter hyperintensity volume; cGM=cortical grey matter volume; BG=basal ganglia volume; THALA=thalamus volume

Primary networks

Networks at baseline and month 12 (Fig. 1) demonstrated close inter-relationships both within and between variable groups. With a focus on fatigue in the networks at baseline and month 12, after adjusting for all other variables included in the network, fatigue severity was most strongly connected with PHQ-9 sum score (baseline: 0.34, 95% bootstrap intervals 0.26 – 0.41; month 12: 0.4, 95% bootstrap intervals 0.32 – 0.47) and EDSS (baseline: 0.18, 95% bootstrap intervals 0.08 – 0.27; month 12: 0.14, 95% bootstrap intervals 0.06 – 0.24) (Fig. 1). The strength of these two edges were significantly different from all other edges linked to FSS. Post-hoc analysis examining the links between FSS, PHQ-9 and EDSS did not show significant differences between baseline and month 12 (FSS-PHQ-9: p=0.29; FSS-EDSS: p=0.57). Weaker connections of FSS were also found with z score of T25FW, GAD-7 and SLEEP (Fig. 1). A weak connection between FSS and PASAT was shown at month 12 only.

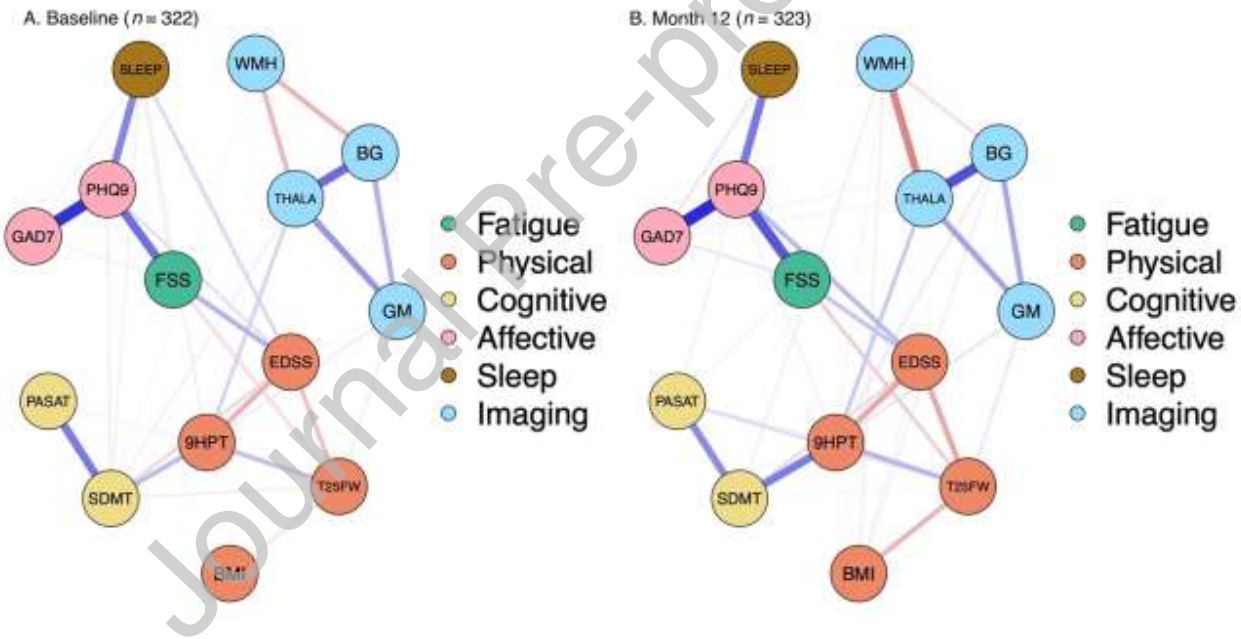

Figure 1 Primary network estimation. Primary networks depicting partial correlations between fatigue and variables of physical disability, affective disorders, cognitive performance, sleep quality, and structural brain imaging. Including PHQ-9 sum scores as measures of depression. (A: Baseline; B: Month 12) Blue edges