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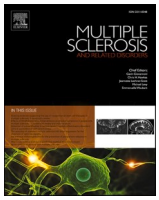

Exploring the relation between reserve and fatigue in multiple sclerosis

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ABSTRACT

Introduction: Intellectual enrichment and brain reserve modulate the expression of cognitive and motor disability in multiple sclerosis (MS). Their association with fatigue, one of the most debilitating and common symptoms of MS, has never been explored.

Materials and Methods: Forty-eight MS patients underwent clinical and MRI examination at baseline and after 1 year. Physical and cognitive MS-related fatigue were evaluated via Modified Fatigue Impact subscales (MFIS-P and MFIS-C). Differences in reserve indexes between fatigued and non-fatigued patients were tested. The relationship between clinico-demographic features, global brain structural damage, indexes of reserve (age-adjusted intracranial volume and cognitive reserve index) and fatigue were tested via correlations and hierarchical linear/binary logistic regression, to predict MFIS-P and MFIS-C (at baseline) or new-onset fatigue and meaningful worsening in MFIS (at follow-up).

Results: At baseline, although a significant difference was identified for cognitive reserve questionnaire between fatigued and non-fatigued patients (18.19 ± 4.76 versus 15.15 ± 3.56, $p = 0.015$), only depression accounted for significant variance in MFIS-P and MFIS-C (R^2=0.248, $p = 0.002$; R^2=0.252, p<0.001). MFIS-T, MFIS-P and MFIS-C changes over time were associated to depression changes over time ($r = 0.56$, $r = 0.55$, and $r = 0.57$, respectively; all p<0.001). Indexes of reserve did not differ between non-fatigued patients and patients developing new-onset fatigue at follow-up. None of the baseline features was able to predict the new-onset fatigue or meaningful worsening in MFIS at follow-up.

Conclusions: Among the explored features, only depression was strongly associated to both physical and cognitive fatigue. Intellectual enrichment and brain reserve did not seem to affect fatigue symptoms in MS patients.

1. Introduction

Fatigue is among the most debilitating and common symptoms in multiple sclerosis (MS) (Strober et al., 2020). Although fatigue pathophysiology remains unclear, there is a combined contribution of both brain structural and functional changes, as well as individual features. (Adibi et al., 2022; Capone et al., 2019; Palotai and Guttmann, 2020; Palotai et al., 2019) Among these, previous studies explored the influence of demographic variables on fatigue, (Bensing et al., 1999; Engberg et al., 2017; Watt et al., 2000) reporting that female patients

Abbreviations: MS, multiple sclerosis; MFIS, modified fatigue impact subscales; MLBG, maximal lifetime brain growth; EDSS, expanded disability status scale; SDMT, symbol digit modalities test; BDI-II, Beck depression inventory-II; CRI, cognitive reserve index; NBV, normalized brain volume; PMS, progressive MS; RR, relapsing-remitting; TLV, total demyelinating lesion volume; DMTs, disease modifying therapies.

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experienced greater fatigue, (Bensing et al., 1999; Engberg et al., 2017; Watt et al., 2000) while the relation with age and education appeared controversial, with conflicting evidence showing more pronounced fatigue in case of both lower (Engberg et al., 2017; Watt et al., 2000) and higher (Bensing et al., 1999) education or older (Watt et al., 2000) and younger (Bensing et al., 1999; Engberg et al., 2017) age.

More recently, the role of sex, age and education on subjective fatigue has been highlighted during the development of norms for the widely used Modified Fatigue Impact Scale (MFIS). (Strober et al., 2020) Whereas the sex did not seem to exert a significant effect, the relationship with age appeared to be non-linear and influenced by other social and medical factors, since younger and older age related to greater cognitive and physical fatigue, respectively. (Strober et al., 2020)

Nonetheless, the fact that individuals with higher education consistently reported less fatigue (Strober et al., 2020) suggests that education might play a protective role towards fatigue.

