Clinical trial

Comparison of sleep complaints and quality of life between patients with neuromyelitis optica spectrum disorder (NMOSD) and healthy controls

Mahdi Barzegar[a,b], D. Sadeghi Bahmani[a,c,d], Nasim Nehzat[a], Marjan Kiani[a], Niloofar Hashemi[a,b], Omid Mirmosayyeb[a,b], Serge Brand[c,d,e], Vahid Shaygannejad[a,f,*]

[a] Isfahan Neurosciences Research Center, Alzahra Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
[b] Student Research Committee, school of medicine, Isfahan University of Medical Sciences, Isfahan, Iran
[c] University of Basel, Psychiatric Clinics, Center for Affective, Stress and Sleep Disorders, Basel, Switzerland
[d] Kermanshah University of Medical Sciences, Sleep Disorders and Substance Abuse Prevention Research Center, Kermanshah, Iran
[e] University of Basel, Department of Sport, Exercise and Health, Division of Sport Sciences and Psychosocial Health, Basel, Switzerland
[f] Department of Neurology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

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ABSTRACT

Background: Neuromyelitis optica spectrum disorder (NMOSD) is a chronic autoimmune disorder which is associated with sleep disturbances and a lower quality of life. The aims of the study were: (1) Comparing sleep characteristics, quality of life, and symptoms of depression and anxiety between patients with NMOSD and healthy controls (HCs). (2) Predicting sleep characteristics among patients with NMOSD based on psychological and illness-related factors.
Method: A total of 41 patients with NMOSD (Mean age = 37.48 years; 73.2% f) and 46 matched HCs took part in the study. Individuals with NMOSD reported on illness duration, fatigue and EDSS scores; further, all participants completed self-rating questionnaires covering sleep quality, daytime sleepiness, symptoms of obstructive sleep apnea and restless legs syndrome, quality of life, depression and anxiety.
Results: Compared to HCs, individuals with NMOSD reported a lower quality of life, higher symptoms of anxiety and depression, and more symptoms of restless legs syndrome. Among individuals with NMOSD, longer illness duration and higher fatigue scores predicted poor sleep quality.
Conclusion: Compared to HCs, individuals with NMOSD reported poorer quality of life and higher levels of depression and anxiety. Further, among individuals with NMOSD, sleep characteristics are predicted by a complex variety of illness-related factors.

1. Introduction

Neuromyelitis optica spectrum disorder (NMOSD/NMO) is a chronic inflammatory disorder characterized by impairments of the optic nerve, the spinal cord and the brain (Katz Sand, 2016; Wingerchuk, 2010). Individuals with NMOSD suffer from (a) visual impairment/decreased visual acuity, (b) spinal cord dysfunction (muscle weakness, reduced sensation, loss of bladder and bowel control), along with an acute and severe spastic weakness of the legs (paraparesis) or all four limbs (quadriparesis) (Flanagan and Weinshenker, 2017; Weinshenker and Wingerchuk, 2017). NMOSD and MS have different pathological and immunological pathways (Barnett and Sutton, 2012; Katz Sand, 2016; Lennon et al., 2004): The detection of pathogenic antibodies to aquaporin-4, a water channel present on astrocytic foot processes mainly expressed in the optic nerves, brainstem, and spinal cord, helped to distinguishing NMOSD from MS (Hinson et al., 2007; Katz Sand, 2016; Lennon et al., 2004; Lennon et al., 2005; Roemer et al., 2007).

Individuals with NMOSD often experience a relapsing course and severe symptoms, which may lead to a severe disability, along with a decreased quality of life (Chanson et al., 2011; Katz Sand, 2016; Sato et al., 2013; Shi et al., 2016). Different factors including fatigue, depression, anxiety and poor sleep quality were associated with decreased quality of life in individuals with NMOSD (Barzegar et al., 2018), while it remained undisclosed, if such dimensions were lower compared to healthy controls. Accordingly, one aim of the present study was to compare levels of psychological functioning (depression, anxiety, quality of life) between individuals with NMOSD and healthy controls.

As regards sleep patterns in individuals with NMOSD,

Ranjbaran et al. (2007) reported that a decreased sleep quality and higher daytime sleepiness were associated with lower quality of life scores. As regards objective sleep parameters, a study with 33 individuals with NMOSD reported a lower sleep efficiency, reduced slow wave sleep (SWS), higher periodic limb movement, and a lower O₂-saturation (Song, Pan, and Fu, 2015), compared to 20 controls. Relatedly, Song et al. (2015) speculated that poor sleep architecture indices might have been associated with a lower quality of life.

