

ORIGINAL ARTICLE

Contribution of sleep disturbances to fatigue in multiple sclerosis: a prospective study using clinical and polysomnographic parameters

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Abstract

Background and purpose: Fatigue is amongst the most frequent and disabling symptoms of multiple sclerosis and a close relation between fatigue and sleep quality has been hypothesized. In this study the contribution of sleep disturbances measured by clinical and polysomnographic parameters to fatigue in multiple sclerosis was investigated.

Methods: This was a prospective instrumental study performed at the Neurocenter of Southern Switzerland. Demographic data and clinical characteristics including fatigue (as measured by the modified fatigue impact scale [MFIS]), neurological disability, psychiatric symptoms, medications and sleep-related variables were collected at baseline visit and by a home full-night polysomnography. The associations between sleep-related variables and the MFIS were tested using partial correlations adjusted by demographic and sleep-unrelated clinical factors.

Results: Seventy-six patients were included in the study, of whom 53 (69.7%) had an MFIS ≥ 38 points (median 49.5, interquartile range 31.0–62.0). MFIS scores were positively associated with age, neurological disability, symptoms of depression and anxiety, and use of benzodiazepines and selective serotonin reuptake inhibitors. When adjusting for these variables, the presence of restless legs syndrome (RLS) ($r = 0.37$, $p = 0.005$) and periodic leg movements index ($r = -0.33$, $p = 0.014$) were associated with MFIS. Excessive daytime sleepiness, total sleep time, sleep efficiency, respiratory disturbances, and percentage of time spent in the different sleep stages (N1, N2, N3 and rapid eye movement) were not associated with fatigue.

Conclusions: Multiple sclerosis patients with a diagnosis of RLS had significantly higher global fatigue scores compared to those without RLS. Future studies should investigate whether medical treatment of RLS can ameliorate fatigue.

KEYWORDS

fatigue, multiple sclerosis, polysomnography, sleep disorders

Gianna C Riccitelli, Giulio Disanto, Claudio Gobbi and Chiara Zecca made equal contributions.

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INTRODUCTION

Multiple sclerosis (MS) is a chronic immune-mediated disease affecting the central nervous system, with widespread demyelination and axonal loss [1]. Fatigue is highly prevalent in MS, affecting up to 90% of patients [2] and amongst the earliest and most disabling symptoms [3]. It is not always easy for patients to describe "fatigue", which is a subjective feeling of exhaustion associated with experience of lack of mental and physical energy. Several factors are known to be associated with fatigue in MS, including the extent of demyelination and axonal loss (i.e., "primary fatigue"), the presence of cognitive impairment, pain, spasticity, gait disorders, medications and depression [3]. Together with other stressful events like infection, fever and intense exercise, sleep disturbance is reported by MS patients amongst those situations with greatest impact on fatigue [4]. Indeed, many patients with MS report sleep disorders [5], with prevalence estimates ranging between 25% and 54% [6], suggesting a close relation between fatigue, sleep quality and excessive daytime sleepiness (EDS) [7,8].

Attarian et al. found an increased frequency of sleep disturbances, as measured by actigraphy, in fatigued than in non-fatigued MS patients [9]. Additionally, associations between poorer subjective sleep quality and greater fatigue have been reported independent of depression [10]. However, the majority of studies assessing sleep in MS patients using subjective scales might fail to distinguish EDS, depression and fatigue. So far, only few small studies have investigated sleep in fatigued MS patients by means of polysomnography (PSG), which represents the gold standard in sleep research. Herein, authors provided conflicting results, with respiratory disturbances, restless legs syndrome (RLS) and quantitative abnormalities in sleep architecture being associated with fatigue in some but not in other studies [8,11-14].

To date, no specific diagnostic recommendations are indicated for systematically investigating sleep disorders in MS patients with fatigue. This is relevant since treatment of sleep disorders may significantly improve symptoms of fatigue in MS [8,15]. The aim was to investigate the potential contribution of sleep disturbances to fatigue in MS, using data from PSG performed in a large cohort of MS patients for whom neurological cognitive, emotional and psychiatric information were also collected.