The concept of education as protective factor is not new in MS. The existence of a "cognitive reserve" strictly related to intellectual enrichment was firstly formulated by Stern. (Stern, 2002) In contrast to the passive model of "brain reserve", (Katzman, 1993) based on the idea that neuronal count or brain size could prevent clinical impairment until the reaching of a fixed threshold, (Satz, 1993) Stern hypothesized that the different trajectories in cognitive decline experienced by Alzheimer's disease patients, as well as the lack of clinical expression in some elders who meet Alzheimer's disease pathology criteria on death, may be influenced by the individual baseline performance in cognitive processing. (Stern, 2009)

A similar effect has also been observed in MS, with several lines of evidence showing that higher educational level along with more premorbid cognitive leisure activities and higher occupational attainment lessened the impact of disease on cognition. (Ghaffar et al., 2012; Ifantopoulou et al., 2019; Rocca et al., 2019; Sumowski and Leavitt, 2013;

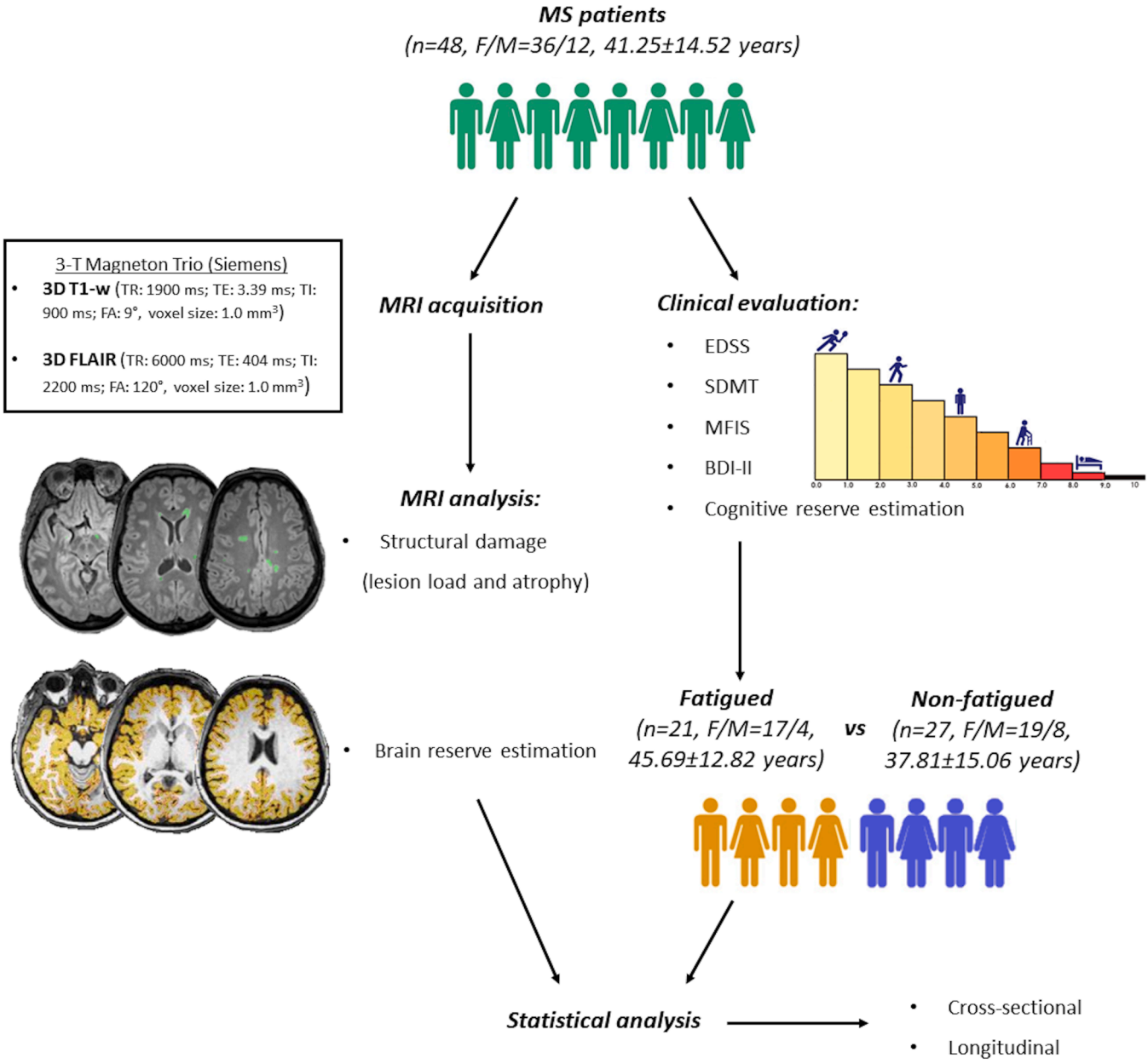

Fig. 1. Graphical representation of the study design.
Abbreviations: MS=Multiple Sclerosis; EDSS=Expanded Disability Status Scale; SMDT=Symbol Digit Modalities Test; MFIS=Modified Fatigue Impact Scale; BDI-II=Beck Depression Inventory-II; MRI=Magnetic Resonance Imaging; TR=Repetition Time; TE=Echo Time; TI=Inversion Time; FA=Flip Angle.

Sumowski et al., 2013; Modica et al., 2015; G Santangelo et al., 2019; G Santangelo et al., 2019)

Indeed, higher cognitive reserve appeared to have a protective role against verbal learning and memory impairment, as well as information processing inefficiency, (JF Sumowski et al., 2009) moderating the effect of brain atrophy (Ifantopoulou et al., 2019; Rocca et al., 2019; Modica et al., 2015; JF Sumowski et al., 2009; JF Sumowski et al., 2010) and white matter lesion load. (Pinter et al., 2014)

It is not clear whether cognitive reserve could influence longitudinal cognitive changes, with contrasting findings pointing towards both the presence (Modica et al., 2015; Sumowski et al., 2014; Benedict et al., 2010) or the lack (Rocca et al., 2019; Amato et al., 2013; Barbu et al., 2018) of mitigating effects over time, leading the way to the hypothesis that the protection may decrease with disease progression. (Rocca et al., 2019)