Next, from studies on sleep in MS extant literature shows that higher fatigue scores and lower sleep quality were associated (Braga et al., 2016; Strober, 2015; Veauthier, 2015; Veauthier and Paul, 2014). Further, compared to healthy controls, patients with MS reported higher scores in restless legs syndrome (RLS) (Braley and Boudreau, 2016; Brass et al., 2010; Caminero and Bartolome, 2011; Ning et al., 2018; Sieminski et al., 2015; Veauthier, 2015); by contrast, only Hyun et al. (2016) reported that individuals with NMOSD had higher RLS scores, compared to healthy controls. Next, while in individuals with MS higher incidence rates of sleep-disordered breathing were repeatedly reported (Braley and Boudreau, 2016; Brass et al., 2010; Caminero and Bartolome, 2011; Veauthier, 2015), only Song et al. (2015) reported such data in individuals with NMOSD.

To conclude, as regards the relationship between sleep, fatigue, sleepiness, and depression in individuals with NMOSD, data are either scarce or missing. Accordingly, a further aim of the present study was to investigate the associations between sleep patterns, including symptoms of OSAs and RLS, fatigue, daytime sleepiness and dimensions of psychological functioning in individuals with NMOSD and to compare these data with healthy controls.

The following five hypotheses were formulated. First, following others, (Barzegar et al., 2018; Popp et al., 2017; Strober, 2015; Veauthier, 2015; Veauthier and Paul, 2014) we expected that compared to controls, individuals with NMOSD reported higher sleep complaints and more issues on psychological functioning (depression, anxiety and quality of life). Second, based on studies in individuals with MS (Popp et al., 2017; Strober, 2015; Veauthier, 2015; Veauthier and Paul, 2014), we expected that poor sleep indices were associated lower indices of psychological functioning such as depression, anxiety, and quality of life. Third, following others (Caminero and Bartolome, 2011; Song et al., 2015; Veauthier, 2015), we expected higher OSAs in individuals with NMOSD, compared to healthy controls. Fourth, following Hyun et al. (2016) we expected higher RLS in individuals with NMOSD, compared to controls. Fifth, following others (Pan et al., 2015; Seok et al., 2017), we hypothesized that poor sleep, higher symptoms of fatigue and poor quality of life were associated. Last we took as exploratory the research questions, if psychological and illness-related dimensions could predict sleep quality, daytime sleepiness, and fatigue.

2. Methods

2.1. Procedure

Individuals with diagnosed NMOSD (see details below) from the Kashani Hospital of the Isfahan University of Medical Sciences (Isfahan, Iran) were approached to participate in the present study. In parallel, an age- and gender-matched sample of healthy participants was recruited (see below). Participants were informed about the study aims and the confidential data handling. Thereafter, participants signed the written informed consent, and completed a booklet of questionnaires on sociodemographic information, sleep quality, obstructive sleep apnea (OSAs), RLS, daytime sleepiness, symptoms of depression and anxiety, quality of life, somatic diseases, and medication (see below). Individuals with NMOSD reported on EDSS scores, duration of illness, and fatigue. The local ethical committee approved the study, which was performed in accordance with the rules laid down in the Declaration of Helsinki and its later amendments.

2.2. Study populations

For participants with NMOSD, inclusion criteria were: 1. Age between 18 and 65 years; 2. Diagnosis of NMOSD, as carried out and ascertained by a trained neurologist, and based on the international consensus diagnostic criteria of NMOSD in 2015 (Wingerchuk et al., 2015). 3. Willing and able to comply with the study conditions. 4. Signed written informed consent. Exclusion criteria: 1. Current exacerbation; 2. Diagnosis of psychiatric disorders or severe cognitive impairments, as ascertained by a trained clinical psychologist. The disease severity of NMOSD was evaluated with the Expanded Disability Status Scale (EDSS) score (Kurtzke, 1983).

