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Hyperstable arousal regulation in multiple sclerosis

Muriel Stoppe[a,b,1], Klara Meyer[a,1], Maike Schlingmann[a], Sebastian Olbrich[c], Florian Then Bergh[a,b,*]

[a] Department of Neurology, University of Leipzig, Germany
[b] Translational Centre for Regenerative Medicine, University of Leipzig, Germany
[c] Department of Psychiatry, University Zurich, Germany

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ABSTRACT

Background: Fatigue is common in multiple sclerosis (MS) patients. Exhaustion of physiological reserves and mental stress are postulated causes, the latter supported by more pronounced hypothalamic-pituitary-adrenal (HPA) axis activation in fatigued patients. Divergent dysregulation of arousal appears to play important roles in depression- (hyperstable arousal) and in cancer-related (unstable arousal) fatigue, where HPA axis is hyperactive or hypoactive, respectively.

Objective: This study assessed arousal regulation in multiple sclerosis patients, explored if fatigue can be physiologically described by altered arousal regulation, and if HPA axis activity corresponds to the type(s) of arousal regulation.

Methods: 51 mildly-affected patients with relapsing-remitting MS (86% on disease-modifying treatment) and 20 healthy controls were analysed via Vigilance Algorithm Leipzig and combined dexamethasone/corticotropin releasing hormone test.

Results: Hyperstable arousal pattern was significantly more frequent in patients than in controls (62.7% vs. 45.0%, $p = 0.011$). Patients scored higher on all fatigue, but not on sleepiness scales. All patients combined showed mild activation of the hypothalamic-pituitary-adrenal axis ($p < 0.05$ for post-CRH ACTH and AUC ACTH; cortisol n.s.). While fatigue was numerically more pronounced in both hyperstable and unstable arousal, HPA axis activity was highest in hyperstable and lowest in unstable arousal ($p = 0.013$ for post-CRH ACTH; $p = 0.087$ for AUC ACTH; cortisol n.s.).

Conclusion: Frequency of arousal patterns are altered in MS. An association with HPA axis activity was weak, possibly because the present sample was stable on immunotherapy.

1. Introduction

Fatigue in multiple sclerosis (MSF) is characterized by an increased need to rest with complaints of generalized weakness, attention and memory deficits (Grzegorski und Losy, 2017). Several mechanisms might underlie fatigue but are incompletely understood. Both depression and sleep disturbance are described as independent factors for developing MSF, with stronger association than physical disability (Strober und Arnett, 2005). Different therapeutic approaches, both pharmacologic and non-pharmacologic, achieve moderate effects at best, which cannot be anticipated on an individual basis. This argues for pathophysiologic heterogeneity of the insufficiently understood syndrome.

Among several plausible hypotheses for the origin of MSF, one postulates that the effort of compensating physical deficits and psychological burden results in constant distress. Since prolonged stress leads to activation of, among others, the hypothalamo-pituitary-adrenal (HPA-) axis, this hypothesis is supported by the observation that the known hyperactivation of the HPA axis in multiple sclerosis patients (Then Bergh et al., 1999b) is more pronounced in patients with MSF (Gottschalk et al., 2005).

A similar activation of the HPA axis can be found in patients with major depression (MD) and can be normalized with antidepressants in both multiple sclerosis (Then Bergh et al., 2001) and MD (Heuser et al., 1996). Diversely, MSF phenomenologically resembles cancer-related fatigue (CRF) and chronic fatigue syndrome (CFS); intriguingly, HPA axis shows reduced (rather than increased) activity in CRF (Bower et al., 2007) and CFS (Scott und Dinan, 1999).

* Corresponding author at: University of Leipzig, Department of Neurology, Liebigstraße 20, 04103 Leipzig, Germany.
E-mail address: ThenBerF@medizin.uni-leipzig.de (F. Then Bergh).
[1] These authors contributed equally.

