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Heart Rate Variability During Sleep and Subsequent Sleepiness in Patients with Chronic Fatigue Syndrome

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Abstract

We determined whether alterations in heart rate dynamics during sleep in patients with chronic fatigue syndrome (CFS) differed from controls and/or correlated with changes of sleepiness before and after a night in the sleep laboratory. We compared beat-to-beat RR intervals (RRI) during nocturnal sleep, sleep structure, and subjective scores on visual analog scale for sleepiness in 18 CFS patients with 19 healthy controls aged 25–55 after excluding subjects with sleep disorders. A short-term fractal scaling exponent (α_1) of RRI dynamics, analyzed by the detrended fluctuation analysis (DFA) method, was assessed after stratifying patients into those who reported more or less sleepiness after the night's sleep (a.m. sleepier or a.m. less sleepy, respectively). Patients in the a.m. sleepier group showed significantly ($p < 0.05$) higher fractal scaling index α_1 during non-rapid eye movement (non-REM) sleep (Stages 1, 2, and 3 sleep) than healthy controls, although standard polysomnographic measures did not differ between the groups. The fractal scaling index α_1 during non-REM sleep was significantly ($p < 0.05$) lower than that during awake periods after sleep onset for healthy controls and patients in the a.m. less sleepy group, but did not differ between sleep stages for patients in the a.m. sleepier group. For patients, changes in self-reported sleepiness before and after the night correlated positively with the fractal scaling index α_1 during non-REM sleep ($p < 0.05$). These results suggest that RRI dynamics or autonomic nervous system activity during non-REM sleep might be associated with disrupted sleep in patients with CFS.

Keywords

heart rate dynamics; autonomic nervous system; sleepiness; chronic fatigue syndrome; unrefreshing sleep

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Introduction

Chronic fatigue syndrome (CFS) is a medically unexplained condition occurring mostly in women and characterized by persistent or relapsing fatigue lasting at least 6 months and producing substantial interference with normal activities. In addition to severe fatigue, one of the symptoms used for diagnosing CFS is unrefreshing sleep, and, in fact, this sleep-related problem is the most common complaint among patients with severe medically unexplained fatigue (Unger et al., 2004).

While research exists showing differences in sleep morphology between CFS patients and healthy controls, relatively little work has been done to identify physiological correlates of both disturbed sleep and patient-based sleep complaints. One study reported an association between unrefreshing sleep and reduced heart rate variability (HRV) during sleep (Burton et al., 2010). Specifically, Burton et al. showed that time- and frequency-domain HRV during sleep were significantly lower in patients with CFS compared to healthy controls and that HRV parameters could predict subjective sleepiness in CFS patients (Burton et al., 2010). A population-based study also showed reduced HRV during sleep in patients with CFS compared to age, sex, and body mass index matched healthy controls (Boneva et al., 2007). However, the effects of sleep architecture were not controlled for in these results. Having not done this could have impacted on the results because sleep architecture can differ between controls and patients with CFS (Fischler et al., 1997; Krupp et al., 1993; Morriss et al., 1993; Sharpley et al., 1997; Togo et al., 2008) and time- and frequency-domain HRV can differ among sleep stages in healthy people (Bonnet et al., 1997; Otzenberger et al., 1998; Togo et al., 2001). Moreover, increased sleep fragmentation manifested by visible electroencephalogram arousal could affect the association between subjective sleepiness and HRV during sleep in CFS patients.

Whether an association exists between HRV and sleep stage in CFS patients also has not been determined, although doing so may help us understand the causes of unrefreshing sleep in these patients. Therefore, we thought an appropriate next step would be to compare the set of all HRV variables within the sleep stages of patients with CFS compared to those of healthy controls. Recent advances in time series analytic techniques using detrended fluctuation analysis (DFA) have allowed for the analysis of short- and long-term HRV. Using DFA to develop fractal scaling exponents allows the researcher to use short runs of as few as 50 beats of heart rate (HR) data to determine their fractal-like properties of short-term HRV (Peng et al., 1995). In view of the fact that some CFS patients without sleep disorders have fragmented sleep (Togo et al., 2008), we thought using such an analysis (Pena et al., 2009) might allow useful comparisons of characteristics of HRV for each sleep stage between healthy controls and CFS patients.

Therefore, in this study, our first purpose was to determine whether HRV during each sleep stage differed between controls and patients with CFS. The second purpose of this study was to determine whether time-domain HRV and fractal HRV dynamics during sleep was associated with changes of sleepiness before and after a night sleep in patients with CFS. We did this because, in earlier work, we had shown sleep morphology to be abnormal in CFS patients reporting being sleepier following sleep than before (Togo et al., 2008).

Materials and Methods

Subjects

The subjects were 52 women (26 healthy controls and 26 with CFS) ranging in age from 25 to 55 years. Subjects older or younger than those selected were excluded because of age effects on sleep. There were no differences in age between patients and controls. Subjects with CFS were either physician-referred or self-referred in response to media reports about our research. Healthy controls were acquaintances of patients or responded to recruitment flyers. Patients fulfilled the 1994 case definition for CFS (Fukuda et al., 1994) and thus had no medical explanation for their symptoms on the basis of history, physical examination or laboratory tests. Psychiatric diagnosis according to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV), was made using the computerized version of the Diagnostic Interview Schedule (Robbins et al., 2000). The psychiatric interview was used to identify and exclude from study the following DSM-IV-based disorders: schizophrenia, eating disorders, substance abuse, or bipolar disorder as well as current major depressive disorder, a psychiatric disorder that can disrupt sleep. Therefore patients and controls were all negative for these exclusionary psychiatric diagnoses. All subjects provided informed consent, approved by the medical school's institutional review board to participate in this research.