For healthy participants, inclusion criteria were: 1. Age between 18 and 65 years; 2. Willing and able to comply with the study conditions. 3. Signed written informed consent. Exclusion criteria were as follows: 1. Diagnosis of psychiatric disorders, above all major depressive disorders, or substance use disorder, as ascertained by a trained clinical psychologist. 2. Severe somatic complaints, as reported during the clinical interview.

2.3. Questionnaires

2.3.1. Sociodemographic and illness-related information

Patients reported on their age, gender, height, weight, highest educational level, civil status, and current state of employment; further, they reported on current somatic complaints (yes vs. no) such as diabetes, hypertension of hyperthyoroidism (Table 1).

Next, individuals with NMOSD reported their current EDSS score and medication. This information was carried out in an interview.

2.3.2. Sleep quality: Pittsburgh Sleep Quality Index (PSQI)

Sleep quality was measured by Persian version of PSQI (Moghaddam, Nakhaee, Sheibani, Garrusi, and Amirkafi, 2012). The PSQI has seven components including sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleep-related medication and daytime dysfunction. This scale consists of 19 items which assesses sleep quality over the last 1 month. Answers are given on 4-points ratings scales, ranging from 0 (= never) to 3 (= always). The sum score ranges from 0–21, with higher scores reflecting a higher sleep impairment, that is to say, a lower sleep quality. Further, the cut-off value of ≥5 indicates poor sleep quality (Buysse et al., 1989).

2.3.3. Daytime sleepiness: Epworth Sleepiness Scale (ESS)

Daytime sleepiness was assessed using ESS (Johns, 1991; Haghighi et al., 2013). The self-rating questionnaire consists of eight items to rate the odds to dozing in different activities. Answers are given on 4-points ratings scales, ranging from 0 (=never) to 3 (=always), with higher sum scores reflecting a higher risk to dozing off during the day. a global score greater than 10 indicates excessive daytime sleepiness (Johns, 1991).

2.3.4. Obstructive sleep apneas (OSAs): STOP-Bang

Participants completed the questionnaire to screen for OSAs. It consists of 8 items including snoring, tiredness, observed apnea, high blood pressure, Body mass index (BMI > 35 kg/m²), age (>50 years), neck circumference (male > 43 cm; female > 41 cm) and gender (male). Assembling the first letters of the items explains the acronym STOP-Bang. The sum scores range from 0–8 points, with a score of ≥3 as the cut-off to indicate moderate and severe risk for OSA (Chung et al., 2008).

2.3.5. Restless legs syndrome

The International Restless Legs Study Group rating scale (Walters et al., 2003) was employed in a face-to-face interview (Allen et al., 2003). Questions focus on RLS-related severity such as RLS

Table 1
Sociodemographic and clinical data of patients with NMOSD and healthy controls.

Dimensions	Groups		Statistics
	NMOSD	Healthy controls	
N	41	46	
	M (SD)	M (SD)	
Age (years)	37.22 (9.53)	35.46 (8.69)	$t(85) = 0.70$
BMI (kg/m^2)	23.47 (4.20)	25 (4.41)	$t(85) = 0.35$
EDSS	2.52 (0.94)	–	
Disease duration (years)	6.93 (5.21)	–	
Fatigue	25.05 (17.51)		
	n (%)	n (%)	
Gender (female/male)	30/11 (73.2/26.8)	31/15 (67.4/13.7)	$X^2(N = 87, df = 1) = 0.35$
Civil status (married/single)	41/0 (100/0)	25/21 (54.3/45.7)	$X^2(N = 87, df = 1) = 34.16$***
Highest educational level (high school/higher education)	24/16 (63.2/36.8)	28/18 (60.9/39.1)	$X^2(N = 87, df = 1) = 0.01$
Employment (yes/no)	8/32 (20//80)	18/28 (39.1/60.9)	$X^2(N = 87, df = 1) = 3.71$
Other diseases			
Diabetes mellitus (yes/no)	2/36 (5.3/94.7)	3/41 (5.6/94.4)	$X^2(N = 87, df = 1) < 1$
Hypertension (yes/no)	2/37 (5.3%)	2/42 (3.7/96.3)	$X^2(N = 87, df = 1) < 1$
Hypothyroidism (yes/no)	2/37 (5.3/94.7)	1/43 (1.8/98.2)	$X^2(N = 87, df = 1) < 1$
Toxoplasmosis (yes/no)	2/37 (5.3/94.7)	–	
Systemic lupus erythematosus (yes/no)	1/38 (2.6/97.4)	–	
AQP4 IgG positive (yes/no)	11/28 (28.9/71.1)	–	
Medication			
Rituximab (yes/no)	30/11 (73.2%)	–	
Azathioprine (yes/no)	9/32 (22%)	–	
Sedative drugs (yes/no)	7/33 (17.5/82.5)	2/44 (4.3/95.7)	$X^2(N = 87, df = 1) = 3.95$*