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One other possible mechanism of MSF could be disturbance of central nervous system arousal regulation, identified as an evolving biomarker for several neuropsychiatric disorders (Olbrich et al., 2012b, a; Hegerl und Hensch, 2014; Hegerl et al., 2012). Two major prototypes of disturbed arousal regulation can be identified: increased propensity to develop drowsiness and to fall asleep, as suggested for CRF (Olbrich et al., 2012a), CFS (Neu et al. 2008; Spitzer und Broadman, 2010) and attention deficit hyperactivity disorder ADHS (Hegerl und Hensch, 2014; Geissler et al., 2014; Lopez et al., 2018), or with a state of neurophysiological hyperarousal, as found in MD (Olbrich et al., 2012b; Hegerl et al., 2012; Schmidt et al., 2016; Ulke et al., 2017). The differentiation is clinically important because opposite neurophysiological alterations of sleep-wake regulation would support different treatment options: Unstable arousal regulation could support the use of psychostimulants (Rojí and Centeno, 2017), whereas for hyperstable arousal regulation, resembling more the situation in depression, antidepressants, that seem to reduce arousal (Alberti et al., 2015), might be a more appropriate treatment (Olbrich et al., 2012b; Hegerl et al., 2012). Moreover, arousal-increasing stimulants are not effective in targeting the core depressive symptomatology (Hegerl und Hensch, 2017).

It is not known if MSF is associated with changes in arousal regulation, and there may exist heterogeneous arousal regulation characteristics in MSF. Subgrouping MSF according to the type of arousal regulation could guide the selection of therapeutic approach – for both individual treatment and design of clinical trials.

The aim of this study was to assess arousal regulation in MS, to explore if MSF can be physiologically described by altered arousal regulation, and if HPA axis activity corresponds to the type(s) of arousal regulation, potentially delineating a pathophysiological heterogeneity within MSF.

2. Materials and methods

2.1. Study outline

51 patients (35 females (68.6%), age 36.1 +/- 8.6 years) with relapsing-remitting multiple sclerosis (RRMS) according to the McDonald 2010 criteria (Polman et al., 2011) with EDSS (Expanded Disability Status Scale) 0–6.0 and without relapse within four weeks before screening were approached at the outpatient clinic of the University of Leipzig´s Department of Neurology. Patients with a personal or family history of neuropsychiatric disorders, especially with a score > 17 in the Beck Depression Inventory (BDI) (Beck et al., 1997), were excluded.

20 age-matched healthy controls (HC, 10 females (50%), age 33.1 +/- 8.8 years) without psychopharmacological medication were recruited. Only subjects without personal or family history of significant physical or mental disorder requiring medical treatment were included.

Current shift work was an exclusion criterion for both groups, as was current use of any centrally-acting medications (e.g. hypnotics, opioid analgesics) within the past three months. The study was approved by the University of Leipzig´s ethics committee (file number 265-12-15072013). Written informed consent was obtained from each patient and healthy control prior to investigation according to the Declaration of Helsinki.

After verification of inclusion and exclusion criteria, RRMS and HC were seen for three visits within 14 days. At baseline, history, EDSS (Kurtzke, 1983) (only RRMS) and baseline blood samples were collected; Clinical Global Impression Scale (CGI) (Guy, 1976) was recorded by the investigator; cognition, fatigue and depressive symptoms were recorded as detailed below. At the second visit (V1), sleep quality and quantity of the preceding night and the feeling of being well-rested after sleep were evaluated using a German sleep questionnaire (SF-A) (Görtelmeyer, 1981), which differentiates between several significant factors influencing the past nights´ sleep. Sleepiness at the beginning of the EEG recording was assessed using the Epworth Sleepiness Scale (ESS) (Johns, 1991). EEG recording was performed as detailed below. At the third visit (V2), ESS was repeated and the combined dexamethasone/corticotropin releasing hormone test (DexCRH-test) was performed as detailed below.

2.2. Assessment of cognition, fatigue and depressive symptoms

Cognition was tested using the Multiple Sclerosis Inventory of Cognition (MUSIC), yielding a cognitive (MUSIC-cognition) and an abbreviated fatigue score (MUSIC-fatigue), respectively (Yildiz et al., 2014). Fatigue was further assessed by subjective perception through direct questioning. At V1 and V2, fatigue was assessed by the Multidimensional Fatigue Inventory (MFI), and by the Würzburg Fatigue Inventory for Multiple Sclerosis (WEIMuS), attributing 17 items to non-physical and physical fatigue (Flachenecker et al., 2006). Depressive symptoms were assessed using the Hamilton Depression Rating Scale (HDRS-21) and the Beck Depression Inventory (BDI).

2.3. Combined dexamethasone/corticotropin releasing hormone test

All participants underwent the combined DexCRH-test as described previously (Schinke et al., 2017).