Experimental procedures

After instructions to refrain from alcohol and caffeine ingestion and to avoid engaging in prolonged and/or strenuous exercise in the daytime of study nights, subjects then underwent one night of PSG recording in a quiet, shaded hospital room. Subjects went to bed at their usual bedtime and slept until 7:15 to 8:00 a.m. the next morning. Subjects were all studied during the follicular phase of their menstrual cycles.

Measures

Subjects underwent full nocturnal polysomnography (Compumedics, Charlotte, NC, USA) consisting of electroencephalogram (EEG) (C3/A2, O1/A2, and FZ/A2), electrooculogram (EOG), submental electromyogram (EMG), anterior tibialis EMG, a lead II electrocardiogram (ECG), thoracic and abdominal motion, airflow using a nasal cannula/pressure transducer and an oral thermistor, and pulse oximetry. Analog signals for EEG, EOG, EMG, ECG, thoracic and abdominal motion, airflow, and pulse oximetry were processed on a real-time basis, using a Dell personal computer (Dell, Round Rock, TX, USA). The sampling rate for the ECG signal was 320 Hz. Sleep was scored every 30 seconds by a single scorer according to standard criteria of Rechtschaffen and Kales (Rechtschaffen et al., 1968). Sleep onset was defined as the first three consecutive epochs of Stage 1 sleep or the first epoch of other stages of sleep. An arousal was defined according to standard criteria of the American Academy of Sleep Medicine (American Sleep Disorders Association, 1992) as a return to alpha- or fast-frequency EEG activity, well differentiated from the background, lasting at least 3 seconds but no more than 15 seconds. Subjects with evidence for clinically evident sleep disorders in the form of restless leg syndrome or sleep disturbed breathing or poor quality PSG data were excluded from further study (7 healthy

controls and 8 with CFS). This left a study sample of 19 healthy controls and 18 CFS patients.

RR interval data correction

The RR interval signal was derived from the ECG. All RR intervals were scanned for extra or missing beats that could affect the results of time- and frequency-domain analysis. The abnormal intervals were corrected by either the insertion (for missing beats) or the omission (for doubled or tripled beats) of beats. The number of beats corrected manually in this way was <0.5%.

Spectral analysis

The HRV data during sleep (from sleep onset to the last epoch of any stages of sleep) were aligned sequentially to obtain equally spaced samples using the mean RR interval (RRI). After eliminating any linear trend by linear regression, a fast Fourier transform was used to obtain the power spectrum density. All the spectra were estimated by averaging spectra obtained from 10-time shifted subsets. Integrated spectral power of high (HF, > 0.15 Hz), low (LF, 0.04–0.15 Hz), and very-low frequency (VLF, 0.003–0.04 Hz) range and LF/HF ratio were calculated (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). HF power and LF/HF have been used to assess cardiac vagal tone and cardiac sympathovagal balance, respectively (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). For supplemental analysis, a fast Fourier transform was also used for 1-min segments of HRV to obtain the power spectrum density after eliminating any linear trend. HF power, LF power, and LF/HF were calculated for every minute epoch without stage transition to obtain mean HF, LF, and LF/HF for each sleep stage for each subject. When arousals were observed during a minute, data for the epoch was used for calculating mean values for arousal. In a previous study, HF and LF powers during rest remained stable with recording duration as brief as 40 s compared with 5-min recordings in healthy subjects (Lim et al., 2011).

DFA analysis

The detrended fluctuation analysis technique was used to quantify the fractal scaling properties of short-term HRV. The root-mean-squares fluctuation of integrated and detrended time series was measured at different observation windows and plotted against the size of the observation window on a log-log scale. The scaling exponent α represents the slope of this line, which relates (log)fluctuation to (log>window size. Values of α close to 0.5 are associated with white noise (uncorrelated signal), whereas values close to 1.5 are associated with Brownian noise (strongly correlated signal). Values near 1 are characteristic of fractal like processes, associated with the dynamic behavior of time series generated by complex systems, such as the autonomic regulation of the sinus rhythm of a healthy subject. Details of DFA have been shown previously (Peng et al., 1995). The short-term (from 4 to 11 beats) scaling exponent (α_1) was calculated for every minute epoch. The short-term scaling exponents for epochs without stage transition were used for obtaining mean α_1 for each sleep stage for each subject. When arousals were observed during a minute, α_1 for the epoch was used for calculating mean α_1 for arousal.

Subjective test

A visual analog scale (0–15.5 cm) was used to estimate perceived sleepiness immediately before and after each PSG recording. Visual analog scales have consistently been shown to provide valid measures of subjective feelings (McCormack et al., 1988; Togo et al., 2008).

Depressed mood

The Centers for Epidemiological Study – Depression scale was used as an indicator of depressed mood. This 20-item scale required respondents to rate how often certain symptoms occurred during the past week on a scale from rarely or more (score = 0) to most of the time (score = 3). Items were summed to yield a total score. High values indicate more depressed mood.