indicate positive associations and red edges indicate negative associations. The width of the edges is proportional to the absolute value of the edge-weight. The colours of the nodes represent different domains. Abbreviation: FSS=Fatigue Severity Scale; EDSS=Expanded Disability Status Scale; zT25FW= Z score of Timed 25 Foot Walk test; BMI=Body Mass Index; z9-HPT= Z score of Nine Hole Peg Test; zPASAT=Z score of Paced Auditory Serial Addition Test; SDMT=Symbol Digit Modality Test;

PHQ-9=Patient Heath Questionnaire-9; GAD-7=Generalized Anxiety Disorder-7 instrument; SLEEP = Multiple Sclerosis Impact Scale-problems sleeping; WMH=Whole-brain white matter hyperintensity volume; cGM=cortical grey matter volume; BG=basal ganglia volume; THALA=thalamus volume

Secondary networks

In the secondary networks including subscores from individual PHQ-9 items (Fig. 2), fatigue severity was connected to EDSS and to the PHQ-9 item "tiredness". However, fatigue severity was also specifically connected to PHQ-9 items measuring appetite ("EAT"), subjective concentration deficits ("CONCE"), psychomotor problems ('MOVE"), and anhedonia ("PLEAS"). Results were consistent at baseline and month 12, with slight differences in very weak associations; for instance, the correlation between FSS and SLEEP was only evident in the secondary network at baseline with PHQ-9 subscores. In contrast, fatigue severity had no links to imaging variables either at baseline or month 12.