2.4. EEG acquisition and EEG-vigilance assessments

We used the well-established EEG-based VIGALL algorithm (Vigilance Algorithm Leipzig, version 1; for manual of newest version see http://research.uni-leipzig.de/vigall), detailed in (Olbrich et al., 2012b), which allows the classification of 1-s EEG-segments into seven different states of wakefulness, ranging from high alertness after closing the eyes to drowsiness and sleep onset. V1 began at about 8.30 a.m. Fifteen minutes of resting-EEG were recorded with closed eyes. Participants were instructed to relax and not to fight a possibly occurring urge to fall asleep. The EEG was recorded with a 40 channel QuickAmp amplifier (Brain Products GmbH, Gilching, Germany) from 31 electrode sites (extended international 10–20 system) at a sampling rate of 1 kHz, referenced against common average. Impedances were kept below 10 k Ω. EOG was recorded with a bipolar channel of the QuickAmp device. Electrodes were placed above the left eye and under the right eye. EEG data were processed using BrainVision Analyzer 2.0 software (Brain Products GmbH, Gilching, Germany). EEG raw data were digitally filtered at 70 Hz (low-pass), 0.5 Hz (high-pass), and 50 Hz (notch-filter, range 5 Hz). EOG channels were screened for periods of open eyes. Eye artefacts and continuous muscle artefacts were removed using an independent component analysis (ICA)-based approach, segments with remaining artefacts were marked but only manually excluded.

2.5. EEG-vigilance staging

Segments were classified into seven different EEG-vigilance stages (see Fig. 1) using the Vigilance Algorithm Leipzig (VIGALL) (Olbrich et al., 2012b).

Fast Fourrier Transformation of the EEG-frequency bands delta, theta, alpha, and beta was computed for all EEG channels to obtain the frequency band power magnitude in μV^2 to approximate the strength of the underlying signal. Since topographical power mapping, but not EEG source solutions, depends upon reference electrode, a low resolution brain electromagnetic tomography (LORETA, Vision Analyzer software) estimated EEG source densities in four predefined regions of interest (ROIs): occipital, parietal, temporal and frontal. Segments were classified based on the EEG-power information of the four ROIs and additional information of the EOG channel amplitude. To avoid misclassification of low amplitude EEG segments that reflect desynchronization during states of high alertness, VIGALL separates high vigilance stage 0 from low vigilance stage B1 by taking into account slow eye movements (SEMs).

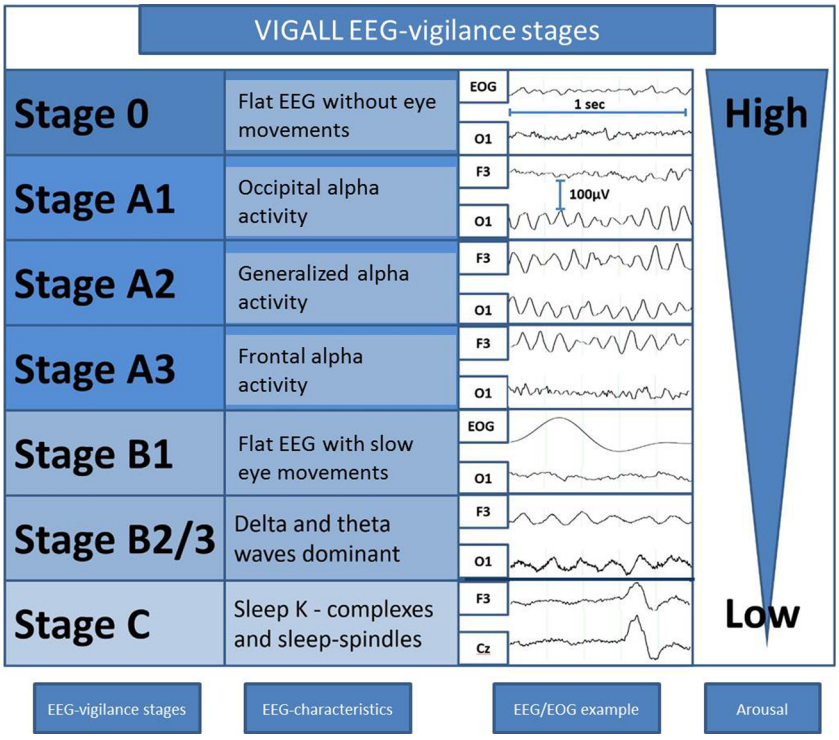

Fig. 1. Stages of CNS arousal classified by EEG-vigilance. EEG-stages are shown reflecting different levels of arousal. Column 2 states criteria of the Vigilance Algorithm Leipzig (VIGALL) for classification of the EEG-vigilance. Column 3 shows examples of EEG and electrooculography (EOG) curves. O1, F3, Cz: standardized occipital, frontal and central electrode placement of 10–20 EEG system.