METHODS

Study population

This was a prospective single center study performed at the MS Center of the Civic Hospital in Lugano (Ticino, Switzerland), which actively follows more than 500 MS patients. Clinical, radiological and treatment-related information are regularly collected, including Expanded Disability Status Scale (EDSS) scores, occurrence of relapses, yearly brain and spinal MRI. Consecutive patients were eligible to be included in the study if they fulfilled the following inclusion criteria: (1) a definite diagnosis of MS or clinically isolated syndrome based on McDonald 2010 criteria; (2) an EDSS score <7.0; (3) having had a brain

MRI performed in the 12 months prior to study inclusion; (4) age above 18 years; (5) willingness to perform the study and a signed informed consent. Exclusion criteria were (1) a Mini Mental State Examination (MMSE) score <24 points; (2) having experienced a relapse within the previous 3 months; (3) a history of drug and/or alcohol abuse; (4) the presence of significant comorbidities potentially interfering with PSG measures, including decompensated cardiopulmonary disease, cancer, renal failure, as well as neurological conditions other than MS.

The study was approved by the local ethics committee (ref. CE 2706) and written informed consent was obtained from all participants.

Collection of demographic and clinical variables unrelated to sleep

All individuals fulfilling the inclusion and exclusion criteria underwent a baseline visit in which the following variables were collected: age, gender, disease course (clinically isolated syndrome, relapsing-remitting MS, progressive MS), EDSS score, current MS disease modifying treatment (DMT), other medical treatments with potential psychotropic effect (i.e., selective serotonin reuptake inhibitors [SSRI], antidepressants other than SSRI, benzodiazepines [BDZ], antiepileptic drugs [7], modafinil and other stimulant drugs). An expert neuropsychologist administered the MFIS scale to all study subjects [16], a multidimensional and exhaustive self-report of 21 items, which intends to analyze different aspects of fatigue on everyday functioning by assessing its impact on physical, cognitive and psychosocial domains. The total MFIS score ranges from 0 to 84, with higher scores indicating more fatigue; a cut-off of 38 has been proposed to identify those patients with a significant impact of fatigue on their daily functioning [17,18]. Patients were also asked to fill in the Montgomery Asberg Depression Rating Scale (MADRS) [19] and the State-Trait Anxiety Inventory (STAI-Y1; STAI-Y2) scale [20].

Collection of sleep-related clinical variables and PSG measures

Excessive daytime sleepiness was subjectively estimated by means of the Epworth sleepiness scale. RLS was assessed by a structured telephone interview conducted by one PSG-blinded neurologist expert in sleep medicine. A patient was considered to be affected by RLS if she/he met the five standard diagnostic criteria [21]. The severity of RLS was evaluated in patients positive for RLS by the validated self-administered International RLS Rating Scale [22]. RLS symptoms were scored as mild (total score of 1-10), moderate (11-20), severe (21-30) and very severe (31-40) [22].

All remaining sleep-related variables were calculated by performing a home full-night PSG by using a portable device (Embletta ST + Proxy), followed by a maintenance of wakefulness test (MWT) the succeeding day. The MWT is a polysomnographic procedure for the evaluation of EDS/wakefulness, assessing the individual's ability to remain awake whilst resisting the pressure to fall asleep during soporific

circumstances (cut-off for normality <20 min). More details regarding PSG and MWT protocols and parameters can be found in Appendix S1.

The following variables were derived from the results of the PSG and MWT: total sleep time (i.e., the total time spent sleeping during the PSG in minutes), sleep efficiency (i.e., the percentage of time spent asleep whilst in bed), the sleep onset latency (the time needed to fall asleep in minutes), arousal index (the average number of arousals and awakenings per hour), wake after sleep onset (i.e., the amount of wake time in minutes during the attempted sleeping period), respiratory disturbance index (RDI) (i.e., the number of apneas, hypopneas and respiratory-effort-related arousals per hour of sleep), periodic limb movements during sleep index (PLMSI, i.e. the number of PLMS per hour of sleep), the percentage of sleep time spent in sleep stages N1, N2, N3 and rapid-eye-movement sleep, and the average sleep latency in minutes across the four MWT trials.