On the other hand, also brain reserve, intended as maximal lifetime brain growth (MLBG), has been defined as a protective factor against cognitive decline, (Ifantopoulou et al., 2019; Sumowski et al., 2013; Sumowski et al., 2014) although there is opposing evidence suggesting an effect limited to cognitive inefficiency (Sumowski et al., 2013) or memory impairment (Ifantopoulou et al., 2019). Furthermore, it has been observed that higher brain reserve may act longitudinally, not only counteracting cognitive decline, (Sumowski et al., 2014) but also physical disability progression. (Sumowski et al., 2016)

Given this background, we investigated whether, similarly to what has been described for cognitive and motor disability expression and progression, intellectual enrichment and brain reserve could affect physical and cognitive fatigue symptoms in MS patients, while accounting for clinico-demographic features and global brain structural damage.

2. Materials and methods

A graphical representation of the study design is shown in Fig. 1.

2.1. Study population

Forty-eight MS patients were prospectively enrolled at the Multiple Sclerosis Clinical Care & Research center of the Federico II University. Study inclusion criteria were: a) clinically definite MS according to the revised McDonald criteria, (Thompson et al., 2018) b) Expanded Disability Status Scale (EDSS) < 7, c) age between 18 and 60 years. Exclusion criteria were: a) critical medical, hematologic, renal, or hepatic conditions, b) pregnancy, c) contraindications to MRI, d) head injury, stroke, seizures, psychiatric disorders or substance abuse.

All subjects underwent clinical examination and MRI acquisition, on the same day, at baseline and after 1 year (mean follow-up 14.31 ± 1.84 months). Written informed consent was obtained from all participants before the beginning of the study procedures, according to the Declaration of Helsinki. The protocol was approved by the Carlo Romano Institutional Review Board (11/20).

