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SCIENTIFIC INVESTIGATIONS

Parasympathetic activity is reduced during slow-wave sleep, but not resting wakefulness, in patients with chronic fatigue syndrome

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Study Objectives: Physiological dearousal characterized by an increase in parasympathetic nervous system activity is important for good-quality sleep. Previous research shows that nocturnal parasympathetic activity (reflected by heart rate variability [HRV]) is diminished in individuals with chronic fatigue syndrome (CFS), suggesting hypervigilant sleep. This study investigated differences in nocturnal autonomic activity across sleep stages and explored the association of parasympathetic activity with sleep quality and self-reported physical and psychological wellbeing in individuals with CFS.

Methods: Twenty-four patients with medically diagnosed CFS, and 24 matched healthy control individuals participated. Electroencephalography and HRV were recorded during sleep in participants' homes using a minimally invasive ambulatory device. Questionnaires were used to measure self-reported wellbeing and sleep quality.

Results: Sleep architecture in patients with CFS differed from that of control participants in slower sleep onset, more awakenings, and a larger proportion of time spent in slow-wave sleep (SWS). Linear mixed-model analyses controlling for age revealed that HRV reflecting parasympathetic activity (normalized high frequency power) was reduced in patients with CFS compared to control participants, particularly during deeper stages of sleep. Poorer self-reported wellbeing and sleep quality was associated with reduced parasympathetic signaling during deeper sleep, but not during wake before sleep, rapid eye movement sleep, or with the proportion of time spent in SWS.

Conclusions: Autonomic hypervigilance during the deeper, recuperative stages of sleep is associated with poor quality sleep and self-reported wellbeing. Causal links need to be confirmed but provide potential intervention opportunities for the core symptom of unrefreshing sleep in CFS.

Keywords: autonomic hypervigilance, chronic fatigue syndrome, fatigue, nocturnal heart rate variability, sleep quality, slow-wave sleep

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Successful bodily recuperation during sleep is marked by autonomic de-arousal, reflected by parasympathetic predominance during deeper stages of sleep. Diminished nocturnal parasympathetic activity (as heart rate variability) in patients with chronic fatigue syndrome (CFS), particularly during deeper recuperative stages of sleep, may contribute to the hallmark symptom of unrefreshing sleep.

Study Impact: Our findings affirm that unrefreshing sleep and impaired self-reported wellbeing are associated with reduced parasympathetic activity during deeper stages of sleep in patients with CFS compared to healthy control participants. The direction of these relationships requires confirmation through longitudinal studies and experimental paradigms but provide support for nocturnal autonomic hypervigilance underpinning the hallmark symptom of CFS, providing a tangible target for future interventions.

INTRODUCTION

Chronic fatigue syndrome (CFS) is a debilitating condition characterized by 6 or more consecutive months of medically unexplained fatigue that is not relieved by rest, accompanied by a range of constitutional and neuropsychiatric symptoms.[1] Despite decades of concerted research internationally, the pathogenesis of this enigmatic condition remains poorly understood.[2,3] A hallmark symptom commonly reported by people with CFS is the experience of unrefreshing, nonrestorative sleep,[4–9] which is sleep that does not relieve the feeling of fatigue and leaves the individual feeling unrested. In addition to waking feeling unrefreshed, individuals with CFS commonly report frequent awakenings throughout the night, and vivid and intense dreams.[10–12]

Several studies using polysomnography (PSG) have investigated whether unrefreshing, nonrestorative sleep in CFS can be explained by alterations or abnormalities in sleep architecture, eliciting mixed results.[10,11,13] In particular, it was anticipated that individuals with CFS would spend less time in the deepest stage of nonrapid eye movement (NREM) sleep, often referred to as slow-wave sleep (SWS), the period of sleep generally to which physical and psychological recuperation is attributed.[14–16] Although one study documented reduced time spent in SWS for those with CFS compared to matched healthy control participants,[17] others have found no differences,[12]

whereas some have identified greater SWS durations for those with CFS relative to healthy control participants.[18–20] Further, SWS duration does not appear to be related to self-reported sleep quality, or physical and psychological health.[21] It is therefore difficult to attribute the experience of nonrestorative sleep by patients with CFS exclusively to differences in the duration of SWS.

Alterations in nocturnal autonomic nervous system activity has been posited as an alternative explanation for unrefreshing sleep in patients with CFS.[7,8] Normal sleep is characterized by alternating predominance of sympathetic and parasympathetic (vagal) activity. Collective evidence from electrocardiography (ECG), direct nerve recordings, and plasma catecholamine levels indicate a withdrawal of sympathetic activity during the period of transition from wake to sleep, minimizing during deep sleep, coupled with an increasing predominance of parasympathetic activity.[22–24] This physiological de-arousal facilitates the transition from wakefulness to deeper SWS and promotes the release of factors supporting cell growth and recuperation, such as prolactin and growth hormone.[25–27] This dynamic is reversed during rapid eye movement (REM) sleep, which is marked by sympathetic predominance and parasympathetic withdrawal.[23]