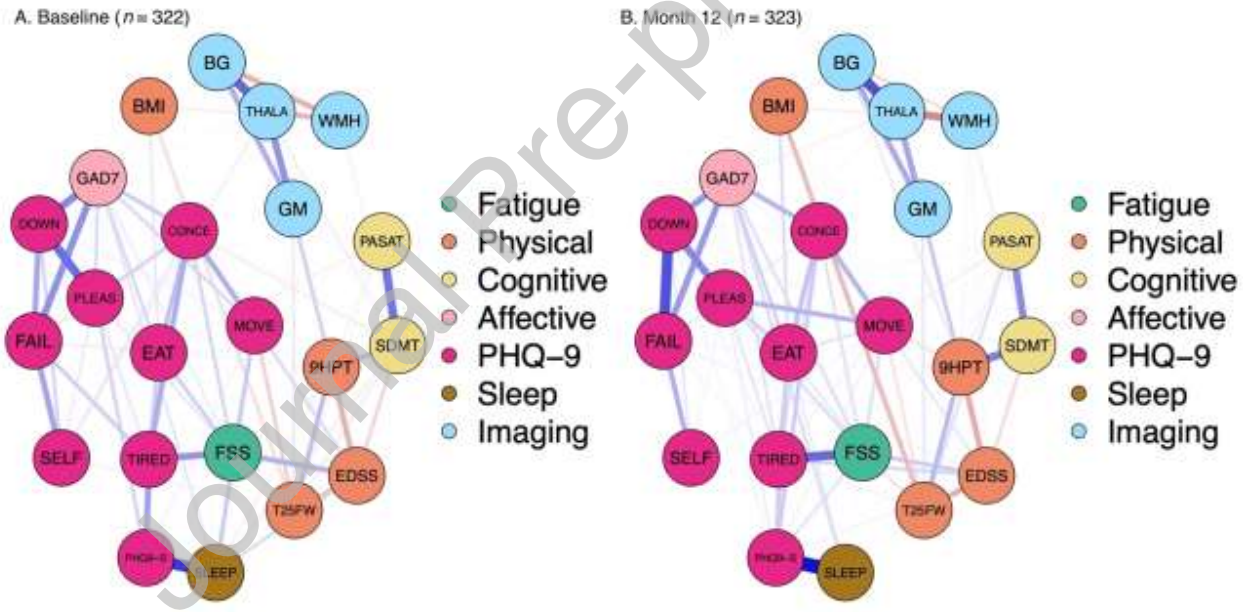

Figure 2 Secondary network estimation. Secondary networks depicting partial correlations between fatigue and variables of physical disability, affective disorders, cognitive performance, sleep quality, and structural brain imaging. Including individual item scores of PHQ-9 as measures of depression. (A: Baseline; B: Month 12) Blue edges indicate positive associations and red edges indicate negative associations. The width of the edges is proportional to the absolute value of the edge-weight. The colors of the nodes represent different domains. Abbreviation: FSS=Fatigue Severity Scale; EDSS=Expanded Disability Status Scale; zT25FW= Z Scores of Timed 25 Foot Walk test; BMI=Body Mass Index; z9-HPT=Z Scores of Nine Hole Peg Test; zPASAT= Z Scores of Paced Auditory Serial Addition Test;

SDMT=Symbol Digit Modality Test; GAD7=Generalized Anxiety Disorder-7 instrument; PHQ-9=Patient Heath Questionnaire-9: PLEAS= little interest or pleasure in doing things, DOWN= feeling down, depressed, or hopeless, PHQ9-S= trouble falling or staying asleep, or sleeping too much, TIRED= feeling tired or having little energy, EAT= poor appetite or overeating, FAIL= feeling bad about yourself - or that you are a failure or have let yourself or your family down, CONCE= trouble concentrating on things, such as reading the newspaper or watching television, MOVE= moving or speaking so slowly that other people could have noticed; or the opposite, being so fidgety or restless that you have been moving around a lot more than usual, SELF= thoughts that you would be better off dead, or of hurting yourself in some way; SLEEP = Multiple Sclerosis Impact Scale-Problems sleeping; WMH=Whole-brain white matter hyperintensity volume; cGM=cortical grey matter volume; BG=basal ganglia volume; THALA=thalamus volume

Centrality analysis and Sensitivity analyses

To identify the most central variable in the primary networks at baseline and month 12, only node strength was compared, since *CS*-coefficients of node strength were all above 0.5 across networks. In addition, although there were some negative correlations in the networks, strength and expected influence were highly correlated (r=0.7), so only node strength was displayed in the main result. In the networks with PHQ-9 sum scores, PHQ-9 had the highest strength (Baseline: 2.24, Month 12: 2.26) (Fig. 3). The differences of node strength between PHQ-9 and other variables were all statistically significant (Supplementary Fig. 3).