2.2. Clinical evaluation

Fatigue was assessed via MFIS. (Larson, 2013)

All patients were classified as fatigued or non-fatigued according to normative data. (Strober et al., 2020) Following published recommendation suggesting the application of MFIS as a multidimensional index, (Larson, 2013) in addition to MFIS total score (MFIS-T), physical and cognitive MS-related fatigue were evaluated with the relative MFIS subscales (MFIS-P and MFIS-C). The psychosocial subscale was not considered in reason of its low internal consistency. (Kos et al., 2005) A 4 point worsening in MFIS-T was considered as cut-off to define meaningful change over time. (Rooney et al., 2019) Physical and cognitive disability were evaluated with the EDSS and the Symbol Digit Modalities Test (SDMT). SDMT raw scores were converted to age, sex and education adjusted z-scores according to published norms. (Goretti et al., 2014) The presence of depressive symptoms was assessed via the Beck Depression Inventory (BDI-II). (Beck et al., 1996)

2.3. Reserve estimates

A cognitive reserve index (CRI) was estimated by combining educational level (years of education), premorbid IQ (estimated through the Italian version of the National Adult Reading Test) (Colombo et al., 2002) and the participation in cognitive leisure activities during the patients' early 20 s before the onset of MS. (JF Sumowski et al., 2010) The scores for each variable were transformed into z-scores, and the mean value of the three z-scores was calculated as previously described. (Amato et al., 2013) Applying this index, we followed the same methodology previously applied in MS research, building on previous knowledge in the field by applying the same constructs for the estimation of reserve. (Rocca et al., 2019; Amato et al., 2013; Conti et al., 2021)

Of note, the CRI questionnaire is based on self-reported information about patients' early 20 s, based on the assumption that this timeframe represents a pre-morbid stage of the disease. (JF Sumowski et al., 2010) As this might not be the case in a young-adult onset disease such as MS, prior to any further statistical analysis, differences in CRI questionnaire between early (age at onset < 24.9 years) and late (≥ 25.0 years) onset patients were tested. MLBG was expressed as the reciprocal of the SIENAX VSF (so that larger values correspond to larger intracranial volume-ICV) regression-adjusted for sex. (Sumowski et al., 2016)

2.4. MRI acquisition and analysis

Exams were acquired on the same 3-T system (Magnetom Trio, Siemens Healthineers) and included a 3D T1-weighted sequence (TR = 1900 ms; TE = 3.39 ms; TI = 900 ms; FA = 9°; voxel size = 1.0 mm^3) for volumetric analyses and a 3D FLAIR sequence (TR = 6000 ms; TE = 404 ms; TI = 2200 ms; FA = 120°; voxel size = 1.0 mm^3) for the quantification of total demyelinating lesion volume (TLV).

In order to assess the role of global brain damage and whether cognitive and brain reserve could mitigate the impact of structural brain damage on fatigue, we estimated TLV (semiautomated segmentation in JIM 8.0, Xinapse Systems, Northants, UK) and normalized brain volume (NBV - SIENAX, FMRIB center, Oxford, UK). Percentage brain volume change was computed with SIENA. New lesions were defined as new FLAIR hyperintensities, visible in at least three consecutive slices (i.e., length of at least 3 mm) and two perpendicular planes, excluding poorly visible or confluent lesions.

2.5. Statistical analysis

2.5.1. Cross-sectional

After testing for each variable distribution, between-group comparisons were run with Chi-square, Mann-Whitney test or T-test, as appropriate. Comparison between early and late onset patients were tested both via T-test and ANCOVA accounting for age, sex, disease duration and baseline EDSS. Bivariate correlations were run between MFIS-T, MFIS-P and MFIS-C and all variables potentially affecting fatigue (age, sex, phenotype, disease duration, EDSS, SDMT-z, BDI-II total score, log transformed TLV, NBV, MLBG, CRI). Exploratory sub-analyses of reserve effect were conducted comparing MBLG and CRI between fatigued and non-fatigued patients, and testing correlations between brain structural damage and fatigue according to MLBG and CRI median split.

Variables surviving this preliminary screening were entered in a hierarchical linear regression, to predict MFIS-T, MFIS-P and MFIS-C, with clinico-demographic features in block 1, markers of brain structural damage in block 2 and indexes of reserve in block 3.

2.5.2. Longitudinal

To further assess the relationship between fatigue, disability and brain damage over time, bivariate correlations were run between the respective percentage changes ($\%_c$). An independent t-test investigated differences in MFIS-T, MFIS-P and MFIS-C change over time between patients with larger and smaller MLBG/CRI.