Statistical analyses

We dichotomized data on the basis of changes in subjects' self-reported sleepiness computed on data collected immediately before and after overnight PSG. We labeled those with more sleepiness in the morning than on the night before as 'a.m. sleepier' and those with less sleepiness in the morning than on the night before as 'a.m. less sleepy'. Differences in measured variables between groups were assessed using the non-paired *t* test or analysis of variance after HRV variables which were not normally distributed were logarithmically transformed to achieve normal distribution. Post hoc analyses used Tukey Student range tests to adjust for multiple comparisons. Changes of self-reported sleepiness before and after sleep were assessed using the paired *t* test. Interrelationships between self-reported sleepiness and measured variables were tested by simple Pearson correlation coefficients. A *p* value of less than 0.05 was considered statistically significant.

Results

Table 1 depicts standard PSG measures of the healthy controls and CFS patients for this study; these data have been published in part previously (Togo et al., 2008). Total sleep time was significantly ($p < 0.05$) longer for healthy controls than patients as were the total durations of Stages 1, 2, and REM sleep, whereas total duration of wakefulness did not differ between healthy controls and patients. As a result, patients had a significantly ($p < 0.05$) lower sleep efficiency (that is, the percentage of the total time asleep after falling asleep relative to the time spent in bed) than healthy controls. Table 1 also shows that sleepiness before and after the PSG night was significantly ($p < 0.05$) higher in patients than healthy controls. Values for self-reported a.m. sleepiness decreased compared with the evening in healthy controls ($p < 0.05$), whereas it did not decrease for patients.

Table 2 shows selected HRV variables of the healthy controls and CFS patients. Mean and SD of RRI, HF and VLF power, and the ratio of LF to HF collected over the entire PSG night significantly ($p < 0.05$) differed between healthy controls and patients. In addition, some HRV variables during each sleep stage differed between the groups. Mean and SD of RRI during Stages 1 and 2 sleep were significantly ($p < 0.05$) lower for CFS patients than healthy controls. Mean of RRI during Stage REM sleep and SD of RRI during Stage 3 sleep were also significantly ($p < 0.05$) lower for patients than healthy controls. Mean fractal

scaling index α_1 during Stages 2 and 3 sleep was significantly ($p < 0.05$) higher for CFS patients than healthy controls. For these sleep stages, HF power and the ratio of LF to HF of 1-min HRV were also significantly ($p < 0.05$) lower and higher for CFS patients than healthy controls, respectively. The fractal scaling index α_1 during Stages 1, 2, and 3 sleep for healthy controls and during Stage 3 sleep for CFS patients was significantly ($p < 0.05$) lower than that during wakefulness after sleep onset and arousal for healthy controls and CFS patients, respectively.

Patients in the a.m. less sleepy group showed significantly ($p < 0.05$) shorter duration of Stage REM sleep than healthy controls (Table 3). However, none of the individual HRV variables differed between healthy controls and patients in the a.m. less sleepy group (Table 4, Figure 1). Patients in the a.m. sleepier group showed neither differences in standard PSG measures from controls (Table 3) nor in HF, LF, and VLF power of HRV collected over the entire PSG night (Table 4). Nonetheless, patients in the a.m. sleepier group showed significantly ($p < 0.05$) lower RRI during Stages 1, 2, 3, and REM sleep, lower SD of RRI during Stage 2, and higher fractal scaling index α_1 during Stages 1, 2, and 3 sleep compared to healthy controls (Figure 1). For Stages 1 and 3, the ratio of LF to HF of 1-min HRV was also significantly ($p < 0.05$) higher for patients in the a.m. sleepier group than healthy controls (Table 4). The fractal scaling index α_1 during Stages 1, 2, and 3 sleep was significantly ($p < 0.05$) lower than that during wakefulness after sleep onset and during arousals for healthy controls and patients in the a.m. less sleepy group, but the fractal scaling index α_1 did not differ among sleep stages for patients in the a.m. sleepier group (Figure 1). Prior to going to sleep, the a.m. less sleepy patient group reported more sleepiness than both healthy controls and patients in the a.m. sleepier group ($p < 0.05$) (Table 3). On the morning, after their night in the sleep lab, patients in the a.m. sleepier group had significantly more sleepiness than both healthy controls and patients in the a.m. less sleepy group ($p < 0.05$) (Table 3). For patients, changes in self-reported sleepiness over the PSG night correlated positively with the fractal scaling index α_1 during Stages 1, 2, and 3 sleep ($r = 0.50, 0.51, 0.51$, respectively; $p < 0.05$). No significant relations were found among changes in self-reported sleepiness and any variables for sleep macro-architecture in patients with CFS.

Discussion

Pitson and Stradling (Pitson et al., 1998) suggested that non-EEG markers of arousal might be important and even more reliable signs of arousals than EEG. For example, somatosensory stimulation during sleep can produce changes in RRI without overt EEG desynchronization (Winkelman, 1999). Repeatedly induced autonomic activations in the absence of visible EEG arousal cause increased objective daytime sleepiness in healthy subjects (Martin et al., 1997b). In addition, autonomic activation could possibly be an index to quantify sleep disturbance in obstructive sleep apnea (OSA). Bennett et al. found significant correlations between autonomic activation during sleep and objective measures of sleepiness on both a pretreatment night and on a night during treatment with nasal continuous positive airway pressure. These data suggest that autonomic activation is a good arousal index for predicting daytime sleepiness in OSA (Bennett et al., 1998). Recently, it has also been suggested that patients with CFS have an association between unrefreshing

sleep and autonomic changes during sleep, although the effects of sleep architecture were unclear (Boneva et al., 2007; Burton et al., 2010).