Sleep spindles and/or K-complexes during sleep onset were marked manually by experienced EEG-raters.

Percentages of vigilance stages were computed by dividing the amount of segments of a certain stage by the amount of non-artefact segments. The type of EEG-vigilance regulation was computed by comparing the individual time series of 1-second vigilance stages with the time series of three different regulation types (hyperstable, slowly declining and unstable type) as defined by a k-means clustering approach from > 100 healthy subjects in a previous study (Olbrich et al., 2012b). EEG data sets were only included if artefacts showed in less than 10% of segments.

2.6. Statistical analysis

Clinical data, number of vigilance stages in VIGALL, MFI, WEIMuS, CGI, SF-A, ESS, MUSIC, BDI and HDRS were evaluated using two-tailed Mann-Whitney *U*-test or Pearson chi square. EEG-pattern frequencies were analysed using chi-square test. For statistical analysis of the DexCRH-test, we selected one measure of acute responsiveness, i.e. ACTH and cortisol 30 min after CRH stimulation ("post-CRH ACTH" and "post-CRH Cort" at 1530 h), and one measure integrating both chronic baseline state and responsiveness, i.e. area under the time course curve above zero according to the trapezoid rule ("ground" area-under-the-curve; AUC). Since these DexCRH-test curve parameters were not normally distributed (Shapiro-Wilk test $p < 0.05$) and skewed to the right in RRMS and HC, indicators were logarithmically transformed to reduce variance and to reach normal distribution. Results were analysed using two-tailed *t*-test or, if more than two groups were compared, using ANOVA with post-hoc Bonferroni correction. Results were considered significant at $p < 0.05$.

3. Results

Demographic data did not differ between RRMS and HC (see Table 1, education not shown). RRMS had a median EDSS of 2.0 (interquartile range 1.5–3.0) with a median of 2.5 relapses (interquartile range, IR 2.0–4.0) since diagnosis of multiple sclerosis and a median of 1.0 relapse (IR 0.0–2.0) within the last two years before V0. Duration from diagnosis to V0 was 35.6 month (IR 16.8–112.8). 44 RRMS (86.3%) were on disease modifying treatment, 7 RRMS (13.7%) were therapy-naïve (n = 5) or had discontinued disease modifying treatment for at least one year (n = 2). Compared to HC, RRMS had significantly higher values for impairment (CGI) and fatigue but not for cognition (MUSIC-cognition) or sleepiness. Depression scores were significantly higher in RRMS for self-reported (BDI), but not for physician-rated (HDRS) scales. Values at V1 and V2 highly correlated for all questionnaires obtained at both visits; therefore, means of both visits are reported (see Table 1).

For RRMS patients EEG-vigilance pattern analyses showed hyperstable pattern in 32 RRMS (62.7%), slowly declining pattern in 10 RRMS (19.6%) and unstable pattern in 9 RRMS (17.6%). This distribution was significantly different from that observed both in literature (Olbrich et al., 2012b) (hyperstable pattern in 56 HC (39.7%), slowly declining pattern in 50 HC (35.5%) and unstable pattern in 35 HC (24.8%); $p = 0.003$) and in our HC (hyperstable pattern in 9 HC (45.0%), slowly declining pattern in 8 HC (40%) and unstable pattern in 3 HC (15%); $p = 0.011$, see Fig. 2).

We next compared RRMS patients grouped based on the EEG-patterns and explored if these patterns might be recognizable by clinically detectable characteristics. Both hyperstable pattern and unstable pattern were associated with higher scores in BDI (median 4.5 (2.0–7.0) and 6.0 (3.0–10.0), respectively, $p = 0.031$) than slowly declining pattern (median 0.0 (0.0–4.0)). A higher percentage of RRMS with unstable pattern (77.8%) had values for MUSIC fatigue above the cut off for clinically relevant fatigue (score 11) compared to slowly declining pattern (30%) or hyperstable pattern (34.4%; $p = 0.047$). Although several fatigue measures were higher in both hyper- and unstable than with slowly declining pattern, these differences were not significant (see Table 2).