A well-validated and noninvasive measure of autonomic nervous system activity is heart rate variability (HRV): the variability in timing between successive heartbeats. Power spectrum density analysis of the beat-to-beat interval timing can be used to determine spectral power in very low frequency (VLF; 0–0.04 Hz), low frequency (LF; 0.04–0.15 Hz), and high frequency (HF: 0.15–0.45 Hz) bands. The teleology and mechanics of VLF and LF power remain debated[28]; however, HF power has been validated as an index of parasympathetic nervous system (vagal) activity, particularly when converted into a normalized metric (HFnu; derived by dividing HF power by the sum of LF and HF power[29,30]). Accordingly, HRV (as HFnu) increases from wakefulness to sleep onset, reaching its peak during SWS, and nadiring during REM sleep.[22,31] Further, higher HRV during deep sleep has been associated with better self-reported sleep quality.[32]

Nocturnal HRV (as HFnu) is reduced in patients with CFS compared to healthy control participants,[7,8,33] suggesting a persistent state of autonomic hypervigilance throughout the night. Indeed, regression analyses indicate that low HRV across the night represents the best predictor of poor-quality sleep in this patient group.[7,8] However, few studies have investigated differences in autonomic activity across sleep stages for patients with CFS compared to healthy control participants.[34,35] Togo and Natelson[35] initially demonstrated that HRV was lower in all measured stages of sleep for patients with CFS, compared with healthy control participants. Orjatsalo and colleagues[34] found that it was only during SWS that HRV power was lower for patients with CFS than fatigued controls; although these controls had a diagnosis of either insomnia or delayed sleep phase syndrome.

Despite promising results, these previous studies have some limitations. The sample size used by Orjatsalo et al[34] was relatively small, consisting of only eight patients with CFS, and eight controls. Further, only Togo and Natelson[35] correlated sleep characteristics with self-reported experience, showing that HRV was not related to sleepiness the following morning. It remains unclear how HRV during different sleep stages is related to other experiences associated with CFS, including unrefreshing sleep and psychological, cognitive, and physical wellbeing. Finally, these studies were conducted in a hospital and laboratory, respectively, using PSG over 1 night. Although full PSG represents the gold standard for the assessment of sleep architecture, it is relatively invasive and costly, and has limited ecological validity when conducted over a single night.[36] The newer, simple-to-use, ambulatory electroencephalography (EEG) devices, which can be worn in participants' own home environment, minimize interruptions to regular sleep routines and are substantially less invasive, and thus may provide a more ecologically valid assessment of sleep architecture.[37–39]

This study aimed to (1) compare HRV (as HFnu) during different sleep stages for patients with CFS and healthy control participants; and (2) explore associations of HRV during different sleep stages with self-reported measures of wellbeing. It was hypothesized that HRV would be higher for control participants compared to patients with CFS during deeper stages of sleep (SWS), and that higher HRV during these sleep stages would be associated with better self-reported sleep quality and greater psychological, cognitive, and physical wellbeing.

METHODS

Participants

Twenty-four participants fulfilling international diagnostic criteria for CFS[1] were recruited after clinician assessment at an academic tertiary referral clinic that specializes in the delivery of a manualized, multidisciplinary outpatient management program for patients with CFS.[40] Twenty-four generally healthy, nonfatigued control participants matched to the patient group for sex, age, and body mass index (BMI) were recruited by convenience and snowball sampling from family and acquaintances of enrolled patients and through community advertisements. Medications known to affect autonomic functioning (including beta blockers, corticosteroids, and benzodiazepine) or use of sedative-hypnotic medications, comorbid self-reported neurological conditions (eg, recent head injury, epilepsy) or any other contraindication to participation (eg, uncontrolled cardiovascular complaints, diagnosed sleep disorder including sleep apnea) were exclusionary. The use of antidepressant medication was documented. The Human Research Ethics Committee of the University of New South Wales approved this research (approval #HC16008). All participants gave informed written consent prior to taking part.

Study procedures

Consenting participants were asked to abstain from caffeine, alcohol, and vigorous exercise for the 12 hours prior to attending a single laboratory-based assessment. Participants completed a series of self-report measures to assess demographic and lifestyle characteristics, wellbeing, and retrospective sleep quality. A 10-minute recording of autonomic activity (via ECG) was obtained while participants were seated comfortably to establish

autonomic activity during wakeful rest. Participants were issued with a brief diary to record sleep parameters, symptoms, and activity over the next 7 days, and were provided with instructions and a demonstration of how to correctly fit and operate the ambulatory EEG device. Participants then left the laboratory and continued their normal daily routines (with no explicit instructions to avoid caffeine, alcohol, or exercise prior to going to bed). In their own homes (approximately 15 minutes before going to bed), participants fitted and activated the ambulatory EEG device as instructed before going to sleep as normal. The following morning, participants removed the device upon waking, rated their sleep quality, mood, and current symptoms, and received a follow-up call from the research team to ensure there were no difficulties experienced with the monitoring device.