To assess the impact of reserve on the development of clinically meaningful fatigue, after selecting patients that were non-fatigued at baseline, we compared MLBG, CRI and its subcomponents between patients that remained non-fatigued at follow-up and patients showing new-onset fatigue, accounting for the interval occurred between baseline and follow-up visits (ANCOVA analysis).

Finally, to explore the impact of baseline variables on fatigue changes over time a binary logistic regression was run, to predict new-onset fatigue and meaningful worsening in MFIS-T at follow-up, with clinico-demographic features in block 1, markers of brain structural damage in block 2 and indexes of reserve in block 3.

3. Results

3.1. Cross-sectional

Demographic and clinical features of the study population are reported in Table 1.

Exploration of differences in the CRI questionnaire between early and late onset patients did not highlight any significant difference. Further analyses were therefore performed on the entire population.

Table 1
Demographic and clinical features of the study population.

	MS patients ($n = 48$)	MS patients with fatigue ($n = 21$)	MS patients without fatigue ($n = 27$)	p-value
Age (years ± SD)	41.25 ±14.52	45.69±12.82	37.81±15.06	0.062
Sex (F/M)	36/12	17/4	19/8	0.510
Disease duration (years ± SD)	10.47 ±8.60	12.79±8.69	8.67±8.24	0.099
Phenotype (RR/PMS)	31/17	13/8	18/9	0.769
EDSS (median, range)	3.5 (0–7)	3.5 (1–7)	2.5 (0–7)	0.063
SDMT z-score (average ± SD)	−1.58 ±1.43	−1.56±1.54	−1.60±1.38	0.926
BDI-II (average ± SD)	8.85±7.14	12.10±7.08	6.33±6.21	0.004
BDI-II (minimal/mild/moderate/severe)	37/4/7/0	13/3/5/0	24/1/2/0	0.090
MFIS-T (average ± SD)	32.48 ±18.81	49.33±14.43	19.37±8.44	<0.001
MFIS-P (average ± SD)	16.10 ±8.83	23.67±6.74	10.22±4.89	<0.001
MFIS-C (average ± SD)	13.96 ±9.62	22.10±7.24	7.63±5.64	<0.001
DMTs (injectables/oral/infusion/none)	8/15/21/4	1/9/10/1	7/6/11/3	0.348
MLBG (cm^3 ± SD)	1084.94 ±101.32	1051.49 ±957.81	1110.95 ±99.46	0.197
CRI (median, range)	0.02 (−1.90, 1.21)	0.38 (−1.90, 1.21)	−0.29 (−1.66, 1.04)	0.063

Demographic and clinical features of the subjects included in this study.
Abbreviations: MS=Multiple Sclerosis; SD=Standard Deviation; RR=Relapsing-Remitting; PMS=Progressive MS; EDSS=Expanded Disability Status Scale; SMDT=Symbol Digit Modalities Test; BDI-II=Beck Depression Inventory-II; MFIS-*T*=Modified Fatigue Impact Scale-Total; MFIS-*P*= Modified Fatigue Impact Scale-Physical; MFIS-C=Modified Fatigue Impact Scale-Cognitive; DMTs=Disease Modifying Therapies; MLBG=Maximal Lifetime Brain Growth; CRI=Cognitive Reserve Index.

At baseline, 44% (21/48) of patients were fatigued. Comparing fatigued and non-fatigued patients, no differences were detected for MLBG, while a trend was identified for CRI, with higher CRI in fatigued patients. When comparing individual components of the CRI, a significant difference was identified for CR questionnaire (18.19 ± 4.76 in fatigued patients versus 15.15 ± 3.56 in non-fatigued patients, $p = 0.015$). MFIS-T was correlated with age, EDSS and BDI-II (r ranging from 0.03 to 0.001). Dividing our sample according to median MLBG, NBV and TLV were not associated with MFIS-T among subjects with lower brain reserve ($r = -0.27$, $p = 0.191$ and $r = -0.05$, $p = 0.829$ respectively) nor among those with higher reserve ($r = -0.18$, $p = 0.411$ and $r = 0.20$, $p = 0.350$ respectively). The full regression model accounted for 31% of the variance in MFIS-T ($p<0.001$). The only variable accounting for significant variance was BDI-II (Beta=0.545, $p<0.001$).