In this study, we looked for relations between HRV and subjective sleep quality in CFS patients while factoring out the effects of sleep architecture on HRV. To do this, we examined RRI dynamics during each sleep stage by using the DFA method to obtain characteristics of 1-min HRV and to examine data across the entire night. As a result, the data reported here indicate that RRI dynamics during non-REM sleep differed between healthy controls and patients with CFS. Mean fractal scaling index α_1 during Stages 2 and 3 sleep was significantly ($p < 0.05$) higher for CFS patients than healthy controls. In addition, as shown in previous studies (Fischler et al., 1997; Krupp et al., 1993; Morriss et al., 1993; Sharpley et al., 1997; Togo et al., 2008), the patients, compared to healthy controls, showed evidence for sleep disruption in the form of significantly reduced total sleep time, reduced sleep efficiency, and changes in whole night HRV in the form of significantly reduced HF and VLF power and increased ratio of LF to HF. In comparison with controls, sleep in CFS had little effect on self-reported sleepiness.

The variability of RRI dynamics during non-REM sleep for the patients was reduced considerably by dichotomizing the patients into a group that felt sleepier after a night's sleep than before and a group that felt less sleepy after a night's sleep. However, the variability of sleep macro-architecture and variables for whole night HRV were not reduced. Those patients reporting less sleepiness after a night's sleep had RRI dynamics for each sleep stage similar to those for healthy controls. In contrast, patients in the a.m. sleepier group had significantly ($p < 0.05$) higher fractal scaling index α_1 during Stages 1, 2, and 3 sleep than healthy controls (Figure 1). Therefore, the net effects of these changes in RRI dynamics during non-REM sleep might be associated with the unrefreshing sleep reported by this group of patients. This is also supported by our results showing that changes in subjective sleepiness over the PSG night correlated positively with the fractal scaling index α_1 during non-REM sleep, but did not with any variables for sleep macro-architecture in patients.

Recent evidence suggests that abnormalities of cardiovascular regulation may play an important role in the pathophysiology of CFS. Patients with CFS develop increased HR, reduced HRV (Yamamoto et al., 2003), and increased symptoms (Bou-Holaigah et al., 1995) during orthostatic challenge. A population-based study also found increased HR and reduced HRV in CFS patients during sleep as well as a significant correlation between high norepinephrine levels and higher HR in CFS patients (Boneva et al., 2007) – possibly reflecting increased sympathetic tone to the heart. In line with these studies, our present study showed lower mean RRI, higher ratio of LF to HF, and a non-significant trend for lower HF, LF, and VLF powers of whole night HRV for patients in the a.m. sleepier group (Table 4).

Furthermore, our study showed that cardiovascular regulation of CFS patients differed from that of healthy controls even when we eliminated effects of sleep macro-architecture. This could be a reason why CFS patients report their sleep to be unrefreshing. Although there is not a standard explanation for the breakdown of fractal like processes related to RRI, fractal scaling index α_1 could be related to the balance between sympathetic and vagal activity. An

increased α_1 is associated with concurrent increased sympathetic activity and decreased vagal activity. In contrast, a decreased α_1 is associated with concurrent coactivation of sympathetic and vagal activity (Tulppo et al., 2005). A previous study showed that overall sympathetic inhibition by clonidine decreased exponents of short-term HRV (Castiglioni et al., 2011). In addition, our supplemental analysis showed that the ratio of LF to HF of 1-min HRV for Stages 1 and 3 sleep was significantly ($p < 0.05$) higher for patients in the a.m. sleeper group than healthy controls. Therefore, cardiovascular regulation during non-REM sleep for the patients might be associated with a shift in the sympathovagal balance toward sympathetic dominance. Further research is needed to determine whether cardiovascular dysregulation during non-REM sleep for patients with CFS is related to activation of sympathetic activity or withdrawal of vagal activity.

Although this study was not designed to assess the physiological mechanisms of the association between cardiovascular regulation and sleepiness in patients with CFS, a relationship between arousal and RRI dynamics during sleep is well known. Arousal from sleep has been found to be associated with a phasic response in RRI (i.e., a bout of tachycardia-bradycardia) (Sforza et al., 2000; Togo et al., 2006). A phasic fluctuation in RRI, similar to that seen during arousal, is also associated with brief microarousals, lasting at least 1.5 seconds (Martin et al., 1997a) and subcortical arousals manifested by the presence of bursts of delta waves or K-complexes in EEG (Sforza et al., 2000). Time series of RRI of the phasic response, which is called autonomic arousal, is correlated signal and not random noise, and therefore could be one of the causes of increasing values in the fractal scaling index α_1 during non-REM sleep. In fact, a previous study indicated that an increase in a fractal scaling index of RRI can be associated with the prevalence of a phasic fluctuation in RRI (Telser et al., 2004). Taken together, it seems possible that higher values in the fractal scaling index α_1 during non-REM sleep shown by a.m. sleeper CFS patients compared to healthy controls might be caused by more occurrences of microarousal and/or subcortical arousal during non-REM sleep. Further studies using larger sample sizes and/or repeated measurements are needed to understand adequately the association between the fractal scaling index α_1 , cardiovascular regulation, and sleepiness in patients with CFS.