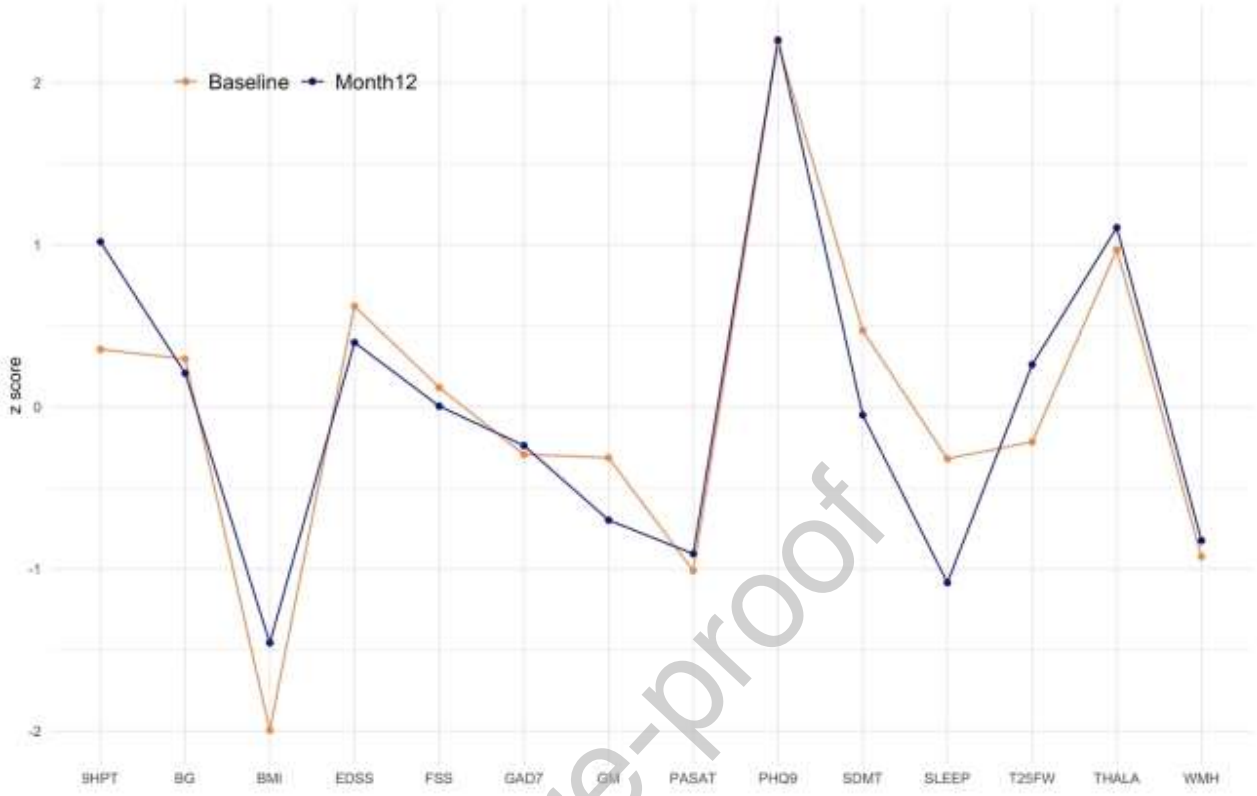

Figure 3 Centrality index ï node strength at baseline and month 12. Y-axis displays the z-scores of node strength. Abbreviation: FSS=Fatigue Severity Scale; EDSS=Expanded Disability Status Scale; zT25FW= Z score of Timed 25 Foot Walk test; BMI=Body Mass Index; z9-HPT= Z score of Nine Hole Peg Test; zPASAT=Z score of Paced Auditory Serial Addition Test; SDMT=Symbol Digit Modality Test; PHQ-9=Patient Heath Questionnaire-9; GAD-7=Generalized Anxiety Disorder-7 instrument; SLEEP = Multiple Sclerosis Impact Scale-problems sleeping; WMH=Whole-brain white matter hyperintensity volume; cGM=cortical grey matter volume; BG=basal ganglia volume; THALA=thalamus volume

In subgroup networks, fatigue severity was associated with EDSS and PHQ-9 in subgroups stratified on DMD initiation, and participant gender, consistent with the cohort as a whole. However, the robustness of networks with male participants (*n*=81) and those who never took DMD (*n*=88) was low (*CS*-coefficients < 0.25) due to small sample sizes.

Comparisons between networks associated with persistent versus remitted fatigue

Comparing baseline networks of those with persistent (*n*=106) versus remitted (*n*=48) fatigue (Fig. 4), NCT showed no significant difference in network structure (*p*=0.14) or global strength (4.89 vs 2.90, *p*=0.11). *CS*-coefficients of node strength were 0.519 and 0.208 among groups manifesting persistent and remitted fatigue, respectively, suggesting low stability within the network of those with remitted fatigue. PHQ-9 sum score had the highest expected influence in both networks (persistent: 1.39, remitted: 1.52), and highest node strength in the persistent-fatigue network (1.78); while 9-HPT had the highest node strength in the remitted-fatigue network (1.73).