Next, we analysed HPA-axis as potentially underlying pathomechanism for arousal regulation and fatigue for all 49 RRMS and 18 HC with complete endocrinological data set. Compared to HC, RRMS showed a higher ACTH rise after CRH application ($Log_{10}ACTH_{1530h}$; $p = 0.001$) and area under the curve ($Log_{10}ACTH_{AUC}$; $p = 0.047$), implicating a higher activation of HPA-axis as described earlier (Then Bergh et al., 1999b). Cortisol output did not differ between HC and RRMS, as was found in a different study (Gottschalk et al., 2005) (see Table 1, Fig. 3).

Table 1
Comparison of healthy controls and patients with relapsing-remitting multiple sclerosis for demographic data, questionnaires concerning illness severity, fatigue, cognition and depression, and for ACTH and Cortisol response to DexCRH-test.

	HC (n = 20)	RRMS (n = 51)	*p*
Demographic data			
Age (years)	31.5 (24.5-37.8)	36.0 (29.0-42.0)	0.148
Gender (female)	10/20 (50%)	35/51 (68.6%)	0.143
Impairment			
Clinical Global Impression Scale (CGI)	1.0 (1.0-1.0)	3.0 (3.0-4.0)	< **0.001****
Fatigue			
Multidimensional Fatigue Inventory (MFI)			
-General Fatigue	6.3 (5.1-7.5)	9.5 (7.0-12.5)	< **0.001****
-Physical Fatigue	5.5 (5.1-7.3)	7.5 (6.0-11.5)	**0.003****
-Reduced Activity	6.5 (5.0-7.5)	7.5 (6.5-10.5)	**0.029***
-Reduced Motivation	5.5 (4.5-6.4)	6.0 (5.0-8.5)	**0.032***
-Mental Fatigue	6.0 (5.0-7.3)	9.0 (6.5-12.0)	< **0.001****
Würzburg Fatigue Inventory for Multiple Sclerosis (WEIMuS)			
-Overall fatigue	6.8 (3.1-11.5)	20.0 (6.0-29.0)	**0.001****
-Non-physical fatigue	3.0 (1.6-6.5)	7.5 (2.5-14.0)	**0.017***
-Physical fatigue	2.8 (1.5-6.4)	10.5 (4.0-16.0)	**0.001****
MUSIC-Fatigue	5.0 (3.0-6.0)	8.0 (6.0-11.3)	< **0.001***
-Clinically relevant fatigue	3/20 (15.0%)	21/51 (41.1%)	**0.036***
Cognition			
MUSIC-Cognition	27.0 (26.0-29.0)	25.5 (23.0-28.0)	0.134
Sleepiness			
Epworth Sleepiness Scale (ESS)	6.5 (4.0-7.9)	8.0 (5.0-11.5)	0.056
German sleep questionnaire (SF-A)			
-Quality of sleep	6.0 (5.8-6.5)	5.9 (5.5-6.1)	0.364
-Feeling of being rested	3.6 (3.2-4.0)	3.7 (3.0-4.1)	0.780
-Mental balance	4.2 (3.7-4.4)	3.9 (3.4-4.3)	0.343
-Mental exhaustion	3.2 (2.6-3.4)	3.2 (2.7-3.7)	0.476
-Psychosomatic symptoms during sleep	1.3 (1.0-1.5)	1.0 (1.0-1.5)	0.959
Depression			
Beck Depression Inventory (BDI)	1.0 (0.0-4.8)	4.0 (1.0-7.0)	**0.040***
Hamilton Depression Rating Scale (HDRS)	0.5 (0.0-3.0)	1.0 (0.0-3.0)	0.341
ACTH and Cortisol response	**HC (n = 18)**	**RRMS (n = 49)**	
$Log_{10}ACTH_{1530h}$	0.025 (0.136)	0.125 (0.197)	**0.023***
$Log_{10}ACTH_{AUC}$	0.662 (0.156)	0.753 (0.175)	**0.047***
$Log_{10}Cortisol_{1530h}$	1.506 (0.290)	1.623 (0.351)	0.208
$Log_{10}Cortisol_{AUC}$	2.244 (0.315)	2.296 (0.359)	0.593

Values are median (interquartile range, analysed by Mann-Whitney U), except for gender and clinically relevant fatigue (proportion, Pearson chi square) and logarithmic values (mean, standard deviation). Mean values from V1 and V2 are displayed for MFI and WEIMuS. P-values < 0.05 are highlighted in bold. * = Significant findings with $p < 0.05$, ** = Significant findings with $p < 0.01$. HC = healthy controls, MFI = Multidimensional Fatigue Inventory, MUSIC = Multiple Sclerosis Inventory of Cognition, RRMS = relapsing-remitting multiple sclerosis, WEIMuS = Würzburg Fatigue Inventory for Multiple Sclerosis.

