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RESEARCH ARTICLE

Reduced heart rate variability predicts poor sleep quality in a case–control study of chronic fatigue syndrome

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Abstract Parasympathetic function is important in the induction and maintenance of sleep. We examined whether nocturnal vagal modulation of heart rate is related to the poor sleep quality commonly reported in chronic fatigue syndrome (CFS). Heart rate (HR, as R–R intervals) was continuously monitored during sleep in 20 patients with CFS and 20 matched control subjects. Questionnaires assessed demographic information, symptoms, functional impairment, and subjective sleep quality. CFS was associated with more sleep problems in general and poorer subjective sleep quality on the study night (all $p < 0.003$), and reports of repeated awakening during the night were 7 times more likely compared to healthy subjects ($p = 0.017$). Time and frequency-domain parameters of HR variability during sleep were significantly lower in patients with CFS (all $p < 0.006$). Multiple regression analyses revealed that heart rate variability (HRV) parameters were the best predictors of subjective sleep measures. This study identified significant reductions in vagal modulation of heart rate during sleep in CFS. Low HRV strongly predicted sleep quality—suggesting a pervasive state of nocturnal sympathetic hypervigilance in CFS.

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Introduction

The statement: "Fatigue is the best pillow" (Franklin 1757) may well be true for healthy individuals where feelings of tiredness naturally follow from daily exertions and a good night's sleep restores a sense of well-being. On the other hand, fatigue is a persistent and pervasive symptom in a myriad of medical and psychiatric conditions and hence the most frequent presenting complaint in primary care (Loblay et al. 2002). The enigmatic clinical disorder chronic fatigue syndrome (CFS) lies at the extreme end of the fatigue spectrum and is characterised by medically unexplained disabling fatigue for 6 months or more and a combination of non-specific accompanying symptoms (Fukuda et al. 1994). Despite decades of hypothesis-driven research the risk factors and pathophysiology of CFS are poorly understood, and effective therapies are not available (Jason et al. 2007).

Unrefreshing sleep, and complaints of disturbed or restless sleep feature prominently in symptom reports of patients with CFS (Komaroff and Buchwald 1991, Vollmer-Conna et al. 2006, Neu et al. 2007). Traditional sleep studies using polysomnography have revealed varied, non-specific changes in sleep structure and efficiency in a substantial minority of patients with CFS but have not produced consistent evidence of primary sleep disorder in CFS (Moldofsky 1993; Reeves et al. 2006; Neu et al. 2009). Moreover, polysomnography in monozygotic twins discordant for CFS (Ball et al. 2004; Armitage et al. 2009) failed to confirm significant aberrations in sleep architecture in CFS. Yet despite the lack of objective evidence of sleep

disorder, across studies the patients consistently reported a significant reduction in sleep quality with unrefreshing sleep a key symptom (Watson et al. 2004; Ball et al. 2004; Vollmer-Conna et al. 2006; Armitage et al. 2009, Neu et al. 2009). Thus, the mechanisms underlying the experience of disturbed sleep remain obscure.

Human sleep can be understood as part of a natural sleep-wake pattern that follows a circadian rhythm. These rhythms refer to the cyclical changes, including fluctuations in body temperature, hormone levels, and metabolic changes that occur over a 24 h period, driven by the brain's biological "clock"—a group of neurons in the hypothalamus called the suprachiasmatic nucleus. These internal 24-h rhythms in physiology and behaviour are synchronized to the external physical environment via light/dark cycles and social/work schedules (Toh 2008). In addition to these complex mechanisms, "falling asleep" is preceded by changes in autonomic nervous system signaling, notably an increase in vagal tone and reduction of sympathetic drive with a concomitant reduction in the heart rate (HR) and blood pressure and an increase in HR variability (Coote 1982; Van de Borne et al. 1994). These changes are thought to be linked to the restorative functions of the parasympathetic nervous system (Thayer and Sternberg 2006) and may be instrumental in the subjective experience of sleep as refreshing (Haley et al. 2004; Irwin et al. 2006).