Notes: NMOSD = Neuromyelitis Optica Spectrum Disorder; BMI = Body Mass Index; EDSS = Expanded Disability Status Scale; AQP4 IgG = Aquaporin 4 immunoglobulin G. * = $p < 0.05$; *** = $p < 0.01$.

discomfort in legs and arms, need to move around for relief from RLS symptoms, and frequency of RLS symptoms. Answers are given on 5-point Likert scales ranging from 0 (=none) to 4 (=very severe), with higher scores reflecting more marked symptoms of RLS (Cronbach's α = 0.81).

2.3.6. Quality of life: 36-Item short health survey (SF-36)

All participants completed the Health Status Questionnaire (SF-36) to self-assess the health status over the last year (Brazier et al., 1992). It consists of 8 subscales including physical functioning, role limitations due to physical problems, general health perceptions, bodily pain, social function, role limitations due to physical problems, role limitations due to emotional problems, mental health, vitality and social function. Each domain scores from 0–100, with higher scores reflecting a higher quality of life. The subscales were aggregated to two summary scales of physical component summary (PCS) and mental component summary (MCS).

2.3.7. Modified Fatigue Impact Scale (MFIS)

The Iranian version of MFIS was used to assess fatigue in individuals with NMOSD (Ghajarzadeh et al., 2013). It consists of 21 items, and answers are given on 5-points rating scales ranging from 0 (=never) to 4 (=always), and with higher scores reflecting a higher fatigue.

2.3.8. The Hamilton Anxiety Rating Scale (HAM-A)

The HAM-A was used to assess anxiety symptoms. It consists of 14 items, and answers are given on five-points rating scales ranging from 0 (=never) to 4 (=always). The sum score ranges was from 0–56, with higher scores reflecting a higher anxiety (Hamilton, 1959).

2.3.9. Symptoms of depression: Beck Depression Inventory-II (BDI-II)

Participants completed the Iranian version of the Beck Depression Inventory II (BDI-II) (Ghassemzadeh et al., 2005). It consists of 21 items, and answers are given on 4-point rating scales ranging from 0 (=never) to 3 (=always). The global score ranges from 0–63, with higher scores reflecting a higher severity of depression (Beck et al., 1996). To avoid biased self-correlations with the PSQI, the item related to sleep was deleted.

2.4. Statistical analysis

A series of X^2-tests and t-tests was performed to compare sociodemographic and anthropometric dimensions between individuals with NMOSD and HCs. Likewise, with a series of t-tests dimensions of sleep (sleep quality, daytime sleepiness, symptoms of Restless Legs Syndrome and sleep-disordered breathing) and psychological dimensions (quality of life, symptoms of depression and anxiety) were compared between individuals with NMOSD and HCs. Among individuals with NMOSD, a series of Pearson's correlations was performed to correlate illness-related dimensions (duration of illness, EDSS, fatigue), sleep-related dimensions (sleep quality, daytime sleepiness, symptoms of sleep-disordered breathing and Restless Legs Syndrome), and psychological dimensions (quality of life, symptoms of depression and anxiety). Last, to predict sleep quality, daytime sleepiness and fatigue, three independent multiple regression analyses (stepwise, backwards) were performed. The level of significance was set at alpha < 0.05. Statistics was performed with SPSS® 25.0 (IBM Corporation, Armonk NY) for Apple®.

3. Results

3.1. Sociodemographic and illness-related information

Table 1 reports the descriptive and inferential statistical indices of sociodemographic and illness-related dimensions between individuals with NMOSD and healthy controls. Accordingly, the statistical indices are not repeated in the text anymore.

A total of 41 individuals with NMOSD (mean age = 37.22 years; 73.2% females) and 46 healthy controls (mean age = 35.46.22 years, SD = 8.69; 67.4% females) took part in the study.