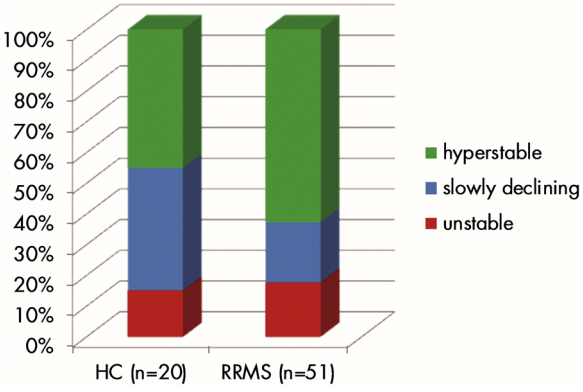

Fig. 2. Frequency of vigilance patterns in healthy controls and patients with relapsing-remitting multiple sclerosis.
Distribution of vigilance patterns was significantly different in patients with relapsing-remitting multiple sclerosis with higher percentage of hyperstable pattern than in healthy controls ($p = 0.011$, Pearson chi square). HC = healthy controls, RRMS = relapsing-remitting multiple sclerosis.

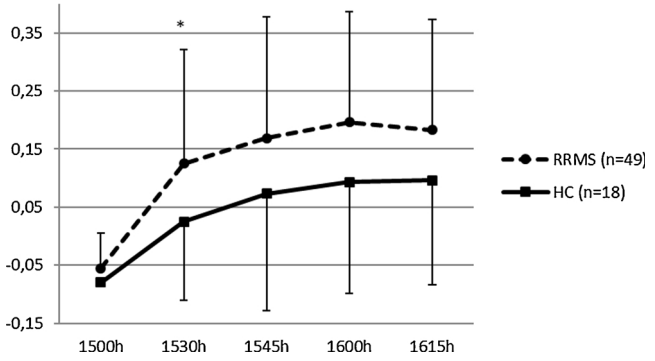

Fig. 3. Time course of ACTH response to DexCRH-test in healthy controls and patients with relapsing-remitting multiple sclerosis.
Time course of ACTH response to DexCRH-test is shown for healthy controls (solid line, squares) and for patients with relapsing-remitting multiple sclerosis (dashed line, circles). Logarithmic ACTH values are displayed. Patients with relapsing-remitting multiple sclerosis showed significantly higher ACTH 30 min after CRH application ($Log_{10}ACTH_{1530h}$). Data are given as mean with standard deviation. * = Significant findings with $p < 0.05$. HC = healthy controls, RRMS = relapsing-remitting multiple sclerosis.

Table 2
Comparison of hyperstable, slowly declining and unstable EEG-vigilance pattern in RRMS for demographic data, questionnaires concerning illness severity, fatigue, cognition and depression, and for ACTH and Cortisol response to DexCRH-test.