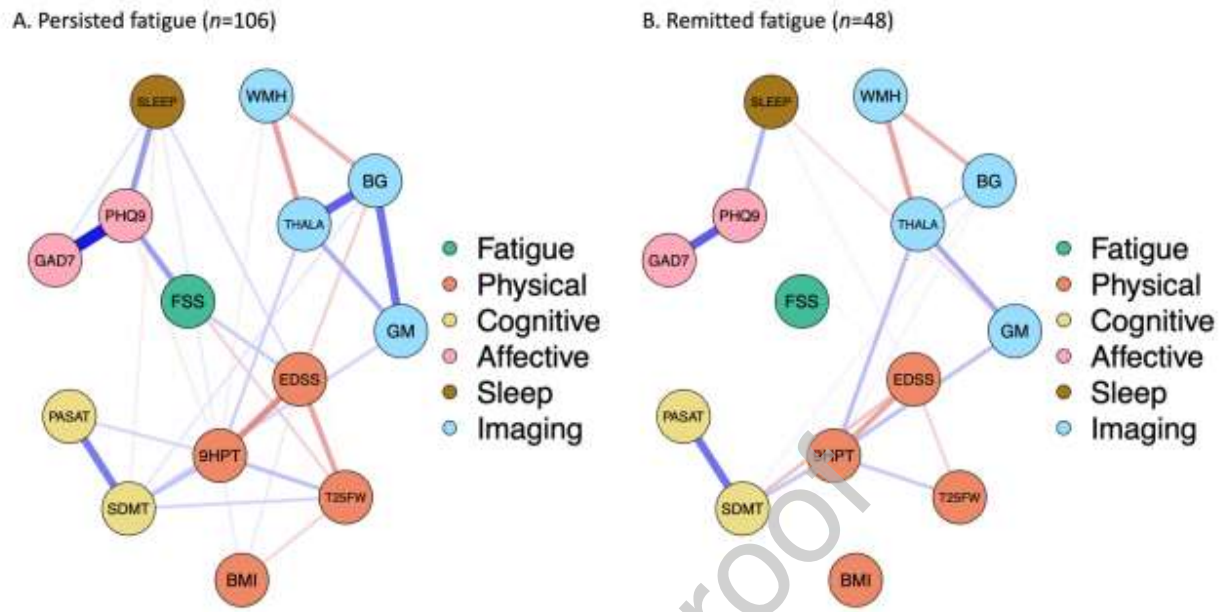

Figure 4 Baseline networks of participants who had persistent or remitted fatigue at one year follow up. Primary networks depicting partial correlations between fatigue and variables of physical disability, affective disorders, cognitive performance, sleep quality, and structural brain imaging. Including PHQ-9 sum scores as measures of depression. (A: Persistent fatigue; B: Remitted fatigue) Blue edges indicate positive associations and red edges indicate negative associations. The width of the edges is proportional to the absolute value of the edge-weight. The colours of the nodes represent different domains. Abbreviation: FSS=Fatigue Severity Scale; EDSS=Expanded Disability Status Scale; zT25FW= Z score of Timed 25 Foot Walk test; BMI=Body Mass Index; z9-HPT= Z score of Nine Hole Peg Test; zPASAT=Z score of Paced Auditory Serial Addition Test; SDMT=Symbol Digit Modality Test; PHQ-9=Patient Heath Questionnaire-9; GAD-7=Generalized Anxiety Disorder-7 instrument; SLEEP = Multiple Sclerosis Impact Scale-problems sleeping; WMH=Whole-brain white matter hyperintensity volume; cGM=cortical grey matter volume; BG=basal ganglia volume; THALA=thalamus volume

DISCUSSION

In this study, we describe the severity and associations of subjective fatigue in a large, nationally representative multi-centre cohort of people recently diagnosed with RRMS. Strikingly, clinically significant fatigue[20] was present in almost half of the cohort at baseline. In initial bivariate analyses, as expected from existing literature,[6–10,12] we confirmed statistically significant correlations between FSS and a wide range of physical, cognitive, and affective variables. We did not however confirm previously-reported[11] correlations with T2 lesion volume nor grey matter volumes. In network analyses accounting for both the included variables and their inter-relationships, fatigue severity was most strongly correlated with depression, and with physical disability measured by EDSS, both at baseline and month 12. Several specific depressive symptoms were reproducibly linked to fatigue severity even after statistical correction for an item assessing "tiredness" in the PHQ-9 instrument. Depression had the highest node strength at both baseline and month 12, indicating its strong potential to influence other variables in the networks.