Between the two groups no differences were found for age, BMI, gender ratio, highest educational levels, employment status, and other diseases. Compared to healthy controls, individuals with NMOSD were all married, and reported a higher intake of sedative drugs.

Table 2

Descriptive and inferential statistical overview dimensions of sleep (Pittsburgh Sleep Quality Index, Restless Legs Syndrome, sleep-disordered breathing; daytime sleepiness), symptoms of depression and anxiety, and quality of life between individuals with NMOSD and healthy controls.

	Group		Statistics
	NMOSD	Healthy controls	
N	39	44	
Pittsburgh Sleep Quality Index	23.49 (7.09)	20.43 (6.89)	$t(52) = 1.46$, $d = 0.30$ (S)
Obstructive Sleep Apnea	14.05 (7.55)	10.17 (5.83)	$t(52) = 1.87$, $d = 0.10$ (T)
Restless Legs Syndrome	13.29 (7.83)	8.63 (5.32)	$t(52) = 2.17$, $d = 1.12$ (L)
Epworth Sleepiness Scale	18.95 (3.53)	15.33 (3.60)	$t(52) = 3.54**$, $d = 0.34$ (S)
Beck Depression Inventory	9.37 (8.42)	5.08 (6.13)	$t(52) = 3.54**$, $d = 0.60$ (M)
Hamilton Anxiety Inventory	9.95 (8.03)	4.91 (5.44)	$t(52) = 3.54**$, $d = 0.74$ (M)
Quality of Life			
Mental component	42.23 (11.68)	52.46 (10.16)	$t(52) = 3.54**$, $d = 0.93$ (L)
Physical component	41.19 (8.22)	46.47 (4.09)	$t(52) = 3.54**$, $d = 0.82$ (L)

Notes: NMOSD = Neuromyelitis Optica Spectrum Disorder * = $p < 0.05$; ** = $p < 0.01$. T = trivial effect size; S = small effect size; M = medium effect size; L = large effect size.

3.2. Comparison of sleep dimensions and psychological functioning between individuals with NMOSD and healthy controls

Table 2 reports the descriptive and inferential statistical indices of quality of sleep, OSA, RLS, sleepiness, and psychological functioning (depression, anxiety, quality of life) between individuals with NMOSD and healthy controls.

No mean differences were observed for sleep quality, OSAs, and daytime sleepiness. Compared to healthy controls, individuals with NMOSD reported higher scores of RLS, along with higher scores in depression, and anxiety, and lower scores in mental and physical quality of life.

3.3. Associations between symptoms of sleep quality, OSAs, restless legs syndrome, daytime sleepiness, EDSS, duration of illness and symptoms of depression and anxiety and dimensions of quality of life in individuals with NMOSD

Table 3 reports the correlation coefficients between sleep quality, OSA, RLS, daytime sleepiness, EDSS, duration of illness and symptoms of depression and anxiety and quality of life in individuals with NMOSD.

Higher age was associated with lower symptoms of depression and anxiety.

A higher EDSS score, that is, a higher impairment, was associated with higher scores of fatigue, illness duration, symptoms of depression and anxiety, along with a lower quality of life (physical and mental).

Higher fatigue scores were associated with higher sleep disturbances, higher symptoms of depression and anxiety, along with a lower quality of life (physical and mental).

Illness duration was not further associated with sleep and psychological functioning (depression, anxiety, quality of life).

Higher sleep disturbances were associated with higher symptoms of depression and anxiety, along with a lower quality of life (physical and mental).

Higher symptoms of restless legs syndrome were associated with higher scores of OSAs, but not with psychological functioning (depression, anxiety, quality of life).

Symptoms of OSAs and daytime sleepiness were not associated with psychological functioning (depression, anxiety, quality of life).

High inter-correlations were found for symptoms of depression, anxiety, and psychological functioning (depression, anxiety, quality of life).

3.4. Predicting sleep quality, sleepiness, and fatigue in patients with NMOSD

As shown in Table 4a, a longer illness duration and higher fatigue levels predicted a lower sleep quality, while EDSS, OSA, RLS, sleepiness, depression, anxiety, and quality of life sores were excluded from the equation.

As shown in Table 4b, higher anxiety scores predicted higher sleepiness, while sleep quality, EDSS, duration of illness, OSA, RLS, depression, fatigue, and quality of life scores were excluded from the equation.