Statistics

Continuous and ordinal variables were measured by median and interquartile range, categorical variables by counts and percentages. The association between demographic and clinical variables (unrelated to

sleep) and fatigue (as measured by the MFIS score) was estimated using Pearson's correlation, Mann-Whitney and Kruskal-Wallis tests as appropriate. Potential associations between sleep-related variables and MFIS were tested using partial correlation adjusted by those demographic and clinical variables (unrelated to sleep) that were identified as associated with fatigue in the previous step.

All analyses were performed using the statistical software SPSS (Statistical Package for the Social Sciences version 22).

RESULTS

A total of 76 patients (median age 49.0 [41.75–54.25] years, 55 [72.4%] females) were included in the study, of whom 70 (92.1%) had either clinically isolated syndrome or relapsing–remitting MS ($n = 5$ and $n = 65$, respectively) and six (7.9%) had progressive MS. Thirty-one patients were treated with injectable DMTs, 18 with oral DMTs, 17 with monoclonal antibodies and 10 were untreated (full details in Table S1) The median global MFIS score was 49.5 (31.0–62.0), and 53 (69.7%) patients were classified as fatigued. Demographic and clinical characteristics of all patients included in the study as well as in fatigued and non-fatigued patients are shown in Table 1.

TABLE 1 Demographic and clinical characteristics unrelated to sleep estimated in all patients and those classified as fatigued ($n = 53$ with MFIS ≥ 38) and non-fatigued ($n = 23$ with MFIS < 38)

| | All patients ($n = 76$) | Fatigued (MFIS ≥ 38 , $n = 53$) | Non-fatigued (MFIS < 38 , $n = 23$) |
|-----------------------|---------------------------|---------------------------------------|--|
| Median age (IQR) | 49.0 (41.75–54.25) | 50.0 (43.0–55.0) | 47.0 (39.5–52.0) |
| Sex | | | |
| F | 55 (72.4) | 40 (75.5) | 15 (65.2) |
| M | 21 (27.6) | 13 (24.5) | 8 (34.8) |
| Median EDSS (IQR) | 2.5 (2.0–3.0) | 2.0 (0.75–3.0) | 2.5 (2.0–3.5) |
| Disease course | | | |
| CIS/RRMS | 70 (92.1) | 48 (90.6) | 22 (95.7) |
| PMS | 6 (7.9) | 5 (9.4) | 1 (4.3) |
| DMTs | | | |
| None | 10 (13.1) | 8 (15.1) | 2 (8.7) |
| Injectables | 31 (40.8) | 18 (34.0) | 13 (56.5) |
| Orals | 18 (23.7) | 13 (24.5) | 5 (21.7) |
| Monoclonal antibodies | 17 (22.4) | 14 (26.4) | 3 (13.0) |
| Median MADRS (IQR) | 9.0 (6.0–14.0) | 12.0 (7.0–16.0) | 6.0 (3.0–7.0) |
| Median STAI-Y1 (IQR) | 48.0 (40.0–54.0) | 49.0 (44.75–57.25) | 40.0 (37.5–43.5) |
| Median STAI-Y2 (IQR) | 54.0 (40.5–63.0) | 58.0 (44.0–65.0) | 43.0 (34.0–49.0) |
| BDZ | | | |
| No | 55 (72.4) | 32 (60.4) | 23 (100.0) |
| Yes | 21 (27.6) | 21 (39.6) | 0 (0.0) |
| SSRI | | | |
| No | 50 (65.8) | 29 (54.7) | 21 (91.3) |
| Yes | 26 (34.2) | 24 (45.3) | 2 (8.7) |

Abbreviations: BDZ, benzodiazepines; CIS, clinically isolated syndrome; DMTs, disease modifying treatments; EDSS, Expanded Disability Status Scale; IQR, interquartile range; MADRS, Montgomery Asberg Depression Rating Scale; MFIS, modified fatigue impact scale; PMS, progressive multiple sclerosis; RRMS, relapsing–remitting multiple sclerosis; SSRI, selective serotonin reuptake inhibitors; STAI -1, State Anxiety Inventory; STAI-Y2, Trait Anxiety Inventory.