Links to fatigue ï depression and physical disability

The link between fatigue and depression is bidirectional and challenging to disentangle. In pwMS, a number of mechanistic hypotheses have been proposed to explain the common co-occurrence of fatigue and depression, such as dysregulation of the hypothalamic-pituitary-adrenal axis.[13] In addition, inflammation and cytokine production in response to underlying pathology of MS have been hypothesised to play a role in the experience of both fatigue[30] and depression[13] in pwMS, perhaps mediated by effects on brain structures implicated in reward processing.[11,13,31] This hypothesis is in accordance with the finding of a significant relationship between fatigue severity and anhedonia in our cohort. However, studies of inflammatory biomarkers in serum and CSF have yielded inconsistent results, with no clear biochemical correlate of subjective fatigue in pwMS emerging in studies to date.[5–7] Another possible explanation may lie in negatively biased recall, or self-report. Because measurement of both fatigue and depression relies on participant self-report of symptoms, negatively biased cognitive processing[32] or recall might result in depressed individuals rating their symptoms or functioning more negatively. However, we argue that the subjective experience of fatigue is of importance since it is distinct from objective performance and may reflect metacognitive perception of lack of control over physiological states.[33]

We report that fatigue may be differentially linked to specific depressive symptoms.[34] Among nine core depressive symptoms,[21,23] and after controlling for an item measuring tiredness, we found four of these (anhedonia, subjective concentration deficits, subjectively altered speed of movement, and appetite) to be specifically related to subjective fatigue. While not previously reported in pwMS, studies of people with major depressive disorder have suggested that separate depressive symptoms may be linked to distinct biological mechanisms, risk factors, and subsequent impairment.[34] Interestingly, median fatigue severity did not vary to a statistically significant degree over the one-year study period, while a reduction in median depression sum score was observed. This finding highlights that fatigue severity is intricately linked to a range of variables, including, but not limited to, severity of depressive symptoms.

The link between fatigue and EDSS may also be bidirectional. It has been hypothesised both that fatigue may occur as a consequence of disease severity,[35] and that, conversely, fatigue-related fear and avoidance might lead to increased

disease severity and physical disability.[36] A large retrospective cohort study[37] found that fatigue at study enrolment was a significant predictor of later sustained EDSS worsening. However, such a link has not been confirmed by other literature.[6,7]

Absent links to fatigue in networks

The discrepancy between the results of bivariate correlations and network analyses could have several possible explanations. First, some weak links might be eliminated from the network estimation due to a sparse (conservative) network structure imposed in our study. Secondly, this may reflect that some apparent links in bivariate correlations are in fact mediated by other variables. For instance, the bivariate correlation between fatigue and BMI may be accounted for by common links with walking speed.[38] Furthermore, in the secondary networks with PHQ-9 subscores (which included an item assessing subjective difficulty in concentrating), fatigue severity was not linked to objective cognitive performance measured by SDMT or PASAT, whilst it was connected with subjective difficulty in concentrating. These findings echoed the dissociation between objective and subjective estimates of cognitive performance previously described in pwMS.[10]

Our study did not find an association between fatigue severity and structural brain imaging variables. A recent review[11] described that associations between fatigue and global brain MRI structural variables, including white matter lesion volume and grey matter volume, were not significant after controlling for important confounding variables, such as EDSS.[7] The absence of a relationship between fatigue severity, and volumes of basal ganglia and thalamus in our findings was however different from some previous studies.[11] In particular, a recent literature review[11] has concluded that macro/microstructural and functional changes involving a cortico-striato-thalamo-cortical loop might contribute to the pathogenesis of fatigue in pwMS. Reasons for contrasting results in our study, in comparison to previous publications, could include methodological considerations such as the disease duration and disease course of enrolled patients.[7] Furthermore, brain structural changes related to fatigue in early RRMS might only be apparent at a microstructural or functional level rather than at the macrostructural levels examined in our study.