There is growing awareness that a shift in the dynamic balance of the autonomic nervous system toward dominance of sympatho-excitatory circuits due to a loss of parasympathetic (vagal) control is associated with various disease states (Brook and Julius 2000; Thayer and Sternberg 2006). The most common and least invasive method to assess autonomic outflow to the heart is by measuring the variability of the timing between successive R-waves—an assessment better known as heart rate variability (HRV).

HRV may be measured in both the time and frequency domains (spectral analysis) to successfully index vagal activity (Task Force of the European Society of Cardiology 1996; Thayer et al. 2009). In the time domain, measuring the root mean square successive differences (RMSSD) between R-waves has been shown to be a useful index of vagal activity; moreover high frequency (HF: 0.15–0.40 Hz) spectral powers have also been used as indices of vagal activity (Task Force of the European Society of Cardiology 1996; Thayer et al. 2009). Whereas there is little debate concerning HF power reflecting primarily parasympathetic influences, low frequency (LF: 0.04–0.15 Hz) power has been shown to reflect both sympathetic and parasympathetic influences making the contributive components of this measurement less clear (Task Force of the European Society of Cardiology 1996; Thayer et al. 2009). However, and increase in the ratio of LF:HF has been used infer a relative enhancement in sympathetic drive to the heart (Task Force of the European Society of Cardiology 1996; Irwin et al. 2006; Burton et al. 2009).

Previous research examining autonomic dysfunction in CFS has provided inconsistent support for functional disturbances in autonomic cardiac regulation associated with orthostatic challenges (e.g. Yataco et al. 1997; Rowe and Calkins 1998; Soetekouw et al. 1999; Schondorf et al. 1999; Poole et al. 2000; Rowe et al. 2001; Wyller et al. 2007, 2008a, b). Among this literature are reports that suggest diminished vagal activity during such challenges. For example, using spectral analysis it was found that patients with CFS had reduced vagal activity in both sitting and standing postures (Sisto et al. 1995) as well as a significant decline in resting vagal power after periods of walking (Cordero et al. 1996). There is only limited evidence of reduced HR variability in CFS during nocturnal sleep (Vollmer-Conna et al. 2006; Boneva et al. 2007).

Whether reduced HRV during sleep is linked to the common experience of sleep problems and unrefreshing sleep in CFS has not been explored. The objective of this study is to examine this link, hypothesising that diminished HRV during sleep is associated with poorer sleep quality in subjects with CFS. The effects of relevant covariates of sleep quality including levels of current stress, and psychological distress were also considered.

Methods

Participants

20 subjects with CFS (3 male, 17 female; 41 ± 11.4 years (S.D.)—see Table 1) were recruited through the Dubbo Infection Outcomes Study (Western New South Wales, Australia) our ongoing cohort study of subjects followed from the onset of documented acute infection due to EBV (infectious mononucleosis); *Coxiella burnetii* (the causative agent of Q fever), or Ross River virus (RRV; epidemic polyarthritis) until complete recovery; or from a tertiary referral assessment clinic at a public hospital in Sydney (A. Lloyd). To participate in the study, patients' current symptom profiles had to fulfill international diagnostic criteria for CFS (Fukuda et al. 1994). Chronic fatigue followed directly from a documented acute infectious illness in 20 subjects (RRV: $N = 7$; EBV: $N = 4$; *Coxiella burnetii:* $N = 1$). In eight patients viral infection was not serologically established. 20 healthy control subjects (5 male, 15 female; 36 ± 13.2 years) matched for age, sex, body mass index (BMI) and activity levels were recruited from community volunteers.