MFIS-P was correlated with age, EDSS, BDI-II, NBV (r ranging from 0.03 to 0.001). Dividing our sample according to median MLBG, NBV and TLV were not associated with MFIS-P among subjects with lower brain reserve ($r = -0.32$, $p = 0.124$ and $r = -0.005$, $p = 0.980$) nor among those with higher reserve ($r = -0.28$, $p = 0.177$ and $r = 0.22$, $p = 0.311$). The full regression model accounted for 25% of the variance in MFIS-P ($p = 0.002$). The only variable accounting for significant variance was BDI-II (Beta=0.417, $p = 0.006$).

MFIS-C was correlated with BDI-II ($p<0.001$). Dividing our sample according to CRI median split, NBV and TLV were not associated with MFIS-C among subjects with lower cognitive reserve ($r = -0.11$, $p = 0.610$ and $r = 0.14$, $p = 0.520$) nor among those with higher reserve ($r = -0.19$, $p = 0.376$ and $r = -0.09$, $p = 0.688$). The regression model accounted for 25% of the variance in MFIS-C ($p<0.001$), with BDI-II as significant predictor (Beta=0.517, $p<0.001$).

3.2. Longitudinal

At follow-up, 38 patients (20 non-fatigued, 18 fatigued) showed stability in self-reported fatigue, 3 fatigued patients at baseline did not meet anymore the cut-off for fatigue clinical meaningfulness at follow-up, while 7 non-fatigued patients at baseline met the criteria for clinically meaningful fatigue at follow-up. CRI and MLBG did not differ between non-fatigued patients and patients developing new-onset fatigue at follow-up. Additionally, MFIS-T, MFIS-P and MFIS-C changes over time did not differ between patients with higher and lower MLBG/CRI values. MFIS-T, MFIS-P and MFIS-C changes over time were associated to BDI changes over time ($r = 0.56$, $r = 0.55$, and $r = 0.57$, respectively; all $p<0.001$). None of the baseline features was associated to MFIS-T, MFIS-P and MFIS-C changes over time nor was able to predict the new-onset fatigue (i.e., onset of fatigue at follow-up in patients that did not report fatigue at baseline) or meaningful worsening in MFIS-T (i.e., 4 point worsening) at follow-up.

4. Discussion

Despite the high prevalence of fatigue in MS, its pathological substrates are not completely understood. (Adibi et al., 2022; Manjaly et al., 2019; Enoka et al., 2021; Braley and Chervin, 2010)

Our findings, in agreement with previous works, underline how fatigue affects MS patients regardless of demographic features or clinical phenotypes (Strober et al., 2020; Rooney et al., 2019; Marchesi et al., 2020), as well as its strong association to depressive symptoms. For the first time, we report that neither cognitive nor brain reserve, which have been widely linked to MS presentation and progression, (Ifantopoulou et al., 2019; Sumowski and Leavitt, 2013; Modica et al., 2015; Sumowski et al., 2014; Sumowski et al., 2016) are associated with fatigue or fatigue changes over time, nor modulate the impact of brain structural damage on fatigue. Indeed, in agreement with previous data suggesting the relevance of structure/circuit-specific damage, (Palotai and Guttmann, 2020; Manjaly et al., 2019) no relationship between global brain damage (TLV and brain volumes) and fatigue was disclosed

in our population once the impact of depressive symptoms was taken into account.

Specifically, depressive symptoms were the only feature to differ between fatigued and non-fatigued patients, and were significantly related not only to global fatigue, but also to physical and cognitive fatigue.