Demographic, neurological and psychiatric correlates of fatigue

Global MFIS scores were positively correlated with age ($r = 0.25$, $p = 0.031$), neurological disability (EDSS, $r = 0.42$, $p < 0.0001$, Figure 1a), depression symptoms (MADRS, $r = 0.56$, $p < 0.0001$, Figure 1b), state anxiety (STAI-Y1, $r = 0.40$, $p < 0.0001$) and trait anxiety (STAI-Y2, $r = 0.53$, $p < 0.0001$). MFIS scores were also higher amongst patients under treatment with SSRI ($p = 0.001$) and BDZ ($p < 0.001$). These associations were also present when motor and cognitive subdomains of MFIS were tested ($p \leq 0.001$ for all). There were instead no significant associations between MFIS and sex ($p = 0.234$), as well as DMTs ($p = 0.203$).

Sleep-related variables associated with fatigue

Excessive daytime sleepiness (as measured by the Epworth sleepiness scale), the prevalence of RLS and PSG parameters (total sleep time, sleep efficiency, RDI, PLMSI, percentage of N1, N2, N3 and rapid-eye-movement sleep, sleep latency at MWT) are shown for the whole group as well as for fatigued and non-fatigued MS patients in Table 2.

Partial correlations were used to test each sleep-related variable for association with global MFIS scores, adjusted by those sleep-unrelated variables associated with fatigue identified

above (i.e., age, EDSS, MADRS, state anxiety, trait anxiety, use of BDZ and of SSRI).

Global MFIS scores were positively associated with the presence of RLS ($r = 0.37$, $p = 0.005$, Figure 2a) and negatively associated with the PLMSI ($r = -0.33$, $p = 0.014$). Only seven patients with RLS also had elevated PLMSI (≥ 15) and no association was present between RLS and PLMSI ($p = 0.877$). None of the remaining sleep-related variables was significantly associated with the global MFIS score (Table S2). The association between RLS and fatigue was also confirmed when either the motor ($r = 0.35$, $p = 0.008$) or cognitive ($r = 0.33$, $p = 0.012$) subdomains of MFIS were considered (Figure 2b,c). PLMSI remained instead significantly and inversely associated with motor MFIS ($r = -0.37$, $p = 0.005$), whilst a non-significant trend for cognitive MFIS was present ($r = -0.24$, $p = 0.073$).

The median RLS severity index in the 22 patients with RLS was 19 (15.5–24.3). The median PLMSI in the 22 patients with RLS was 9 (3.5–21.3). Within the group of patients with a diagnosis of RLS, no difference in global MFIS scores was present in those with RLS severity index ≥ 20 versus < 20 ($p = 0.494$) and in those with PLMSI ≥ 15 versus < 15 ($p = 0.731$).

DISCUSSION

Fatigue is amongst the most prevalent and disabling symptoms of MS, with current symptomatic treatments being of limited benefit.