Measures

Self-reported wellbeing

Fatigue severity, mood disturbance, and cognitive complaints were assessed using the Somatic and Psychological Health Report, a tool developed to concurrently screen for fatigue states and mood disorders "over the past few weeks."[41] Physical and mental health-related quality of life over the past month was assessed via the mental component score and physical component score of the Medical Outcomes Study 36-Item Short Form health survey.[42] The McGill Pain Questionnaire was used to indicate the quality and intensity of any pain currently being experienced by participants.[43] Psychological distress over the past 4 weeks was measured using the Kessler 10,[44] and emotional distress via the Patient Health Questionnaire-9.[45] Self-reported daytime sleepiness was measured via the Epworth Sleepiness Scale.[46]

Self-reported sleep quality

The Pittsburgh Sleep Quality Index[47] was used to measure retrospective sleep quality for the month preceding assessment. Participants also completed sleep diaries for the night using the ambulatory EEG device, and for an additional 6 days. These diaries included visual analog scales from 1 to 10 to rate perceived sleep quality and feeling of refreshment upon waking, along with self-reported bed and wake time. From this, sleep quality indices were calculated individually for the EEG study night, as well as averaged across the full 7-day period.

ECG and EEG

Laboratory-based autonomic recordings were acquired using a PowerLab 16/35 sampling at 1 kHz and recorded in LabChart Pro 8 (ADInstruments, Bella Vista, Australia). Standard Ag/AgCl chest electrodes with a three-lead ECG (0.1 Hz high-pass, 45 Hz low-pass filtering) were used to record heart rate. Expansion-derived respiration was monitored via a strain gauge transducer. Raw ECG and respiratory data were used to calculate mean resting heart rate (beats/min) and breathing rate (breaths/min) respectively.

In-home nocturnal EEG and ECG was obtained simultaneously using a Sleep Profiler X8 (Advanced Brain Monitoring, California, United States) at a sampling rate of 256 Hz (with 0.1 Hz high-pass and 100 Hz low-pass filtering; ±1000 μV gain). The lightweight device is worn on the forehead and held in place with an adjustable neoprene headband, recording signals from three conductive wet-gel Ag/AgCl custom electrodes (Vermed, New York, United States). The EEG signal is acquired from the differential recording between electrodes at AF7 and AF8. Impedance checks are automatically conducted by the Sleep Profiler device at the start of recording, which if unacceptably high, provides a vocal prompt to reapply the electrodes. ECG is obtained from two Ag/AgCl electrodes placed on the left and right collarbone. The device also incorporates triaxial actigraphy, allowing the orientation of the participant (ie, whether they are upright) to be determined.

Data processing

Acquired EEG signals were uploaded onto the Sleep Profiler Portal (Advanced Brain Monitoring), an Internet-based software application and subjected to automated sleep stage scoring using an algorithm largely consistent with American Academy of Sleep Medicine scoring rules[48] and validated against manual interrater agreement[49–51] and PSG.[37] Briefly, the staging algorithm decomposes the input signals into spectral bands; computes descriptors of sleep microstructure and macrostructure; detects artifacts; and performs classification per 30-second epoch into one of five sleep stages: wake, REM, NREM1, NREM2, or SWS.[51,52] Indices of sleep time (recording time minus wake time), efficiency (sleep time divided by recording time), sleep stage latency (elapsed time from sleep onset until first sleep stage epoch), and proportion of time spent in each sleep stage (hours of valid staged sleep for each stage, divided by hours of sleep time) are calculated.

HRV indices were derived using the HRV 2.0 module of LabChart Pro 8 for consecutive 5-minute epochs of artifact-free laboratory and ambulatory ECG traces. Frequency domain measures of HRV were obtained using the Lomb periodogram. The area under the power spectrum density curve from 0 to 0.04 Hz (VLF), 0.04 to 0.15Hz (LF), and 0.15 to 0.45 Hz (HF) indicate the spectral power in each frequency band (as ms^2 / Hz). Normalized HF power (HFnu) was calculated by dividing HF power by the sum of LF and HF powers.[29]

Extracted 5-minute HRV epochs were allocated to a single sleep stage (ie, awake, NREM1, NREM2, SWS, or REM) based on the modal value of time-synchronized 30-second sleep classification epochs. HRV epochs where the modal sleep stage represented less than 60% of the classified epochs were excluded from the analysis. That is, at least 6 of the 10 sleep stage epochs needed to match for the HRV epoch to be classified as that stage and therefore be included in the analysis set. Sensitivity analyses conducted on the primary outcome (HRV as HFnu) using stricter cutoff thresholds (70% through to 100% of epochs matching for inclusion in analysis) resulted in no substantive differences in the conclusions drawn.

Statistical analysis

Analyses were conducted using SPSS v24 (IBM Corporation, Armonk, New York, United States) and Stata v15.1 (Stata Corp., College Station, Texas, United States). Statistical significance was indicated by two-tailed values of $P < .05$.