Exclusion criteria were pregnancy, primary sleep disorder (obstructive sleep apnoea or narcolepsy); endocrine (untreated diabetes, uncontrolled thyroid disease) or

Table 1 Demographic and clinical characteristics of participants

Subject characteristics			
	Healthy subjects (n = 20)	CFS patients (n = 20)	Statistical significance P value
Demographics			
Age	36 (13.2)	41 (11.4)	0.21
Female:male (n)	15:5	17:3	0.69
BMI	24 (3.7)	25 (4.2)	0.28
Exercise (h/week)	4.2 (3.0)	3.0 (2.1)	0.18
Symptoms			
SPHERE	2.6 (2.6)	27.8 (13.1)	**<0.001**
BDQ	1.4 (1.8)	11.8 (8.5)	**<0.001**
PSQ	61.1 (10.3)	71.1 (14.4)	**0.03**
K10	12.9 (3.1)	20.2 (6.7)	**<0.001**

Values are group means and (standard deviations)

BMI body mass index, *SPHERE* somatic and psychological health report, *SOMA* somatic subscale of the SPHERE, *PSYCH* psychological subscale, *BDQ* brief disability questionnaire, *PSQ* perceived stress questionnaire, *K10* kessler 10

SPHERE Sleep Specific Questions

(6) Waking up tired? (13) Needing to sleep longer? (15) Poor sleep? (26) Feeling tired after rest or relaxation?

Significance levels were derived from t test for group comparisons and Fisher's exact test for female to male ratios

neurological (uncontrolled epilepsy, stroke, dementia, autonomic neuropathy) co-morbidities; uncontrolled/untreated cardiovascular disease (hypertension, heart failure) or pacemaker; active autoimmune disease (e.g. SLE, Sjogren's syndrome, rheumatoid arthritis); major depressive disorder, psychotic or substance abuse disorders. Additionally, medications known to affect autonomic functioning including beta blockers, benzodiazepines, corticosteroids (e.g. prednisone, cortisone acetate, fludrocortisone), other centrally active drugs (e.g. methylphenidate, dexamphetamine, tricyclic and SSRI antidepressants) were exclusionary. All subjects were non-smokers and abstained from alcohol and caffeine use for 12 h prior to falling asleep.

Self-report questionnaires

The 30-item perceived stress questionnaire (PSQ) was used to assess current levels of stress (Levenstein et al. 1993) and common symptoms of psychological distress were reported via the Kessler 10 (K10; Kessler et al. 2002). Functional impairment was assessed by The Brief Disability Questionnaire (BDQ; Von Korff et al. 1996). The 34-item Somatic and Psychological Health Report (SPHERE; Hickie et al. 2001) was used to assess a wide range of physical and psychological symptoms. Two validated subscales, PSYCH and SOMA, can be derived within the SPHERE questionnaire. The PSYCH subscale consists of six questions relating to psychological distress, with a score of two or greater predicting depression or anxiety. The SOMA subscale consists of six somatic symptom items with a score of 3 or greater (out of a possible 12) predicting a clinically significant fatigue state associated with disability ratings, as well as both patients' and doctors' reports of the need for medical care demonstrating a sensitivity of 94% and a specificity of 83% (Hickie et al. 2001). Four questions in the SPHERE specifically target sleep problems, including waking up tired, needing to sleep longer, poor sleep, feeling tired after rest and relaxation, were used to obtain a measure of subjective sleep quality in general over the past months (possible range of scores 0–8). A brief clinical questionnaire was used to assess subjective sleep quality parameters including overall quality (on a Likert scale ranging from 1, "very poor sleep" to 10, "perfect sleep") and the experience of repeated awakenings during sleep rated categorically as 'Yes' or 'No'.

Polar watch, software and analysis

Continuous monitoring of HR (as R–R intervals) during sleep (Brosschot et al. 2007) was attained with an ambulatory Polar Heart Rate Monitor (Model S810i, USA; Model RS800, USA) and Polar Wearlink W.I.N.D. heart rate chest band transmitter (Polar Electro Oy, Kempele, Finland). Subjects wore the watch and heart rate transmitter, activating the watch when going to bed that night, following detailed written instructions. HRV results were obtained using Polar Protrainer v5.35.161 software for analysis (Polar Electro Oy, Kempele, Finland). Analysis algorithms consisted of both time domain measurements (RMSSD) and spectral analysis. Power spectral density calculated using autoregressive modelling to derive HRV parameters included a high frequency component (HF: 0.15–0.40 Hz) which is reflective of vagal drive to the heart and low frequency component (LF: 0.04–0.15 Hz) which is comprised of both vagal and sympathetic influences. The LF/HF ratio (an index of sympathetic modulation (Pagani et al. 1997; Hall et al. 2004) was derived from normalised units of LF and HF components. The first hour of recording was discarded (Brosschot et al. 2007) and transient noise and movement artefact were manually removed.