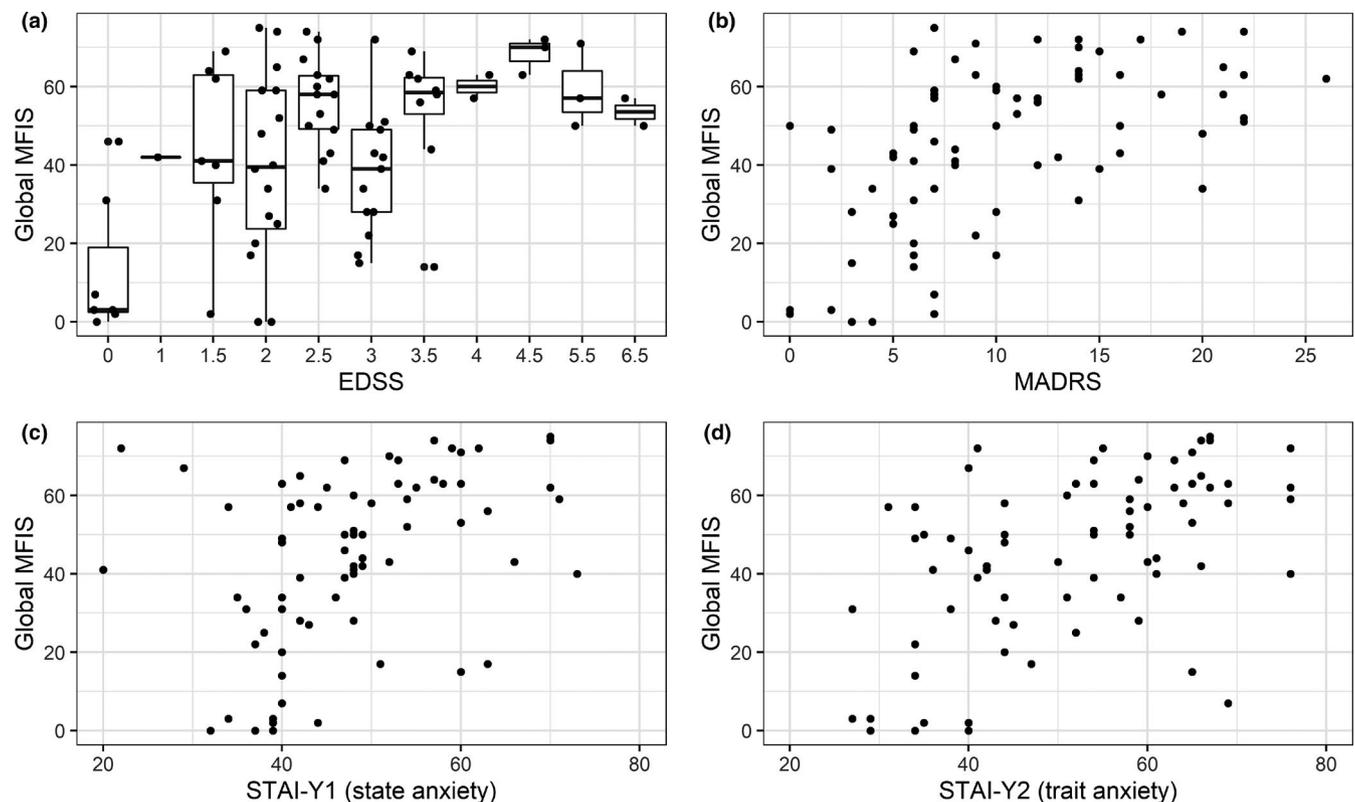
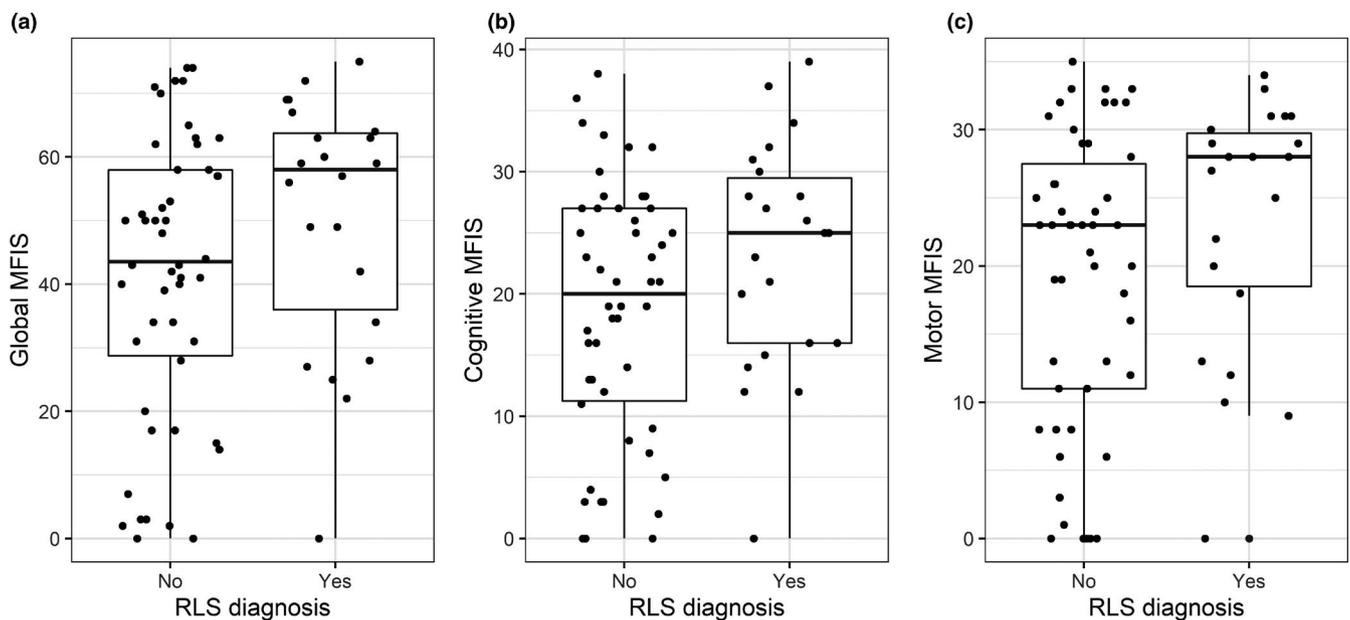