Nonnormally distributed HRV parameters were transformed using a natural logarithm prior to analysis. Demographic and clinical characteristics, and laboratory-obtained autonomic parameters were compared between patients with CFS and healthy control participants using independent *t* tests for continuous variables, and chi-square tests for categorical variables. Differences in self-reported and objective measures of sleep quality were compared between groups using independent sample *t* tests. Linear mixed models (LMM) were used to compare HRV (as HFnu) across sleep stages between the two groups, with sleep stage (wake before sleep onset, NREM1, NREM2, SWS, REM), participant group (CFS, control), and their interaction included as fixed effects, and participant identification treated as a random effect. Age and antidepressant medication use were also included in these models as fixed effects. As the mechanisms underlying modulation of power in the LF spectral band are yet to be fully understood, this parameter was not analyzed; values for this parameter along with nonnormalized HF power across sleep stages has been included in the supplmental material (**Table S1**). Finally, associations between self-reported measures of wellbeing and sleep quality, and proportion of time spent in SWS and averaged HFnu HRV by sleep stage were explored using Spearman correlations.

RESULTS

Sample characteristics

Demographic, clinical, lifestyle, and autonomic characteristics for participants are presented in **Table 1**. No significant differences were identified between groups in age, sex distribution, or BMI. Consistent with the symptom profile of CFS, individuals with CFS reported significantly greater somatic, psychological, and cognitive symptoms, impairment of physical and mental health-related quality of life, greater psychological distress, reduced emotional wellbeing, and greater levels of physical pain compared to control participants (all $P < .01$). Consequently, a greater proportion of participants with CFS were taking antidepressant medication ($P < .001$). Control participants reported consuming more caffeine and alcohol than participants with CFS. Similarly, control participants indicated engaging in greater levels of physical activity per week on a single-item question; yet diarized reporting of physical activity across a 1-week period suggests comparable amounts of weekly physical activity between participants with CFS and controls. No significant differences in autonomic or HRV parameters between groups were found for assessment during wakeful rest.

Self-reported and objective indices of sleep quality

As shown in **Table 2**, despite being asleep for comparable durations to control participants, participants with CFS had significantly lower sleep efficiency, self-reported sleep quality, and self-reported refreshment, greater time to sleep onset, and more time spent awake during the night after initial onset of sleep. Individuals with CFS also spent a greater percentage of time in SWS sleep compared to control participants.

HRV across sleep stages

Both age and antidepressant medication use were initially included in the LMM analyses; however, there was no statistical evidence of a difference in HRV (as HFnu) on average as a function of antidepressant medication use ($P = .74$). As such, antidepressant medication use was excluded from the analyses. LMM analysis of HRV (as HFnu, controlling for age; displayed in **Figure 1**) identified strong evidence of a main effect of group ($\chi^2_1 = 10.21$, $P = .001$), with control participants having higher HRV on average than participants with CFS. A main effect of sleep stage was also strongly supported ($\chi^2_4 = 351.2$, $P < .001$), with HRV increasing substantially during NREM2 ($P = .005$) and SWS ($P < .001$), and significantly decreasing during REM ($P < .001$) compared to wake before sleep. The interaction of group × sleep stage was also highly significant ($\chi^2_4 = 32.06$, $P < .001$), driven by the differences in HRV between REM and both NREM2 and SWS being significantly lower (both $P < .001$) for participants with CFS compared to control participants. Notably, pairwise comparisons between groups provided strong evidence that HFnu HRV was lower during NREM2 and SWS sleep for participants with CFS (both $P < .001$), but not different during NREM1 or REM sleep (**Figure 1**).

Associations between nocturnal HRV, wellbeing, and sleep quality

Exploratory bivariate associations between HFnu HRV measures (during wake before sleep, NREM2, SWS, and REM sleep) and the self-reported measures of wellbeing and sleep quality are displayed in **Table 3**. Associations with NREM1 were not explored due to the small number of available data points (n = 26). Higher HRV during both NREM2 and SWS was related to better self-reported physical and mental wellbeing, but not daytime sleepiness. Commensurately, higher HRV during NREM2 and SWS were both significantly associated with better overall sleep quality (Pittsburgh Sleep Quality Index) and perceived refreshment upon waking (when averaged across the subsequent seven days). Higher HRV during NREM2 was also significantly associated with better perceived sleep quality (averaged across the following seven days). Higher HRV during the period of wake before sleep and all sleep stages was associated with lower self-reported ratings of pain. By contrast, greater HRV during REM sleep was associated with higher levels of daytime sleepiness. Self-reported alcohol and caffeine intake were not significantly associated with HFnu HRV during any sleep stage. However, there was statistical evidence of a positive association between diarized physical activity levels and HFnu HRV during NREM2 and REM sleep.

Associations of wellbeing and sleep quality parameters with the proportion of time spent in SWS (SWS%) were also explored. Reduced mental and physical health, and greater emotional distress were associated with a greater proportion of time spent in SWS (associations driven broadly by the symptom profile of individuals with CFS, who also spent a greater amount of time in SWS compared to control participants). Sleep quality parameters showed no significant associations with SWS%.

Table 1—Participant demographic, clinical and lifestyle characteristics, and autonomic parameters obtained during laboratory-based resting wakefulness.