	Hyperstable pattern (n = 32)	Slowly declining pattern (n = 10)	Unstable pattern (n = 9)	*p*
Demographic data				
Age (years)	36.2 (9.5)	36.4 (7.4)	35.3 (6.8)	0.958
Gender (females)	68.8%	60.0%	77.8%	0.706
Impairment				
Clinical Global Impression Scale (CGI)	3.2 (1.1)	2.7 (1.3)	3.3 (0.5)	0.360
Fatigue				
Multidimensional Fatigue Inventory (MFI)				
-General Fatigue	10.0 (3.8)	9.1 (3.3)	10.1 (2.7)	0.758
-Physical Fatigue	8.5 (3.0)	8.9 (5.4)	8.9 (4.1)	0.920
-Reduced Activity	8.6 (3.4)	8.1 (3.0)	9.7 (5.2)	0.604
-Reduced Motivation	7.0 (2.2)	6.1 (1.9)	6.9 (2.9)	0.564
-Mental Fatigue	9.3 (3.4)	7.8 (2.9)	10.4 (4.1)	0.244
Würzburg Fatigue Inventory for Multiple Sclerosis (WEIMuS)				
-Overall fatigue	21.1 (13.0)	13.2 (12.4)	23.2 (15.1)	0.197
-Non-physical fatigue	10.0 (7.6)	5.4 (4.8)	10.6 (8.1)	0.188
-Physical fatigue	11.1 (6.7)	7.8 (8.5)	10.6 (8.1)	0.327
MUSIC-Fatigue	9.1 (4.6)	7.8 (4.0)	11.3 (4.1)	0.221
-Clinically relevant fatigue	11/32 (34.4%)	3/10 (30.0%)	7/9 (77.8%)	**0.047***
Cognition				
MUSIC-Cognition	26.0 (3.6)	25.8 (4.2)	23.3 (3.4)	0.182
Sleepiness				
Epworth Sleepiness Scale (ESS)	8.2 (4.3)	7.7 (3.8)	8.7 (3.3)	0.860
German sleep questionnaire (SF-A)				
-Quality of sleep	5.7 (0.8)	5.9 (0.5)	5.9 (0.7)	0.492
-Feeling of being rested	3.5 (0.9)	3.4 (0.5)	3.7 (0.9)	0.701
-Mental balance	3.7 (0.7)	4.1 (0.7)	4.0 (1.0)	0.191
-Mental exhaustion	3.2 (0.7)	3.2 (0.5)	2.9 (0.9)	0.524
-Psychosomatic symptoms during sleep	1.3 (0.5)	1.4 (0.5)	1.4 (0.6)	0.786
Depression				
Beck Depression Inventory (BDI)	5.2 (4.3)$^{\#}$	1.3 (2.7)$^{\#+}$	6.4 (4.1)$^{+}$	**0.031***
Hamilton Depression Rating Scale (HDRS)	2.3 (2.3)	1.2 (2.3)	3.6 (5.5)	0.251
ACTH and Cortisol response				
$Log_{10}ACTH_{1530h}$	0.185 (0.207)$^{\#}$	0.063 (0.155)	−0.007 (0.111)$^{\#}$	**0.013***
$Log_{10}ACTH_{AUC}$	0.788 (0.191)	0.740 (0.139)	0.652 (0.121)	0.087
$Log_{10}Cortisol_{1530h}$	1.669 (0.351)	1.542 (0.428)	1.563 (0.256)	0.313
$Log_{10}Cortisol_{AUC}$	2.344 (0.350)	2.230 (0.483)	2.209 (0.219)	0.299

Values are mean (standard deviation), except for gender and clinically relevant fatigue (proportion, Pearson chi square) and logarithmic values (mean, standard deviation). Mean values from V1 and V2 are displayed for MFI and WEIMuS. P-values < 0.05 are highlighted in bold. Asterisks mark significant differences for comparison of the three groups (ANOVA, *=p < 0.05, $^{\#+}$=significant differences in post-hoc Bonferroni testing where ANOVA was significant). MFI = Multidimensional Fatigue Inventory, MUSIC = Multiple Sclerosis Inventory of Cognition, WEIMuS = Würzburg Fatigue Inventory for Multiple Sclerosis.

When dividing RRMS into the three EEG-vigilance patterns, this hyperactivation was found to be mainly driven by RRMS with hyperstable pattern with significant difference for $Log_{10}ACTH_{1530h}$ (p = 0.013) and a trend towards significance for $Log_{10}ACTH_{1545h}$ (p = 0.052), compared to RRMS with unstable pattern (see Table 2).

4. Discussion

This is, to our knowledge, the first study to describe EEG-vigilance patterns in multiple sclerosis patients. Classifying brain arousal regulation using the VIGALL algorithm, our study revealed that only a minority of multiple sclerosis patients regulates arousal during rest in a slowly declining fashion, while a significantly higher prevalence of hyperstable arousal regulation occurs in RRMS patients than in healthy controls. Since we did not detect differences in reported sleep duration or sleepiness in RRMS, vigilance regulation appears not to be driven by the amount of sleep itself. Patients with major depression (MD) show hyperstable arousal regulation as well (Olbrich et al., 2012b) and fatigue in those patients is not associated with sleepiness either, but with a reduced sleep propensity. Interestingly, MD patients report exhaustion and a state of inner tension but not sleepiness (Hegerl et al., 2013). Thus, fatigue in multiple sclerosis patients, experienced as lack of mental and physical resources, could be mainly driven by hyperstable arousal regulation, expected to prematurely exhaust multiple sclerosis patients.

Most clinical data did not allow for reliable attribution of patients to one of the three different EEG-vigilance patterns. Only “clinically relevant fatigue”, as classified by the self-reported MUSIC-fatigue, was significantly higher in patients with the unstable pattern. This finding appears plausible, and it is rather surprising that all other measures of fatigue were so mildly elevated in the hyperstable and unstable compared to the slowly declining groups.