The respiratory rhythm can affect the fractal scaling index α_1 and produce a crossover between short- and long-term scaling because a sinusoidal signal increases the scaling index (Perakakis et al., 2009). The crossover occurs at smaller scales as breathing becomes more rapid (Perakakis et al., 2009). Thus the effect of respiration needs to be interpreted cautiously, however, previous studies analyzing HRV during sleep (Bonnet et al., 1997; Otzenberger et al., 1998; Togo et al., 2001) reported that the respiratory modulation of HR, i.e., respiratory sinus arrhythmia, became regular during deep sleep which is related with increases in the index α_1 . In addition, results of this study pertaining to healthy controls support our previous study which reported that the fractal scaling exponent of 10-min HRV during non-REM sleep for good sleepers obtained by using coarse graining spectral analysis was significantly decreased compared to awake and REM sleep (Togo et al., 2001).

Using a larger data set than used here, we examined sleep architecture of a sample of female CFS patients (Togo et al., 2008). Although, in that study, we reported that sleep architecture was associated with changes of sleepiness in CFS patients, we did not find this result in this

study – probably due to the fact that we used a smaller sample here – resulting in less statistical power. Nonetheless, the possibility remains that sleep macro-architecture is one of the factors which affects changes in sleepiness over a night's sleep in CFS patients.

In conclusion, short-term HRV dynamics during non-REM sleep is associated with increased sleepiness in the morning in CFS patients following a night's sleep. Sleep micro-structure or autonomic nervous system activity during non-REM sleep for CFS patients could be an important objective measure to identify and perhaps quantify disrupted and unrefreshing sleep in CFS patients. Future research is needed to understand the underlying pathophysiologic mechanism of this association.

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References

- American Sleep Disorders Association. EEG arousals - scoring rules and examples. *Sleep*. 1992; 15:174–184.
- Bennett LS, Langford BA, Stradling JR, Davies RJ. Sleep fragmentation indices as predictors of daytime sleepiness and nCPAP response in obstructive sleep apnea. *Am J Respir Crit Care Med*. 1998; 158:778–786. [PubMed: 9731004]
- Boneva RS, Decker MJ, Maloney EM, Lin JM, Jones JF, Helgason HG, Heim CM, Rye DB, Reeves WC. Higher heart rate and reduced heart rate variability persist during sleep in chronic fatigue syndrome: a population-based study. *Auton Neurosci*. 2007; 137:94–101. [PubMed: 17851136]
- Bonnet MH, Arand DL. Heart rate variability: sleep stage, time of night, and arousal influences. *Electroencephalogr Clin Neurophysiol*. 1997; 102:390–396. [PubMed: 9191582]
- Bou-Holaiigah I, Rowe PC, Kan J, Calkins H. The relationship between neurally mediated hypotension and the chronic fatigue syndrome. *JAMA*. 1995; 274:961–967. [PubMed: 7674527]
- Burton AR, Rahman K, Kadota Y, Lloyd A, Vollmer-Conna U. Reduced heart rate variability predicts poor sleep quality in a case-control study of chronic fatigue syndrome. *Exp Brain Res*. 2010; 204:71–78. [PubMed: 20502886]
- Castiglioni P, Parati G, Di Rienzo M, Carabalona R, Cividjian A, Quintin L. Scale exponents of blood pressure and heart rate during autonomic blockade as assessed by detrended fluctuation analysis. *J Physiol*. 2011; 589:355–369. [PubMed: 21115648]
- Fischler B, Le Bon O, Hoffmann G, Cluydts R, Kaufman L, De Meirleir K. Sleep anomalies in the chronic fatigue syndrome. A comorbidity study. *Neuropsychobiology*. 1997; 35:115–122. [PubMed: 9170115]
- Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. *Ann Intern Med*. 1994; 121:953–959. [PubMed: 7978722]
- Krupp LB, Jandorf L, Coyle PK, Mendelson WB. Sleep disturbance in chronic fatigue syndrome. *J Psychosom Res*. 1993; 37:325–331. [PubMed: 8510058]
- Lim PB, Malcolm-Lawes LC, Stuber T, Koa-Wing M, Wright IJ, Tillin T, Sutton R, Davies DW, Peters NS, Francis DP, Kanagaratnam P. Feasibility of multiple short, 40-s, intra-procedural ECG recordings to detect immediate changes in heart rate variability during catheter ablation for arrhythmias. *J Interv Card Electrophysiol*. 2011; 32:163–171. [PubMed: 21647641]
- Martin SE, Engleman HM, Kingshott RN, Douglas NJ. Microarousals in patients with sleep apnoea/hypopnoea syndrome. *J Sleep Res*. 1997a; 6:276–280. [PubMed: 9493529]
- Martin SE, Wraith PK, Deary IJ, Douglas NJ. The effect of nonvisible sleep fragmentation on daytime function. *Am J Respir Crit Care Med*. 1997b; 155:1596–1601. [PubMed: 9154863]