As shown in Table 4c, higher anxiety scores and lower scores in physical and mental quality of life predicted higher fatigue levels, while sleep quality, EDSS, duration of illness, OSA, RLS, depression, and fatigue were excluded from the equation.

Table 3

Correlation coefficients between age, sleep dimensions (Pittsburgh Sleep Quality Index; Epworth Sleepiness Scale, Restless Legs Syndrome; sleep-disordered breathing), Expanded Disability Status Scale, fatigue, duration of illness, symptoms of depression and anxiety, and quality of life in patients with NMOSD.

		Dimensions										
		1	2	3	4	5	6	7	8	9	10	11	12
1	Age	–	−0.15	−0.20	.05	−0.11	.04	0.20	−0.30	−0.24	−.34*	0.14	0.24
2	Expanded Disability Status Scale		–	0.68**	0.37*	0.36*	0.16	−0.03	0.15	0.48**	0.45**	−0.60**	−0.54**
3	Fatigue			–	0.02	0.37*	0.11	0.23	0.30	0.77**	0.65**	−0.75**	−0.76**
4	Duration; illness				–	0.24	−0.22	−0.28	0.14	−0.02	0.08	0.16	−0.12
5	Sleep Quality (PSQI)					–	0.22	0.31	0.13	0.40*	0.54**	−0.34*	−0.41*
6	Restless legs syndrome						–	0.38*	−0.05	0.12	0.03	−0.13	0.05
7	Obstructive sleep apnea							–	−0.20	0.26	0.13	−0.04	−0.07
8	Daytime sleepiness								–	0.09	0.30	−0.15	−0.39*
9	Depression									–	0.73**	−0.62**	−0.63**
10	Anxiety										–	−0.38*	−0.49**
11	Quality of life: Physical component											–	0.48**
12	Quality of life: Mental component												–

Notes: PSQI = Pittsburgh Sleep Quality Index; * = $p < 0.05$; ** = $p < 0.01$.

Table 4a

Multiple linear regression with Pittsburgh Sleep Quality Index as dependent variable, and EDSS, illness duration, fatigue, obstructive sleep apnea, restless legs syndrome, daytime sleepiness, depression, anxiety, and quality of life scores as predictors.

Dimension	Variables	Coefficient	Standard error	Coefficient β	t	p	R	R^2	Durbin-Watson coefficient
Pittsburgh Sleep Quality Index	Intercept	3.972	.927	–	4.286	0.000	0.617	0.380	1.715
	Illness duration	0.200	0.078	0.451	2.549	0.019			
	Fatigue	0.056	0.026	0.380	2.150	0.044			
Excluded variables	EDSS, OSAs, RLS, daytime sleepiness, depression, anxiety, quality of life scores: $p > .05$								

4. Discussion

The key findings of the present study were that compared to healthy controls, individuals with NMOSD reported higher scores of depression and anxiety, a lower quality of life, along with higher symptoms of self-rated RLS, while sleep quality, OSA and daytime sleepiness did not differ. Among individuals with NMOSD, longer illness duration and higher fatigue scores predicted poor sleep quality, higher anxiety scores predicted daytime sleepiness, and a poorer quality of life and higher anxiety scores predicted higher fatigue scores. The present results add to the current literature in an important way in that we showed that individuals with NMOSD report a specific pattern of decreased psychological functioning, which appeared to be related to poor sleep, higher EDSS scores and above all fatigue.

Five hypotheses and an exploratory research question were formulated, and each of these is considered now in turn.

With the first hypothesis we assumed that compared to controls, individuals with NMOSD would report higher sleep complaints and more issues on psychological functioning, though, data did not fully support this. While, indeed, individuals with NMOSD reported higher scores of depression, anxiety and quality of life, this was not the case for sleep complaints. Accordingly, as regards sleep complaints, the present results do not match previous results, at least those results from individuals with MS (Popp et al., 2017; Strober, 2015; Veauthier, 2015; Veauthier and Paul, 2014). However, again in individuals with MS at disease onset, in two previous studies (Sadeghi Bahmani et al., 2016, 2018) we showed that subjective sleep patterns did not differ from healthy young adults and that sleep patterns remained stable also two years after disease onset. Likewise, the present results do not support the assumption that poor sleep should be considered a response to chronic inflammatory diseases (Lashley, 2003; Lorton et al., 2006; Ranjbaran et al., 2007) and neurodegenerative disorders (Iranzo, 2016). By contrast, the present results were in accord with those studies suggesting that individuals with NMOSD would report lower scores of quality of life (Chanson et al., 2011; Katz Sand, 2016; Sato et al., 2013; Shi et al., 2016), and more specifically symptoms of depression and anxiety (Barzegar et al., 2018; Shi et al., 2016). However, the present results expand upon previous findings, in that the present pattern did also emerge among individuals with NMOSD, when compared to healthy controls (see also Table 2).