Statistical analysis

Statistical analyses were performed using SPSS for Windows version 17 (SPSS Inc., Chicago, IL, USA). Key variables were normally distributed. Simple group comparisons were made using t tests, and Fisher's exact test was used to assess independence of categorical data. Linear

Table 2 Results for heart rate variability and sleep quality

	Healthy subjects ($n = 20$)	CFS patients ($n = 20$)	Statistical significance P value
Average heart rate (beats/min)	65.7 (7.6)	68.5 (9.2)	0.29
Nocturnal HRV sample duration (h:min)	2:43 (1:52)	3:32 (2:01)	0.20
RMSSD (ms)	53.6 (40.8)	24.6 (10.2)	**0.006**
LF (0.04–0.15 Hz) (%)	23.5 (8.1)	21.1 (6.2)	0.30
HF (0.15–0.40 Hz) (%)	30.3 (17.3)	11.0 (6.7)	**<0.001**
LF/HF ratio	1.01 (0.62)	2.50 (1.54)	**<0.001**
Sleep problems (SPHERE)	0.7 (1.2)	5.9 (1.5)	**<0.001**
Overall rating of sleep last night (1–10, higher is better)	7.0 (1.0)	4.9 (2.0)	**0.003**
Repeated awakenings	40%	75%	**0.017**

Significance levels were derived from t test (2-tailed) for group comparisons

multiple regression was used to explore the relative contribution of cardiac parameters (i.e. HR, RMSSD, LF and HF components) to subjective reports of disturbed sleep. Logistic regression models were used when the outcome variables were binary. In these analyses, perceived stress and psychological distress scores were also included as these covariates can affect sleep quality in their own right. Pearson's correlation was used to determine relationships between variables. All results are expressed as mean ± standard deviation. $P < 0.05$ was taken as the level of significance for all statistical analyses.

Results

There were no statistically significant differences with CFS and control subjects on the matching variables of age, sex distribution, BMI, activity/exercise or length of recording (Table 1).

Clinical measures

Between-group differences were significant for current symptoms (SPHERE), the somatic and psychological subscales of the SPHERE (SOMA and PSYCH) and BDQ; higher scores on these measures is consistent with a diagnosis of CFS (Table 1). Furthermore CFS subjects showed increased stress and anxiety levels evidenced by significant differences in perceived stress (PSQ) and K10 tests (Table 1).

Sleep measures

CFS subjects rated overall sleep quality as poorer than controls as reflected in the higher scores on the SPHERE sleep questions ($p < 0.001$; Table 2), and on the night HR was recorded ($p = 0.003$). The likelihood of whether a subject reported repeated awakenings during sleep was 40% and 75% for healthy control subjects and patients with CFS respectively—patients with CFS were almost 7 times more likely to report repeated awakenings during sleep [odds ratio: 6.9 (95% C.I. 1.5–32.0]).

Autonomic parameters

During sleep, RMSSD and HF parameters were significantly reduced (Table 2), suggesting a decrease in vagal modulation of heart rate in subjects with CFS when compared with healthy controls (RMSSD: $p = 0.006$; HF: $p < 0.001$). Consequently, there was a significant between-group difference in the LF/HF ratio: ($p < 0.001$). While average heart rate appeared to be higher in patients with CFS than in control subjects, this failed to reach statistical significance ($p = 0.29$). We found no relationship between BMI and HRV parameters in subjects with CFS (RMSSD: $r = -0.099$, $p = 0.74$; HF: $r = 0.055$, $p = 0.85$).