FIGURE 1 Association between fatigue as measured by global MFIS scores and neurological disability as measured by EDSS (a), symptoms of depression as measured by MADRS (b), as well as symptoms of state (c) and trait (d) anxiety

TABLE 2 Sleep-related clinical variables, PSG and MWT measures in all patients and those classified as fatigued ($n = 53$ with MFIS ≥ 38) and non-fatigued ($n = 23$ with MFIS < 38)

| | All patients ($n = 76$) | Fatigued (MFIS ≥ 38 , $n = 53$) | Non-fatigued (MFIS < 38 , $n = 23$) |
|---|---------------------------|---------------------------------------|--|
| Median ESS (IQR) | 9.0 (5.75–12.0) | 11.0 (7.0–14.0) | 5.0 (4.0–7.5) |
| Number of RLS | | | |
| No | 50 (65.8) | 33 (62.3) | 17 (73.9) |
| Yes | 22 (28.9) | 16 (30.2) | 6 (26.1) |
| Missing | 4 (5.3) | 4 (7.5) | 0 (0.0) |
| Sleep efficiency (%) | 81.1 (74.1–88.0) | 79.5 (73.0–88.9) | 82.2 (79.4–86.6) |
| Median total sleep time (min) (IQR) | 375.0 (314.6–407.1) | 353.0 (305.5–404.0) | 392.0 (356.0–407.2) |
| Median sleep onset latency (min) (IQR) | 20.2 (8.1–38.0) | 22.0 (6.5–40.0) | 18.0 (10.0–36.8) |
| Median arousal index (IQR) | 6.3 (4.2–7.9) | 5.5 (3.9–7.7) | 7.2 (5.8–8.0) |
| Median wake after sleep onset (min) (IQR) | 43.2 (25.4–75.5) | 42.2 (24.0–79.0) | 48.5 (30.8–71.2) |
| Number of MWT | | | |
| ≥ 20 min | 63 (82.9) | 44 (83.0) | 19 (82.6) |
| < 20 min | 8 (10.5) | 6 (11.3) | 2 (8.7) |
| missing | 5 (6.6) | 3 (5.7) | 2 (8.7) |
| Median RDI (IQR) | 2.2 (0.6–9.3) | 2.3 (1.0–9.6) | 0.8 (0.3–5.8) |
| Median PLMSI (IQR) | 4.9 (1.2–20.4) | 4.2 (1.0–19.4) | 8.9 (1.7–23.1) |
| Sleep stage | | | |
| N1 (%) | 9.3 (7.2–12.7) | 8.7 (6.9–12.1) | 9.8 (8.3–13.3) |
| N2 (%) | 41.2 (35.2–48.0) | 41.9 (35.5–50.3) | 38.8 (34.9–45.2) |
| N3 (%) | 19.1 (13.9–24.6) | 19.5 (13.6–25.7) | 18.8 (16.0–21.8) |
| REM (%) | 15.9 (10.5–21.3) | 13.6 (10.1–21.3) | 18.3 (15.3–22.5) |