In contrast to clinical variables, some endocrinological characteristics were distinct among groups: HPA axis showed significantly highest activity in hyperstable, and lowest activity in unstable arousal regulation, which was interestingly limited to ACTH output. Since the same co-occurrence of hyperactive HPA-axis and hyperstable arousal has been observed in patients with depression (Hegerl et al., 2012), we propose hyperstable arousal in multiple sclerosis patients to be pathophysiologically akin to depression. Conversely, hypofunction of the HPA axis has been observed in patients with the ill-explained chronic fatigue syndrome (Scott und Dinan, 1999) and in cancer-related fatigue (Bower et al., 2007), and at least cancer-related fatigue has been associated with unstable arousal regulation. This, again, is echoed in our cohort of RRMS patients, where the group with unstable arousal revealed the lowest HPA axis activity. Even though higher fatigue scores in both hyper- and unstable arousal groups did not reach statistical significance, we still regard this as suggestive (while obviously no proof) for a relationship to the pathomechanisms of fatigue, proposing two diverse basic principles: On the one hand, hyperactive HPA-axis and hyperstable arousal regulation, resulting in a state of neurophysiological hyperarousal, as found in major depression (Olbrich et al.,

2012b; Hegerl et al., 2012; Schmidt et al., 2016; Ulke et al., 2017) and potentially responding to antidepressants. On the other hand, relative hypofunction of the HPA-axis and unstable arousal with increased propensity to develop drowsiness and to fall asleep, as found in CRF (Olbrich et al., 2012a), CFS (Neu et al., 2008; Spitzer und Broadman, 2010) and ADHS (Hegerl und Hensch, 2014; Geissler et al., 2014; Lopez et al., 2018) with potential benefit from treatment with psychostimulants.

While the association of arousal regulation and HPA axis activity is supported by the analogy to other neuropsychiatric disorders, an intertwined role of HPA axis dysregulation in MS fatigue has been shown before (Gottschalk et al., 2005). It is also anatomically plausible, since resting state fMRI and MR spectroscopy in fatigued MS patients has implicated disruption of connections of basal ganglia and thalamus, next to (pre-)frontal and parietal regions (e.g. Calabrese et al., 2010; Finke et al., 2015; Jaeger et al., 2019; Kantorová et al., 2017).

The observed HPA axis hyperactivation in our sample was less pronounced than described earlier in therapy-naïve RRMS, let alone patients with progressive multiple sclerosis (Then Bergh et al., 1999a). This probably results from the large proportion of RRMS patients receiving disease modifying treatments, which appear to have a blunting effect on HPA axis activity (Kümpfel et al., 2014). This may be an important reason for the relatively weak association between arousal regulation, HPA axis activity and fatigue, and thus limits the generalizability of our study.

The suggested pathophysiological heterogeneity of MS fatigue may, if confirmed, explain the inconsistent effect of pharmacological treatments in clinical studies (Rojí und Centeno, 2017; Schwid und Murray, 2005): patients may not adequately distinguish effects of fatigue from those of motor limitations, cognitive impairment, and other symptoms commonly caused by multiple sclerosis, complicating the interpretation of clinical studies (Schwid und Murray, 2005), and stratification according to pathophysiological mechanisms (largely then unknown) was so far impossible. Since objective measurement of fatigue is impractical, we may have missed firmer correlations between fatigue, HPA axis activation and EEG-vigilance pattern. Currently available fatigue scores appear insufficient to reflect fatigue in its entirety (Flachenecker et al., 2002; Littleton et al., 2010), let alone identify the underlying pathophysiology on clinical grounds.

In conclusion, we report on hyperstable arousal regulation in the majority of patients with relapsing-remitting multiple sclerosis, an association with the mildly dysregulated HPA-axis activity, and propose two opposing pathophysiological correlates existing in clinically homogeneous fatigue in multiple sclerosis. We therefore propose that future treatment studies of fatigue in multiple sclerosis should be more likely to show effectiveness if treatment allocation were stratified by EEG-arousal pattern and HPA-axis activity. The design of such trials should also include efforts to develop clinical tools allowing for the allocation to the patterns of arousal regulation.

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Declaration of Competing Interest

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K. Meyer, M. Schlingmann and S. Olbrich declare that there is no conflict of interest.

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