Relationship between autonomic variables and sleep quality

Multiple regression analysis was used to examine the relative contribution of autonomic (heart rate, LF, HF, RMSSD) and relevant psychological (K10 and PSQ) variables to sleep quality. For sleep problems in general the model ($R^2 = 0.55$, $p < 0.001$) identified RMSSD as the only and highly significant predictor ($\beta = -0.47$, $p = 0.005$) thus, with other variables held constant, a reduction in RMSSD by 1 unit was linked to a 0.47 of a score increase in rated severity of sleep difficulties (maximal score is 8). Subjective sleep quality rated for the night of testing (rated 0–10) was best predicted by HF (an index of vagal modulation of heart rate) ($R^2 = 0.41$, $p = 0.004$; $\beta = -0.43$, $p = 0.007$) with PSQ ($\beta = 0.50$, $p = 0.02$) a second independent predictor.

Logistic regression was used to evaluate the experience of repeated awakenings during the study night as this question was categorically scored. Reduced RMSSD was the only significant predictor for repeated awakenings during sleep ($\chi^2 = 12.2$, $p = 0.002$; Exp $[B] = 0.951$, $p = 0.029$). That is, with other variables held constant, for every 1 unit decrease in RMSSD, the odds of experiencing repeated awakenings during the night increased by 0.951.

Discussion

Results from this study revealed a strong connection between nocturnal measurements of autonomic drive to the heart and commonly reported sleep problems including the hallmark symptoms of unrefreshing sleep.

Consistent with many previous studies, we found that patients with CFS rated their sleep quality as significantly poorer than healthy controls (Watson et al. 2004; Ball et al. 2004; Vollmer-Conna et al. 2006; Reeves et al., 2006, Armitage et al. 2009, Neu et al. 2009). As there is little evidence for altered sleep architecture in CFS (Reeves et al. 2006; Majer et al. 2007), the significant reduction in nocturnal vagal tone, as inferred from reduced HR variability indices documented here may offer an alternative explanation for the prevailing perception of poor sleep quality in this disorder. Indeed we found that the best predictor for poor sleep was reduced HRV. Moreover, this relationship held true whether sleep quality was assessed more broadly via questionnaire, as a rating of sleep quality on the night of testing, or simply as the perception of repeated awakenings.

Togo and colleagues (2008) suggested that subjective ratings of poor sleep quality in patients with CFS was not due to diagnosable sleep disorders but rather to a decrease in the length of periods of uninterrupted sleep. Such sleep disruption may, in turn, explain the debilitating fatigue, reports of unrefreshing sleep, and pain in this group of patients. Our data document a link between the experience of fragmented sleep and reduced HR variability during sleep.

It has been suggested that decreased HRV could be interpreted as a state of autonomic hypervigilance (Thayer and Sternberg 2006; Thayer et al. 2009). This conceptualisation is consistent with documented effects of daily stress on HRV during sleep (Hall et al. 2004; Brosschot et al. 2007) and the current finding of perceived stress levels as a second independent predictor of sleep quality.

The possibility of changes in HRV parameters during sleep in CFS was first suggested by Boneva et al. 2007, who additionally reported higher norepinephrine levels and lower plasma aldosterone—indicative of a state of sympathetic predominance. Although our results cannot direct support a increase in sympathetic outflow to the heart during sleep in CFS, the significant reduction in vagal modulation of heart rate favours a sympathetically driven system by default.

Evolution's answer to uncertainty, novelty or threat was to preserve fast acting sympathoexcitatory preparation for action—exemplified by the "fight or flight response" (Ledoux 1998; Thayer and Sternberg 2006). In order to enhance parasympathetic responses for vegetative and restorative functions, and more generally under conditions of normal modern life, this response needs to be tonically inhibited. Accordingly, sympathoexcitatory subcortical threat circuits are normally under inhibitory control by the prefrontal cortex (Amat et al. 2005; Thayer 2006; Thayer and Sternberg 2006). Hypoactivity in the prefrontal circuits and a lack of inhibitory neural processes typically characterise psychopathological states, including anxiety, depression, and post-traumatic stress disorder (Thayer and Friedman 2004, Thayer 2006).