Abbreviations: ESS, Epworth sleepiness scale; IQR, interquartile range; MFIS, modified fatigue impact scale; MWT, maintenance of wakefulness test; PSG, polysomnography; RDI, respiratory disturbance index; REM, rapid eye movement; RLS, restless legs syndrome; PLMSI, periodic limb movements during sleep index.

**FIGURE 2** Boxplots of global MFIS (a), cognitive MFIS (b) and motor MFIS (c) scores compared between MS patients with versus without a diagnosis of RLS

Sleep features and PSG parameters of a large cohort of MS patients, variably affected by symptoms of fatigue, were comprehensively analyzed. The high prevalence of fatigue in MS (approximately 70% of our cohort) and its association with several clinical variables, whereby older patients, those with higher disability scores, symptoms of depression and anxiety and those under treatment with SSRI and BDZ were at higher risk of presenting fatigue, was confirmed. In contrast, no clear effect of classes of DMTs (injectable vs. oral vs. monoclonal antibodies) on fatigue was observed. One could expect treatment with interferons to be associated with fatigue, but this was not the case in our population, potentially because patients with milder disease and therefore less susceptible to fatigue were usually treated with first line DMTs.

The relation between depressive symptoms and fatigue in MS patients is widely acknowledged [23,24]. In contrast, the role of anxiety has been less investigated [24,25]. This study supports a strong relation between fatigue and anxiety (both state and trait). Apart from this, our results mirror those of the literature on fatigue in MS [23,25,26], suggesting that our cohort is adequately representative of the general MS population.

After adjustment for relevant sleep-unrelated variables, fatigue scores were not associated with either subjective or objective EDS. This result suggests that EDS and fatigue belong to two distinct clinical dimensions and that the respective assessment tools currently used in clinical practice can successfully distinguish between them.

The most common PSG parameters did not correlate with fatigue in our sample. In contrast, it was observed that MS patients with a diagnosis of RLS had significantly higher global fatigue scores compared to those without RLS. Notably, this association was also present when physical and cognitive fatigue were analyzed separately. The association between RLS and fatigue has already been suggested by several studies, which were hampered, however, by small sample sizes, by the administration of unidimensional instruments to measure fatigue symptoms [25] and by the absent or limited adjustment for relevant confounding variables [7,13,27,28]. Our findings indicate a potential causal role for RLS in the development of fatigue in MS, and that this is independent of age, disability scores, and symptoms of depression and anxiety. This is relevant since successful management of RLS in MS patients may provide benefits in terms of fatigue.

A significant association, but in the opposite direction, was also present between PLMSI and fatigue, whereby patients with higher PLMSI had lower fatigue scores. This is intriguing since more than 80% of idiopathic RLS patients present PLMS and their presence is indeed a supportive criterion for RLS diagnosis [29].

Notably, our study highlighted a lower prevalence of PLMS in patients with MS-related RLS. This provides evidence for a possible symptomatic RLS form, secondary to central nervous system damage in MS and predominantly sensory, with a poor motor component. Not only fatigue but also RLS might be the consequence of the pathophysiological processes of MS, particularly at the spinal cord level. According to this, MS-related RLS might phenotypically differ from idiopathic and other RLS forms, and therefore not be associated with PLMS.