Limitations and strengths

There are some limitations in our study. Firstly, we measured fatigue severity using FSS, which despite validation for use in pwMS, has been suggested to preferentially focus on physical aspects of fatigue. However, we note a strong association between fatigue severity as described by FSS, and other correlates of fatigue, particularly depressive symptomatology, in the current study. Secondly, causality cannot be inferred from cross-sectional analyses included in this study. Future studies including data collection at multiple time points to build longitudinal networks are needed. Interpretation of changes in cognitive measures over the period of the study, while not key to our analyses, may be influenced by practice effects. Lastly, due to the availability of data in this cohort, we could not include all variables that could possibly link to fatigue, such as pain, and some serum and CSF biomarkers (such as IL-6).[5–7] Future studies that include these measures might further mechanistic understanding.

Nevertheless, this study has four major strengths. First, the data is drawn from the FutureMS cohort study, which showed geographically and demographically representative coverage of Scottish patients diagnosed with RRMS.[18] Secondly,

none of the study participants had received DMDs at study baseline, which allowed us to examine the associations of interest without effects from DMDs at study baseline, and to contrast findings with those one year later, when 72.7% had commenced disease modifying therapy. Also, only two participants used Amantadine for fatigue, and thus our results were unlikely to be affected by medication for MS-related fatigue. Thirdly, in light of the deep phenotyping in the FutureMS cohort, we were able to employ a wide range of relevant clinical, neuropsychological and imaging phenotyping which allows a unique opportunity to examine the associations of fatigue with a broad range of relevant variables. Lastly, use of a multivariate network approach allows for assessing the relationships between fatigue, clinical measures, and brain structure assessed by MRI, after correction for all other variables in the network. This method is well grounded in psychological research, but relatively new in the area of neurological diseases.

Implications for future studies and clinical practice

From a clinical perspective, the strong links identified between subjective fatigue and depression, particularly specific depressive symptoms, may assist focussed recognition and assessment of comorbid fatigue and depression. Besides the beneficial outcomes that have been shown in interventions simultaneously targeting fatigue and depression,[39] a recent study found that early intervention in reducing depressive symptoms was associated with overall reduction in fatigue severity, and vice versa.[40] The findings in our study also suggested that a focus on identification and modification of depression and physical disability may be particularly important in clinical treatment of subjective fatigue. Furthermore, post-hoc analysis showed that the links of fatigue severity were not significantly different between baseline and month 12, suggesting that the underlying contributory factors of subjective fatigue remained stable in this timeframe. However, longer-duration longitudinal studies are needed to determine whether there is a shift in correlations of fatigue severity throughout the disease course.

From a research perspective, data-driven multivariate approaches such as network analysis could be especially useful in guiding selection of the most important research and clinical targets in MS-related fatigue, particularly where relevant variables are known to be inter-related. The stability of estimated networks can furthermore usefully be quantified, along with strength and influence of network nodes. We did not find a significant difference between networks among those with persistent and remitted fatigue. Considering stability of subgroup networks, however, future studies are needed to investigate any links between network structure and clinical outcomes.

Conclusion

Our analysis suggests that fatigue is preferentially linked to specific key depressive symptoms in early RRMS, as well as to physical disability measured by EDSS. Network analyses did not support significant associations between fatigue severity and objective cognitive performance, or structural brain imaging variables. Our findings that subjective fatigue in early RRMS is preferentially linked to specific key depressive symptoms, may have mechanistic as well as clinical relevance.

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CRediT author contribution statement:

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Agniete Kampaite	Formal analysis, Writing - review + editing
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Adam D. Waldman	Funding acquisition, Writing - review + editing
Siddharthan Chandran	Funding acquisition, Methodology, Writing - review + editing
Peter Foley	Conceptualization, Formal analysis, Methodology, Writing - review + editing

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