Characteristic	Group		*t* test / χ^2 *P*
	Control (n = 24)	CFS (n = 24)	
Female sex, n (%)	18 (75)	21 (87.5)	.267
Age (years)	35.42 (11.99)	35.63 (13.73)	.956
Body mass index (kg/m^2)	23.98 (3.66)	23.50 (5.81)	.734
Caffeine consumption (cups/day)	1.73 (1.34)	0.94 (0.91)	.021
Alcoholic drinks (standard drinks/week)	3.04 (3.51)	0.71 (1.23)	.004
Antidepressant medication use, n (%)	0 (0)	11 (46)	< .001
TCA	–	2 (18)	
SSRI	–	4 (36)	
SNRI	–	3 (27)	
Reversible monoamine oxidase inhibitor	–	1 (9)	
TCA + SNRI	–	1 (9)	
Self-reported total exercise (hours/week)	6.47 (3.29)	2.94 (3.74)	.002
Diarized total exercise (hours/week)	8.58 (4.84)	8.40 (10.37)	.938
SPHERE			
Somatic symptoms	0.92 (1.41)	5.75 (3.05)	< .001
Psychological symptoms	1.25 (1.57)	3.33 (2.73)	.002
Cognitive symptoms	0.42 (0.97)	2.29 (1.88)	< .001
Short form health survey (SF36)*			
Mental component summary	82.06 (8.86)	50.04 (11.12)	< .001
Physical component summary	90.49 (7.15)	42.27 (16.73)	< .001
Pain (McGill)	2.29 (4.33)	10.08 (7.20)	< .001
Psychological distress (K10)	12.92 (2.72)	19.19 (3.95)	< .001
Sleepiness (ESS)	4.75 (3.05)	6.17 (4.72)	.223
Emotional distress (PHQ-9)	1.92 (1.77)	9.38 (3.97)	< .001
Autonomic activity (resting wakefulness)			
Heart rate (beats/minute)	74.37 (11.22)	68.76 (7.74)	.050
Respiration (breaths/minute)	13.02 (4.04)	12.75 (3.28)	.807
Frequency domain HRV parameters			
LF Power (ln ms^2 / Hz)	6.09 (1.44)	6.71 (1.24)	.116
HF Power (ln ms^2 / Hz)	5.91 (1.06)	6.51 (1.49)	.113
HFnu (%)	47.31 (25.62)	45.89 (25.50)	.848

Data presented as mean (standard deviation) or n (%) as indicated. *A higher score reflects better functioning. CFS = chronic fatigue syndrome, ESS = Epworth Sleepiness Scale, HF = high frequency, HFnu = high-frequency normalized units, HRV = heart rate variability, K10 = Kessler Psychological Distress Scale, LF = low frequency, PHQ-9 = Patient Health Questionnaire-9, SF-36 = 36-Item Short Form, SNRI = serotonin–norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, SPHERE = Somatic and Psychological Health Report, TCA = tricyclic antidepressant.

DISCUSSION

The biological basis underlying the hallmark symptom of unrefreshing, nonrestorative sleep experienced by patients with CFS remains poorly understood.[5,6] This study examined autonomic nervous system activity (as HRV) across sleep stages in patients with CFS and explored the association of HRV with self-reported ratings of sleep quality and wellbeing. Individuals with CFS reported impaired sleep quality and poorer physical and mental wellbeing compared to healthy control participants yet showed no indication of deficits for overall sleep duration, or the proportion of time spent in any particular sleep stage. Parasympathetic nervous system activity, as indexed by HFnu HRV, was significantly lower for patients with CFS than control participants only during NREM2 and SWS stages of sleep. Exploratory correlational analyses indicated that lower HFnu HRV during NREM2 and SWS sleep stages was associated with poorer self-reported sleep quality and wellbeing.

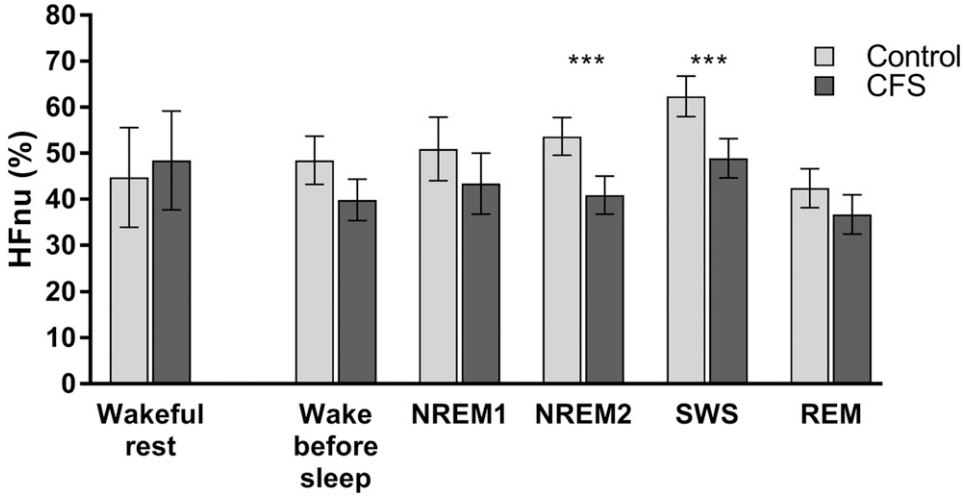
Patients with CFS report impaired sleep quality and unrefreshing nonrestorative sleep; however, consistent differences in sleep architecture have not been found.[10,11,13] In the current

Table 2—Participant sleep timing, duration, and quality characteristics.