With the second hypothesis, we expected that in individuals with NMOSD poor sleep indices would be associated with lower indices of psychological functioning such as depression, anxiety and quality of life, and data did fully support this assumption. Accordingly, the present results are in accord with a host of studies among non-clinical samples (Brand et al., 2010; Brand et al., 2010), clinical samples (Alvaro et al., 2013; Baglioni et al., 2010; Goldstein and Walker, 2014), and above all among samples with MS and NMOSD (Amtmann et al., 2015; Bamer et al., 2010; Barzegar et al., 2018; Braga et al., 2016; Viana et al., 2015). However, the present study results expand upon previous results, in that we showed (see also Table 3) that such associations were also tightly related to increased EDSS and fatigues scores. The cross-sectional character of the study design does not allow to draw causal relationships. However, though speculative, a bi-directional influence is highly conceivable (Jansson-Fröjmark and Lindblom, 2008), while there is also sufficient reason to assume that poor sleep preceded the onset of impaired psychological functioning (Baglioni et al., 2010; Baglioni et al., 2016; Hertenstein et al., 2018; Riemann et al., 2010).

With the third hypothesis we assumed that compared to healthy controls, individuals with NMOSD would report higher scores of sleep apnea and snoring, and data did confirm this. Accordingly, the present pattern of results is in accord with studies among individuals with MS (Caminero and Bartolome, 2011; Veauthier, 2015), while to the best of our knowledge, beside the study of Song et al. (2015) this is the second study to show that individuals with NMOSD reported higher sleep-disordered breathing.

Similarly to the third hypothesis, with the fourth hypothesis we assumed that compared to healthy controls, individuals with NMOSD reported higher RLS scores, and again data did confirm this, and again, the present results add to the current literature in that besides the study of Hyun et al. (2016) this was the second study to observe higher RLS scores in individuals with NMOSD, always compared to healthy controls.

With the fifth and last hypothesis, we assumed that poor sleep, higher symptoms of fatigue and poor quality of life were associated, and data did fully confirm this (see Table 3). Accordingly, the present findings are in accord with those from other studies in individuals with NMOSD (Pan et al., 2015; Seok et al., 2017), and in individuals with MS (Strober, 2015). Importantly, Veauthier et al. (2013) showed in individuals with MS that the successful treatment of sleep disorders positively impacted on fatigue. In this vein, future interventional studies in individuals with NMOSD might focus on sleep to improve both sleep complaints and fatigue.

With the exploratory and research question we explored, if and if so, which psychological and illness-related dimensions could predict sleep quality, daytime sleepiness, and fatigue in individuals with NMOSD. Results showed that a longer illness duration and higher fatigue scores predicted poor sleep quality, higher anxiety scores predicted daytime sleepiness, and a poorer quality of life and higher anxiety scores predicted higher fatigue scores. Or in other words: Both a broad variety of illness-related and psychological dimensions predicted sleep, daytime sleepiness and fatigue scores (see Tables 4).

Table 4b

Multiple linear regression with Epworth Sleepiness Scale as dependent variable, and sleep quality, EDSS, illness duration, fatigue, Obstructive Sleep Apnea, Restless Legs Syndrome, depression, anxiety, and quality of life scores as predictors.

Dimension	Variables	Coefficient	Standard error	Coefficient β	t	p	R	R^2	Durbin–Watson coefficient
Daytime sleepiness	Intercept	3.228	1.142	–	2.827	0.010	0.423	0.179	1.238
	Anxiety	0.178	0.083	.423	2.139	0.044			
Excluded variables	EDSS, illness duration, fatigue, OSAs, RLS, sleep quality, depression, quality of life scores: $p > 0.05$								

Table 4c
Multiple linear regression with fatigue as dependent variable, and sleep quality EDSS, illness duration, daytime sleepiness, Obstructive Sleep Apnea, Restless Legs Syndrome, depression, anxiety, and quality of life scores as predictors.