In contrast to RLS, fatigue scores did not appear to be associated with respiratory disturbances during sleep as measured by RDI. Previous studies on this have been conflicting, with a positive association between fatigue and respiratory problems during sleep (especially obstructive sleep apnea syndrome) in a cohort of 66 MS patients from Germany [7], and instead no association between fatigue and respiratory events in a larger cohort of MS patients from India [12].

Although inconsistencies are possibly related to differences in patients' and population characteristics, methods of PSG scoring and definitions of sleep disturbances, our study shows that in a population of Swiss MS patients respiratory sleep disturbances measured by PSG do not represent a main determinant of fatigue. The Indian study by Chinnadurai et al. reported a significant association between cognitive fatigue and quantitative measures of sleep such as sleep efficiency, sleep onset latency and proportion of sleep stages, although results were not adjusted for relevant clinical and neurological variables [12]. These associations were not observed in our cohort, in which somnolence (i.e., the main sleep breathing associated symptom) was not in fact correlated with fatigue.

The strengths of this study are represented by the large sample size, the prospective design and the use of PSG to investigate sleep disturbances. There are limitations, however. Information on spinal and brain magnetic resonance, which may be relevant since the presence of spinal cord lesions has been found to increase the risk of RLS in patients with MS [30], was not included. Also, only one scale was used to measure fatigue in MS patients. However, although several others are available, MFIS is the most widely used in MS studies [23]. Finally, a significantly higher proportion of fatigued MS patients were using BDZ and SSRI that can also influence fatigue and the prevalence of RLS. The relation between psychiatric symptoms, use of BDZ and SSRI, RLS and fatigue is likely to be complex and not unidirectional. An effort was made to overcome this issue by adjusting the association between RLS and fatigue by the use of BDZ and SSRI, but potential confounding by such medications remains possible.

To conclude, this study provides a comprehensive assessment of sleep-related variables in a large group of MS patients who were variably affected by fatigue. When confounding relevant variables were taken into account (age, neurological disability, psychiatric symptoms and related therapies), a diagnosis of RLS was the only sleep disturbance found to be associated with both physical and cognitive fatigue.

Based on this study and available data, there is currently no evidence to routinely perform a PSG in MS patients suffering from fatigue, unless additional symptoms suggesting an underlying sleep disorder are present. Particular attention should instead be reserved to symptoms of RLS, and future studies should aim at investigating whether symptoms of fatigue in MS patients with a diagnosis of RLS are ameliorated by medical treatments targeting RLS.

CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Gianna Carla Riccitelli: Conceptualization (lead); data curation (lead); formal analysis (lead); investigation (lead); methodology (lead); writing—original draft (lead); writing—review and editing (lead). **Giulio Disanto:** Conceptualization (lead); data curation (lead); formal analysis (lead); methodology (lead); writing—original draft (lead); writing—review and editing (lead). **Rosaria Sacco:** Resources (equal); writing—review and editing (equal). **Davide Sparasci:** Data curation (equal); formal analysis (equal); funding acquisition (equal); methodology (equal). **Leonardo Sacco:** Supervision (supporting); writing—review and editing (equal). **Anna Castelnovo:** Methodology (equal); visualization (equal). **Silvia Miano:** Methodology (equal); resources (equal); supervision (equal); visualization (equal). **Mauro Manconi:** Conceptualization (supporting); data curation (equal); formal analysis (supporting); methodology (supporting); resources (equal); writing—original draft (supporting); writing—review and editing (supporting). **Claudio Gobbi:** Conceptualization (lead); funding acquisition (lead); methodology (lead); supervision (lead); writing—review and editing (lead). **Chiara Zecca:** Conceptualization (lead); funding acquisition (lead); methodology (lead); project administration (lead); supervision (lead); writing—review and editing (lead).

DATA AVAILABILITY STATEMENT

Data are available on reasonable request. The data that support the findings of this study are available from the corresponding author on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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