Sleep Characteristics	Group		*P*
	Control (n = 24)	CFS (n = 24)	
Retrospective sleep quality (PSQI)	2.96 (1.52)	7.91 (4.39)	< .001
TST (hours)[a]	6.64 (1.27)	6.81 (1.48)	.677
Total time in bed (hours)[a]	7.78 (1.16)	9.00 (1.22)	.001
Sleep efficiency (% time asleep)[a]	85.36 (9.03)	75.71 (12.62)	.004
Sleep onset (minutes)[a]	14.25 (11.66)	33.38 (42.33)	.038
Wake after sleep onset (minutes)[a]	53.87 (38.09)	97.83 (72.13)	.011
REM latency (minutes)[a]	93.37 (48.34)	107.21 (53.61)	.353
SWS latency (minutes)[a]	22.29 (21.20)	23.37 (35.01)	.897
REM (%TST)[a]	22.51 (12.25)	18.19 (8.98)	.170
NREM1 (%TST)[a]	8.08 (3.50)	11.98 (8.84)	.050
NREM2 (%TST)[a]	53.80 (11.32)	47.26 (11.37)	.052
SWS (%TST)[a]	15.60 (7.95)	22.57 (10.59)	.013
Cortical arousals (per hour of sleep)	11.97 (4.26)	15.70 (9.07)	.075
Self-reported sleep quality (1–10 Likert Scale)[a]	6.57 (1.90)	5.31 (2.08)	.037
Self-reported refreshment (1–10 Likert Scale)[a]	6.43 (1.95)	4.48 (1.86)	.001
Self-reported sleep quality (1–10 Likert Scale)[b]	7.25 (1.23)	5.59 (1.92)	.007
Self-reported refreshment (1–10 Likert Scale)[b]	7.07 (1.51)	4.78 (1.64)	.001

Data presented as mean (standard deviation). [a]EEG monitoring night only. [b]Average of all 7 days in the sleep diary. CFS = chronic fatigue syndrome, NREM = non-rapid eye movement, PSQI = Pittsburgh Sleep Quality Index, REM = rapid eye movement, SWS = slow-wave sleep, TST = total sleep time, WASO = wake after sleep onset.

Figure 1—Heart rate variability across sleep stages.



Heart rate variability as high-frequency power in normalized units (HFnu %) during wakeful rest, wake before sleep onset, and across sleep stages for individuals with chronic fatigue syndrome (CFS) and control participants, controlling for age. Individuals with CFS had significantly reduced heart rate variability during non-rapid eye movement (NREM) sleep stage 2 and slow wave sleep (SWS) relative to control participants. Estimates are provided at the overall sample mean age (35.5 years). Error bars indicate the 95% confidence interval. Triple asterisks indicate pairwise contrast $P < .001$.

study, participants with CFS reported poorer sleep quality. Their sleep was characterized by delayed sleep onset, and more frequent awakenings during sleep. Although it is possible that repeated awakenings may contribute to a perception of unrefreshing sleep, participants with CFS spent more time in SWS, and were equivalent in total sleep time as well as all other aspects of sleep architecture. Accordingly, unrefreshing sleep in those with CFS does not appear to be explained exclusively by differences in sleep structure.

Instead, patients with CFS have previously been shown to have reduced nocturnal HRV compared to healthy control patients.[8,33] A previous study found that patients with CFS show reduced HRV specifically during SWS,[34] although another study suggests that HRV is reduced during all stages of

Table 3—Correlations between objective sleep and self-reported wellbeing and sleep quality parameters.