Dimension	Variables	Coefficient	Standard error	Coefficient β	t	p	R	R²	Durbin–Watson coefficient
Fatigue	Intercept	62.269	12.752	–	4.883	0.000	0.935	0.875	1.846
	Anxiety	0.702	0.228	.338	3.077	0.007			
	PQoL	−0.625	0.207	−0.340	3.021	0.007			
	MQoL	−0.627	0.166	−0.427	3.776	0.001			
Excluded variables	EDSS, illness duration, OSAs, Restless Legs Syndrome, sleep quality, depression: $p > 0.05$								

Notes: PQoL = Physical quality of life; MQoL = mental quality of life.

While the quality of the present data does not allow a deeper understanding of the underlying neurophysiological and psychological mechanisms, we follow the hyperarousal hypothesis of Riemann et al. (2010). Briefly, the hyperarousal hypothesis claims that an increased psychological arousal in terms of increased psychological tension leads to neurophysiological adaptions such as an increased hypothalamus-pituitary-adrenocortical axis activity, which among others leads to a higher cortisol secretion along with a higher physiological arousal. As a result, sleep duration decreases, gets more fragmented and leads to a further up-regulation of the organism.

While the hyperarousal hypothesis of Riemann et al. (2010) allows to explain the associations between poor psychological functioning and impaired sleep, the hyperarousal hypothesis does not allow to explain, as to why higher scores of RLS and OSAs were observed individuals with NMOSD. For want of thorough patho-neurophysiological and evidence-based concepts, we rely on theoretical concepts drawn from individuals with MS. Trenkwalder and Paulus (2010) and Dauvilliers and Winkelmann (2013) claimed impairments in metabolic iron pathways and in the dopaminergic transmission in individuals with RLS. Further, higher RLS scores were observed in individuals with MS (Auger et al., 2005; Braley and Boudreau, 2016; Caminero and Bartolome, 2011; Kotterba et al., 2018; Li et al., 2012; Manconi et al., 2007; Manconi et al., 2008; Miri et al., 2013; Shaygannejad et al., 2013; Sieminski et al., 2015; Vavrova et al., 2012; Veauthier, 2015). Analogically, though highly speculative, one might assume that similar pathophysiological mechanisms also underpin the associations between increased RLS scores in individuals with NMOSD.

As regards OSAs in individuals with NMOSD, to our knowledge, research on the pathophysiological mechanisms is missing, and again we rely on research on individuals with MS: Braley et al. (2012) claimed that lesions in the brain stem were associated with higher odds of suffering from OSAs. Kaminska et al. (2012) summarized previous studies, which showed that OSAs increased the risk to cause gray matter abnormalities, that could exacerbate MS-related changes such as reduced cerebral glucose metabolism and a hypoperfusion of specific gray matter regions, which in turn were associated with higher symptoms of fatigue. Though again highly speculative, one might assume similar pathophysiological pathways also in individuals with NMOSD.

Despite the novelty of the results, the following limitations warn against the overgeneralization of the findings. First, the samples sizes were rather small, though, we largely relied on effect sizes, which are not sensitive to sample sizes. Second, to assess sleep disturbances, we relied on self-reports, while an actigraphic monitoring over a period of seven days, and a thorough polysomnography, including pulse oximetry, limb movements, and respiratory monitoring, along with a detailed sleep-related clinical interview might have yielded further and robust information. Accordingly, future studies might consider to assess sleep and sleep-related dimensions also objectively. Fourth, latent and unassessed psychological and physiological dimensions might have biased two or more variables in the same or opposite directions. Specifically, in previous studies in individuals with MS, it turned out that sleep patterns and physical activity levels were associated (Sadeghi Bahmani et al., 2016, 2018), while higher physical activity levels were also associated with lower symptoms of major depressive disorders

(Bailey et al., 2017; Booth et al., 2012; Schuch et al., 2017; Stubbs et al., 2018). Accordingly, assessing physical activity levels might have yielded further protective factors against poor sleep and symptoms of depression and anxiety. Last, a longitudinal study design would have allowed to further explore the causal relationships between sleep patterns and psychological functioning.

Acknowledgments

Conflict of interest

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