Indeed, the link between depression and fatigue seems hard to disentangle, with both symptoms jointly affecting more than half of MS patients, (Tarasiuk et al., 2021) and possibly sharing a common pathophysiology involving altered reward processing due to mesocorticolimbic pathways dysfunction. (Heitmann et al., 2022)

Although this hypothesis is an intriguing one, we should also consider that fatigued patients are more prone to develop psychological distress, lowered sense of self-worth, feelings of sorrow and lowered positive affect, (Strober et al., 2020) feeding a vicious cycle that further worsens the feeling of fatigue. Finally, regardless from the fact that fatigue and depression might share or not share the same pathophysiological mechanisms, their clinical manifestations partly overlap, and the instruments at our disposal to measure fatigue lack the specificity to disentangle the two conditions, with MFIS score being affected by the concomitant presence of depressive symptoms, as suggested by our findings.

Our longitudinal observations support the dynamicity of the state of fatigue, (Enoka et al., 2021) and suggest that the driving pathophysiological mechanism acts like a predisposing background, that leads to a clinical meaningful manifestation of fatigue as a function of the patient's psychological state. (Enoka et al., 2021)

Despite the lack of association between fatigue and reserve, when comparing MS patients with and without fatigue, we observed a trend for age and, interestingly, CRI. While the notion that older patients experience more fatigue could appear intuitive, it is tempting to speculate that the lack of energy could act more heavily on the psychological state of patients who were used to spend more time in leisure activities, with possible repercussions on fatigue perception. On the other hand, given the subjective nature of the CR questionnaire, which refers to patients' early 20 s, (JF Sumowski et al., 2010) we cannot exclude that patients who experience fatigue may unconsciously focus on positive aspects of the past, thus obtaining higher scores at the questionnaire. Although no difference in terms of engagement in leisure activities emerged between early and late onset patients in the current analysis, further studies are needed to clarify these aspects.

The present study does not come without limitations. As we assessed fatigue exclusively via MFIS, it could be of interest trying to replicate our results with other measures of fatigue and fatigability, separately assessing the possible role of the subjective and objective components of this latter. (Enoka et al., 2021) Moreover, the present study has to be considered exploratory, as no formal power analysis was conducted and the final sample size was relatively small. Further studies with larger sample sizes are warranted. In particular, results of the longitudinal analysis should be considered exploratory, as only 7 patients developed new-onset fatigue over the follow-up. Additionally, we cannot exclude that the lack of association between reserve indexes and fatigue modification over time might be due to the short observation period. In this light, future studies should build on these preliminary data over longer follow-up. Finally, we used rather crude biomarkers of structural damage, not suited for the exploration of pathophysiological mechanisms sustaining fatigue, which was beyond the aim of the present work. Future studies should focus on the relationship between structural and functional abnormalities of specific brain areas and networks and fatigue expression and dynamic changes over time.

Despite these limitations, our study sheds light on a complex and multifactorial phenomenon such as fatigue in MS, giving further evidence of its strong correlation with depressive symptoms and its independency from global brain damage, intellectual enrichment and brain reserve.

Ethics approval statement

The study was conducted in compliance with ethical standards and approved by the Carlo Romano Institutional Review Board (11/20).

Patient consent statement

Written informed consent was obtained from all subjects according to the Declaration of Helsinki.

Data availability

All data generated during the current study can be made available upon reasonable request from the corresponding author.

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CRediT authorship contribution statement

Mario Tranfa: Conceptualization, Investigation, Formal analysis, Writing – original draft. **Valentina Virginia Iuzzolino:** Conceptualization, Data curation, Formal analysis. **Pierpaolo Perrella:** Data curation, Investigation. **Antonio Carotenuto:** Data curation, Writing – review & editing. **Giuseppe Pontillo:** Data curation, Writing – review & editing. **Marcello Moccia:** Data curation, Writing – review & editing. **Sirio Cocozza:** Data curation, Writing – review & editing. **Andrea Elefante:** Supervision, Writing – review & editing. **Roberta Lanzillo:** Data curation, Writing – review & editing. **Arturo Brunetti:** Supervision, Writing – review & editing. **Vincenzo Brescia Morra:** Conceptualization, Supervision, Writing – review & editing. **Maria Petracca:** Conceptualization, Methodology, Supervision, Writing – review & editing.

Declaration of Competing Interest

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