	Wake Before Sleep Onset (n = 41)	NREM2 (n = 45)	SWS	REM	SWS%
Self-reported wellbeing and lifestyle					
Somatic symptoms (SPHERE)	−.19 (.236)	**−.29 (.044)**	**−.37 (.013)**	−.10 (.514)	.23 (.110)
Cognitive symptoms (SPHERE)	−.30 (.059)	**−.45 (.001)**	**−.48 (.001)**	−.18 (.238)	.16 (.285)
Mental health (SF-36 MCS)*	.18 (.264)	**.33 (.022)**	**.33 (.025)**	.11 (.459)	**−.31 (.031)**
Physical health (SF-36 PCS)*	**.34 (.028)**	**.41 (.004)**	**.47 (.001)**	.20 (.170)	**−.29 (.043)**
Pain (McGill)	**−.39 (.012)**	**−.46 (.001)**	**−.40 (.006)**	**−.31 (.036)**	.17 (.243)
Daytime sleepiness (ESS)	−.00 (.984)	.00 (.975)	−.01 (.971)	**.32 (.031)**	−.14 (.338)
Emotional distress (PHQ-9)	−.27 (.089)	**−.38 (.008)**	**−.33 (.026)**	−.10 (.498)	**.31 (.030)**
Psychological distress (K10)	−.18 (.268)	**−.41 (.004)**	**−.45 (.002)**	−.10 (.519)	.18 (.216)
Alcohol (units/week)	−.07 (.653)	.20 (.185)	.15 (.342)	−.01 (.939)	−.17 (.256)
Caffeine (cups/day)	.00 (.996)	−.02 (.919)	.06 (.703)	−.08 (.608)	.26 (.077)
Body mass index (kg/m^2)	−.26 (.102)	−.06 (.670)	−.11 (.463)	−.20 (.180)	−.16 (.291)
Diarized weekly physical activity (hours/week)	.19 (.230)	**.29 (.045)**	.24 (.118)	**.40 (.006)**	.01 (.950)
Self-reported sleep quality					
Total PSQI	−.26 (.106)	**−.35 (.014)**	**−.31 (.041)**	−.21 (.166)	.19 (.203)
Sleep quality on night of assessment*	.04 (.805)	.12 (.415)	.16 (.290)	.06 (.692)	.13 (.377)
Refreshment on night of assessment*	.27 (.091)	.23 (.115)	.25 (.108)	.05 (.731)	−.07 (.620)
Average sleep quality across week*	.24 (.125)	**.36 (.014)**	.27 (.074)	.14 (.350)	−.04 (.807)
Average refreshment across week*	**.45 (.003)**	**.45 (.001)**	**.34 (.023)**	**.30 (.043)**	−.16 (.283)

Spearman correlation coefficients (*P* value) between proportion of time spent in slow wave sleep and heart rate variability (as HFnu) across sleep stages, and self-reported wellbeing, lifestyle and sleep quality parameters; n = 48 unless indicated. Values in bold indicates significance at $P < .05$. *A higher score reflects better functioning. ESS = Epworth Sleepiness Scale, HFnu = high-frequency power in normalized units, K10 = Kessler Psychological Distress Scale, MCS = mental composite score, NREM = non-rapid eye movement, PCS = physical composite score, PHQ-9 = Patient Health Questionnaire, PSQI = Pittsburgh Sleep Quality Index, REM = rapid eye movement, SF-36 = 36-Item Short Form, SPHERE = Somatic and Psychological Health Report, SWS = slow-wave sleep.

sleep, as well as when awake.[35] In the current study, nocturnal HFnu HRV was shown to be significantly reduced in participants with CFS compared to control participants, and these differences were specific to deeper stages of sleep (NREM2 and SWS). Slight inconsistencies between our results with previous research may be due to methodological differences. Orjatsalo et al[34] and Togo and Natelson[35] both conducted laboratory-based sleep assessments over 1 night so that participants may have been affected by the "first-night effect"; wherein their sleep was potentially disrupted on their first night of assessment while habituating to an unfamiliar environment and nighttime routine. In contrast, we assessed participants in their own home using a minimally invasive EEG device, removing the need for environmental familiarization, and thus potentially providing a more ecologically valid reflection of participants' regular nocturnal behavior and autonomic activity.

Nocturnal HFnu HRV has previously been shown to be the best independent predictor of unrefreshing sleep in patients with CFS.[7,8] Further, overall nocturnal HRV is positively associated with aspects of self-reported wellbeing in healthy control patients.[32] Building on these findings, in the current study higher HFnu HRV during deeper sleep (NREM2 and SWS), but not during resting wakefulness or REM sleep, was associated with better self-reported sleep quality and refreshment, as well as increased physical and psychological wellbeing (ie, less somatic and cognitive symptoms, pain, and psychological distress, and greater emotional wellbeing). Consistent with previous research,[21] percentage of time spent in SWS was not significantly associated with any measures of sleep quality or refreshment, nor was it positively associated with psychological or physical wellbeing.

Implications

These results, alongside previous research, provide insights into the biological basis of unrefreshing sleep in patients with CFS. They suggest that 'recuperation of energy' during sleep is associated with autonomic de-arousal (indicated by parasympathetic predominance) during deep sleep.