There is some evidence that individuals with CFS may exhibit anatomical and functional alterations in the prefrontal cortex—as evidenced by lowered cerebral activity in the dorsolateral and dorsomedial prefrontal cortices during fatigue provoking tasks (Caseras et al. 2008) and a bilateral reduction of grey-matter volume in the prefrontal cortex (Okada et al. 2004; De Lange et al. 2009). However, dissection of the mechanisms involved in this process need to be interpreted with caution: it is not known whether the changes seen in the prefrontal cortex in CFS are a symptom or a cause of CFS (De Lange et al. 2009). Nevertheless, since the role of the prefrontal cortex is essential in active tonic inhibition of sympathoexcitatory threat circuits, such alterations in the prefrontal cortex seen in CFS subjects could be expected to lead to a decrease in vagal drive defaulting to a sympathetically driven system.

We speculate that changes in the prefrontal cortex seen in CFS may not only contribute to the reduction of tonic vagal activity as seen in our study, but may also be manifested in other forms of dysautonomia seen in CFS. Animal studies have shown that descending efferent projections from the ventromedial prefrontal cortex innervate and regulate a wide range of subcortical autonomic centres, including the nucleus tractus solitarius (NTS) and ventrolateral medulla (VLM) (Gabbott et al. 2007; Kimmerly et al. 2007). The NTS and VLM are involved in mediating the physiological adjustments required to maintain arterial blood pressure and cerebral perfusion during orthostatic challenges (Kimmerly et al. 2007). Further down this pathway, the dorsal motor nucleus of the vagus receive glutamatergic projections from NTS activating vagal cardiac efferents—thus slowing the heart (Wang et al. 2001). It follows then, that a putative hypoactivity of the prefrontal cortex in CFS could manifest in an inability of the autonomic nervous system to dynamically respond to cardiovascular

challenges. Indeed, while there have been inconsistencies in this literature, it is not surprising that orthostatic intolerance in tilt-table or lower body negative pressure have been documented in patients fulfilling diagnostic criteria for CFS (Schondorf et al. 1999; Wyller et al. 2007, 2008a, b, 2009).

Heart rate variability can be affected by a number of mechanisms. For example, it can be directly affected by levels of activity—it can be increased as a result of exercise training (Levy et al. 1998; Malfatto et al. 1996). Relating to this, previous authors have speculated that the reduced HRV seen in CFS may be a result of cardiovascular deconditioning (Freeman and Komaroff 1997; De Lorenzo et al. 1998). In the current study, the patients with CFS were matched for age, BMI and activity, and additionally there was not substantive between-group difference in resting HR. It is therefore unlikely that cardiac deconditioning was a determinant of the documented differences in HRV. Comorbidity of sleep apnoea may also confound findings relating to nocturnal cardiac activity (Gilman et al. 2008; Narkiewicz and Somers 2001) however, subjects with a known history of sleep apnoea were excluded from this study and there was no evidence to suggest that the participating subjects had undiagnosed sleep apnoea due to the relative stability/stationarity of heart rate (r–r intervals).

A limitation of this study is that polysomnography was not included to monitor specific sleep stages. The recorded differences in HRV data can thus not be related to specific sleep stages but rather to nocturnal sleep pe se. Importantly, as the literature does not support altered sleep architecture in subjects with CFS compared with healthy subjects, it is unlikely that the differences in HRV relate specifically to differences in sleep stages in patients with CFS compared to healthy control subjects. Additionally, it should be noted that evidence derived from cross-sectional studies need to be interpreted with caution: it is possible that uncontrolled between-group differences may impact on findings. Although our subject groups were carefully matched on key variables, a more definitive answer may be obtained from a twin study.

Conclusions

This study provides evidence of a significant reduction in cardiac vagal modulation of heart rate during nocturnal sleep in CFS and has identified indices of HRV as the best predictors of sleep quality. The low levels of nocturnal HRV found in our study, are suggestive of a pervasive state of sympathetic hypervigilance—one which is consistent with previous reports of hypoactivity in the prefrontal cortex in this population.

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