- McCormack HM, Horne DJ, Sheather S. Clinical applications of visual analogue scales: a critical review. *Psychol Med.* 1988; 18:1007–1019. [PubMed: 3078045]
- Morriss R, Sharpe M, Sharpley AL, Cowen PJ, Hawton K, Morris J. Abnormalities of sleep in patients with the chronic fatigue syndrome. *BMJ.* 1993; 306:1161–1164. [PubMed: 8499816]
- Otzenberger H, Gronfier C, Simon C, Charloux A, Ehrhart J, Piquard F, Brandenberger G. Dynamic heart rate variability: a tool for exploring sympathovagal balance continuously during sleep in men. *Am J Physiol.* 1998; 275:H946–950. [PubMed: 9724299]
- Pena MA, Echeverria JC, Garcia MT, Gonzalez-Camarena R. Applying fractal analysis to short sets of heart rate variability data. *Med Biol Eng Comput.* 2009; 47:709–717. [PubMed: 19184157]
- Peng CK, Havlin S, Stanley HE, Goldberger AL. Quantification of Scaling Exponents and Crossover Phenomena in Nonstationary Heartbeat Time-Series. *Chaos.* 1995; 5:82–87. [PubMed: 11538314]
- Perakakis P, Taylor M, Martinez-Nieto E, Revithi I, Vila J. Breathing frequency bias in fractal analysis of heart rate variability. *Biol Psychol.* 2009; 82:82–88. [PubMed: 19559748]
- Pitson DJ, Stradling JR. Autonomic markers of arousal during sleep in patients undergoing investigation for obstructive sleep apnoea, their relationship to EEG arousals, respiratory events and subjective sleepiness. *J Sleep Res.* 1998; 7:53–59. [PubMed: 9613428]
- Rechtschaffen, A.; Kales, A. A Manual of Standardized Terminology, Techniques and Scoring System for Sleep States of Human Subjects. US Government Printing Office, National Institutes of Health Publication; Washington (DC): 1968.
- Robbins, LN.; Cotter, LB.; Bucholz, KK.; Compton, WM.; North, CS.; Rourke, KM. Diagnostic interview schedule for the DSM-IV (DISIV). Washington University School of Medicine; St. Louis: 2000.
- Sforza E, Jouny C, Ibanez V. Cardiac activation during arousal in humans: further evidence for hierarchy in the arousal response. *Clin Neurophysiol.* 2000; 111:1611–1619. [PubMed: 10964073]
- Sharpley A, Clements A, Hawton K, Sharpe M. Do patients with “pure” chronic fatigue syndrome (neurasthenia) have abnormal sleep? *Psychosom Med.* 1997; 59:592–596. [PubMed: 9407577]
- Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Circulation.* 1996; 93:1043–1065. [PubMed: 8598068]
- Telser S, Staudacher M, Ploner Y, Amann A, Hinterhuber H, Ritsch-Marte M. Can one detect sleep stage transitions for on-line sleep scoring by monitoring the heart rate variability. *Somnologie.* 2004; 8:33–41.
- Togo F, Cherniack NS, Natelson BH. Electroencephalogram characteristics of autonomic arousals during sleep in healthy men. *Clin Neurophysiol.* 2006; 117:2597–2603. [PubMed: 17011823]
- Togo F, Natelson BH, Cherniack NS, FitzGibbons J, Garcon C, Rapoport DM. Sleep structure and sleepiness in chronic fatigue syndrome with or without coexisting fibromyalgia. *Arthritis Res Ther.* 2008; 10:R56. [PubMed: 18474105]
- Togo F, Yamamoto Y. Decreased fractal component of human heart rate variability during non-REM sleep. *Am J Physiol Heart Circ Physiol.* 2001; 280:H17–21. [PubMed: 11123213]
- Tulppo MP, Kiviniemi AM, Hautala AJ, Kallio M, Seppanen T, Makikallio TH, Huikuri HV. Physiological background of the loss of fractal heart rate dynamics. *Circulation.* 2005; 112:314–319. [PubMed: 16009791]
- Unger ER, Nisenbaum R, Moldofsky H, Cesta A, Sammut C, Reyes M, Reeves WC. Sleep assessment in a population-based study of chronic fatigue syndrome. *BMC Neurol.* 2004; 4:6. [PubMed: 15096280]
- Winkelman JW. The evoked heart rate response to periodic leg movements of sleep. *Sleep.* 1999; 22:575–580. [PubMed: 10450592]
- Yamamoto Y, LaManca JJ, Natelson BH. A measure of heart rate variability is sensitive to orthostatic challenge in women with chronic fatigue syndrome. *Exp Biol Med (Maywood).* 2003; 228:167–174. [PubMed: 12563023]

Figure 1.

Mean and SD of RR interval (RRI) and fractal scaling index α_1 of RRI during each sleep stage in healthy controls (white bars) and chronic fatigue syndrome (CFS) patients who were either less sleepy (grey bars) or sleepier (black bars) after polysomnography. Values are means $\pm$ SE. DFA, detrended fluctuation analysis, Full, full length; W, wakefulness; A, arousal; S1, Stage 1 sleep; S2, Stage 2 sleep; S3, Stage 3 sleep; R, Stage REM sleep. * $p < 0.05$ relative to healthy controls; $^{\dagger}p < 0.05$ relative to patients with a.m. less sleepy group.

Table 1

Selected sleep stage variables in healthy controls and chronic fatigue syndrome (CFS) patients without sleep abnormalities

	Healthy	CFS
<i>n</i>	19	18
Age (year)	37 ± 9	39 ± 8
BMI (kg/m ²)	22.9 ± 3.3	25.8 ± 6.5
CES-D	8 ± 7	17 ± 9*
Sleepiness Evening	6 ± 4	9 ± 5*
Morning	1 ± 1 [#]	9 ± 2*
<i>Sleep architecture</i>		
Lights-off time (h:min)	23:41 ± 0:59	23:45 ± 0:42
Time in bed (min)	435 ± 37	413 ± 50
Total sleep time (min)	391 ± 38	352 ± 55*
Sleep efficiency ^a (%)	87 ± 7	80 ± 10*
# of arousal (/hr)	7.9 ± 4.8	6.4 ± 4.0
Wakefulness (min)	44 ± 34	62 ± 40
Stage 1 (min)	44 ± 21	32 ± 14*
Wakefulness plus Stage 1 (min)	88 ± 38	93 ± 42*
Stage 2 (min)	224 ± 34	205 ± 32*
Stage 3 (min)	30 ± 22	45 ± 24*
Stage 4 (min)	7 ± 13	7 ± 12
SWS (Stage 3+4) (min)	37 ± 27	52 ± 31
Stage REM (min)	87 ± 26	63 ± 28*
Sleep latency ^b (min)	17 ± 22	28 ± 27
REM latency ^c (min)	104 ± 54	130 ± 58

Values are means ± SD. BMI, body mass index; CES-D, Centers for Epidemiological Study – Depression; SWS, slow wave sleep; REM, rapid eye movement;

* Significantly different from healthy controls ($p < 0.05$, non-paired t test);

[#] Significantly different from evening ($p < 0.05$, paired t test);

^a total sleep time/time in bed × 100%;

^b time from lights out to sleep onset;

^c time from lights out to first epoch of Stage REM sleep.

Table 2

Selected heart rate variability (HRV) variables in healthy controls and CFS patients without sleep abnormalities

	Healthy	CFS
<i>full-length HRV</i>		
mean RRI (ms)	959 ± 126	888 ± 88*
SD RRI (ms)	96 ± 32	77 ± 23*
HF power (ms ²)	761 ± 788	336 ± 441*
LF power (ms ²)	596 ± 364	460 ± 533
VLF power (ms ²)	1490 ± 1024	871 ± 513*
LF/HF	1.21 ± 0.69	1.72 ± 0.70*
DFA α ₁	0.98 ± 0.21	1.09 ± 0.22
<i>1-min HRV</i>		
mean RRI (ms)		
Wakefulness	880 ± 107	825 ± 101
Arousal	953 ± 130 ^a	889 ± 95 ^a
Stage 1	982 ± 122 ^{abc}	907 ± 102 ^{*ac}
Stage 2	978 ± 129 ^{ab}	913 ± 95 ^{*ac}
Stage 3	954 ± 145 ^a	884 ± 102 ^a
Stage REM	940 ± 124 ^a	866 ± 76*
SD RRI (ms)		
Wakefulness	75 ± 32	75 ± 34
Arousal	91 ± 26	76 ± 41
Stage 1	62 ± 30 ^b	46 ± 24 ^{*ab}
Stage 2	55 ± 22 ^{ab}	39 ± 15 ^{*ab}
Stage 3	47 ± 24 ^{ab}	33 ± 15 ^{*ab}
Stage REM	56 ± 20 ^b	44 ± 23 ^{ab}
DFA α ₁		
Wakefulness	1.10 ± 0.19	1.13 ± 0.20
Arousal	1.10 ± 0.24	1.15 ± 0.21
Stage 1	0.89 ± 0.23 ^{ab}	1.00 ± 0.21
Stage 2	0.85 ± 0.16 ^{ab}	0.99 ± 0.16 ^{*b}
Stage 3	0.78 ± 0.21 ^{ab}	0.93 ± 0.21 ^{*ab}
Stage REM	0.93 ± 0.29	0.98 ± 0.40
HF power (ms ²)		
Wakefulness	514 ± 312	305 ± 319
Arousal	895 ± 911 ^a	387 ± 439*
Stage 1	850 ± 639 ^{ac}	333 ± 373*

	Healthy	CFS
Stage 2	891 ± 1035	338 ± 340 [*]
Stage 3	883 ± 1177	297 ± 329 [*]
Stage REM	546 ± 452 ^b	312 ± 744
LF power (ms ²)		
Wakefulness	672 ± 421	590 ± 480
Arousal	952 ± 743	638 ± 666
Stage 1	659 ± 561 ^d	436 ± 697
Stage 2	469 ± 380 ^{bd}	302 ± 321 ^{ab}
Stage 3	287 ± 195 ^{ab}	162 ± 165 ^{*ab}
Stage REM	481 ± 328 ^b	415 ± 780
LF/HF		
Wakefulness	2.12 ± 1.15	2.95 ± 1.42 [*]
Arousal	1.63 ± 0.84 ^{ab}	2.32 ± 1.15 [*]
Stage 1	0.92 ± 0.49 ^{ab}	1.34 ± 0.82 abcd
Stage 2	0.76 ± 0.35 ^{abc}	1.10 ± 0.45 ^{*abcd}
Stage 3	0.52 ± 0.30 ^{abc}	0.77 ± 0.55 ^{*abc}
Stage REM	1.37 ± 0.93	2.08 ± 0.82 [*]

Values are means ± SD. RRI, RR interval; HF, high frequency (> 0.15 Hz); LF, low frequency (0.04 – 0.15 Hz); VLF, very-low frequency (0.003 – 0.04 Hz); DFA, detrended fluctuation analysis;

^{*} Significantly different from healthy controls (p < 0.05, analysis of variance [ANOVA]);

^a Significantly different from wakefulness (p < 0.05, ANOVA);

^b Significantly different from arousal (p < 0.05, ANOVA);

^c Significantly different from REM sleep (p < 0.05, ANOVA);

^d Significantly different from Stage 3 (p < 0.05, ANOVA).

Table 3

Selected sleep stage variables in healthy controls and CFS patients who were either less sleepy or sleepier after polysomnography

	Healthy	CFS AM less sleepy [§]	CFS AM sleepier [§]
<i>n</i>	19	10	8
Age (year)	37 ± 9	39 ± 9	39 ± 8
BMI (kg/m ²)	22.9 ± 3.3	24.8 ± 7.2	27.0 ± 5.9
CES-D	8 ± 7	19 ± 10*	15 ± 7
Sleepiness Evening	6 ± 4	12 ± 2 [†]	5 ± 4
Morning	1 ± 1 [#]	7 ± 2 ^{†#}	10 ± 3 ^{†#}
<i>Sleep architecture</i>			
Lights-off time (h:min)	23:41 ± 0:59	23:54 ± 0:40	23:34 ± 0:45
Time in bed (min)	435 ± 37	403 ± 55	426 ± 45
Total sleep time (min)	391 ± 38	338 ± 54	369 ± 54
Sleep efficiency (%)	87 ± 7	80 ± 10	80 ± 11
# of arousal (/hr)	7.9 ± 4.8	6.5 ± 3.9	6.3 ± 4.4
Wakefulness (min)	44 ± 34	65 ± 41	57 ± 41
Stage 1 (min)	44 ± 21	31 ± 12	33 ± 17
Wakefulness plus Stage 1 (min)	88 ± 38	96 ± 42	90 ± 46
Stage 2 (min)	224 ± 34	196 ± 26	216 ± 36
Stage 3 (min)	30 ± 22	42 ± 22	47 ± 27
Stage 4 (min)	7 ± 13	10 ± 13	4 ± 11
SWS (Stage3+4) (min)	37 ± 27	52 ± 30	51 ± 34
Stage REM (min)	87 ± 26	59 ± 18*	68 ± 38
Sleep latency (min)	17 ± 22	24 ± 22	34 ± 32
REM latency (min)	104 ± 54	126 ± 70	136 ± 45

Values are means ± SD.

[§]Data dichotomized based on difference between daytime and nighttime self-reported ratings of sleepiness ($p < 0.05$, ANOVA).

* Significantly different from healthy controls ($p < 0.05$, ANOVA);

[†] Significantly different from other groups ($p < 0.05$, ANOVA);

[#] Significantly different from evening ($p < 0.05$, paired t test).

Table 4

Selected HRV variables in healthy controls and CFS patients who were either less sleepy or sleepier after polysomnography

	Healthy	CFS AM less sleepy [§]	CFS AM sleepier [§]
<i>full-length HRV</i>			
HF power (ms ²)	761 ± 788	432 ± 549	217 ± 234
LF power (ms ²)	596 ± 364	597 ± 691	289 ± 126
VLf power (ms ²)	1490 ± 1024	997 ± 610	714 ± 331
LF/HF	1.21 ± 0.69	1.58 ± 0.63	1.89 ± 0.79*
<i>1-min HRV</i>			
HF power (ms ²)			
Wakefulness	514 ± 312	390 ± 393	198 ± 159
Arousal	895 ± 911	498 ± 545	248 ± 216*
Stage 1	850 ± 639 ^{ac}	422 ± 433	222 ± 266
Stage 2	891 ± 1035	412 ± 387	246 ± 266
Stage 3	883 ± 1177	301 ± 234	292 ± 438
Stage REM	546 ± 452	462 ± 990	124 ± 115
LF power (ms ²)			
Wakefulness	672 ± 421	680 ± 590	477 ± 294
Arousal	952 ± 743	781 ± 881	459 ± 115
Stage 1	659 ± 561	543 ± 885	303 ± 371
Stage 2	469 ± 380 ^b	390 ± 411	192 ± 93
Stage 3	287 ± 195 ^{abd}	177 ± 183 ^{ab}	144 ± 150
Stage REM	481 ± 328 ^b	557 ± 1045	237 ± 94
LF/HF			
Wakefulness	2.12 ± 1.15	2.43 ± 1.03	3.61 ± 1.62*
Arousal	1.63 ± 0.84	1.93 ± 0.88	2.81 ± 1.31*
Stage 1	0.92 ± 0.49 ^{ab}	1.05 ± 0.78 ^a	1.69 ± 0.78 ^{*ab}
Stage 2	0.76 ± 0.35 ^{abc}	1.12 ± 0.53 ^{ab}	1.07 ± 0.37 ^{abcd}
Stage 3	0.52 ± 0.30 ^{abc}	0.67 ± 0.50 ^{abc}	0.89 ± 0.61 ^{*abcd}
Stage REM	1.37 ± 0.93 ^a	1.75 ± 0.76	2.50 ± 0.72 ^{*a}

Values are means ± SD.

[§]Data dichotomized based on difference between daytime and nighttime self-reported ratings of sleepiness (p < 0.05, ANOVA).

*Significantly different from healthy controls (p < 0.05, ANOVA);

^aSignificantly different from wakefulness (p < 0.05, ANOVA);

^bSignificantly different from arousal (p < 0.05, ANOVA);

^cSignificantly different from REM sleep (p < 0.05, ANOVA);

^dSignificantly different from Stage 1 sleep (p < 0.05, ANOVA).