The functional role of SWS is not completely understood; however, multiple hypotheses suggest that one primary function is energy recuperation.[53] It is somewhat surprising then, that proportion of time spent in SWS is elevated in patients with CFS compared to control patients but is not associated with better self-reported wellbeing or sleep quality. Instead, sleep for patients with CFS is marked by diminished parasympathetic nervous system activity during deep sleep, which is also associated with poorer self-reported wellbeing and reduced longer-term sleep quality and refreshment. The inability to de-arouse (ie, reduction in sympathetic activity and concomitant

increase in parasympathetic activity) during sleep has been proposed as an explanation for unrefreshing sleep in those with CFS, evidenced by reduced HRV during sleep.[8] This was also true in the current study, but only during deeper sleep stages, suggesting that autonomic de-arousal is particularly important during this time. Thus, patients with CFS may be lacking in quality, rather than quantity, of recuperative SWS. Indeed, the increased percentage of time spent in SWS for those with CFS in the current study, as well as previous studies[12, 17–20] may be explained by poor-quality SWS. Accumulating evidence supports the homeostatic nature of SWS, in that time spent in SWS is influenced by previous sleep patterns (eg, SWS deprivation on a single night will lead to increased SWS percentage on the following night[53]). Although SWS is not reduced in duration for those with CFS, impaired energy recuperation during this sleep stage due to insufficient autonomic de-arousal, could similarly lead to a compensatory increase in SWS time. It is possible that the greater proportion of sleep time spent in SWS in individuals with CFS is due to inadequate autonomic de-arousal during this time, but this proposal requires further investigation.

These findings also provide further support for a growing body of evidence for dysautonomia in patients with CFS[54] and link such disruptions (particularly during deep sleep) with poor sleep quality and self-reported wellbeing. Without longitudinal or experimental studies, it is not clear if these autonomic disturbances are a by-product of CFS, or causally linked to the symptomatology. However, if future studies can show that autonomic disturbances underlie the experience of unrefreshing sleep, there arise opportunities for interventions that alter autonomic activity during deep sleep, possibly alleviating a hallmark symptom of CFS.

Limitations and future studies

The current findings are correlational in nature, and although we speculate that disruptions in autonomic activity may underlie unrefreshing sleep in those with CFS, there are plausible alternate explanations. For example, disrupted autonomic activity during deep sleep may also arise from habitual poor sleep, or emerge as a secondary symptom of reduced physical activity, which is common in patients with CFS.[55,56] Exploratory analyses indeed indicated a positive association between increased physical activity and higher HFnu HRV during NREM2 and REM stages of sleep, which may be a result of greater physical conditioning.

Study participants were also not explicitly instructed to avoid caffeine, alcohol, or exercise prior to sleep recordings, but rather were encouraged to engage in their normal daytime and evening routines so that recordings were indicative of a typical night of sleep. As such, it is possible that differences in these behaviors prior to sleep contributed to the between-group differences observed. However, it should be noted that additional experimental control of these behaviors may also have impacted sleep and autonomic parameters and would therefore no longer be representative of an individual's usual sleep.

Control participants in the current study were well matched to participants with CFS on relevant demographic variables including age, sex, and BMI; however, nocturnal respiratory rate was not measured and therefore not explicitly compared between groups nor controlled for in analyses. Respiratory parameters may influence HRV[30] and could therefore confound the observed group differences in HFnu HRV. Yet, respiratory rate during wakeful rest was comparable between groups, and respiration has been shown to be relatively stable across the night.[57] Further, the assessment of nocturnal respiratory rate would have required additional invasive equipment (eg, a respiratory belt or nasal cannula), reducing ecological validity (a major strength of the study). The use of additional monitoring equipment including surface EMG would, however, allow for exploration of the potential differential incidence of periodic limb movements between groups, which may also account in part for the observed group differences.

Antidepressant medication use was reported by almost half of the CFS group; this is not surprising given the prevalence of depressive symptoms in CFS and the symptom management approach to treatment in the absence of curative options. Although psychotropic medication, in particular tricyclic antidepressants,[58] may influence HRV parameters, the inclusion of antidepressant medication use in analysis provided no statistical evidence of an effect. However, the sample size was inadequate to conduct specific within-group contrasts by antidepressant medication class, which may be useful to explore in more appropriately powered future studies.

This study investigated sleep architecture using automated scoring algorithms applied to EEG signals acquired from portable devices. Although full PSG is considered the gold standard for sleep assessment, portable devices using automated scoring have been validated.[37,49–51] Further, autonomic activity across the identified sleep stages was consistent with other nocturnal HRV studies,[59] supporting the validity of the staging classifications derived from the portable device. Finally, sleep stage allocations were assigned to 5-minute HRV epochs requiring at least 60% of the included sleep epochs to be of the same stage. As such, some epochs may have been influenced by autonomic activity from minority adjacent sleep stages. However, sensitivity analysis employing stricter threshold values for inclusion in the analysis set (ranging from 70% to 100%) generated highly compatible results, albeit with substantially reduced sample sizes. Thus, it is unlikely that this parameterization of epochs influenced the conclusions drawn; however, an alternative parametrization by identifying 5 consecutive minutes of sleep epochs of the same stage and analyzing HRV during this time[60] could be used in future studies.

CONCLUSIONS

Unrefreshing sleep in patients with CFS is unlikely a function of abnormal total sleep time, or percentage of time spent in each sleep stage. Rather, using an ecologically valid assessment of nocturnal EEG and simultaneous HRV, the current study affirms that unrefreshing sleep and impaired self-reported wellbeing is associated with reduced parasympathetic activity during deep sleep (NREM2 and SWS) in patients with CFS. Experimental and longitudinal studies are required to establish causal links, potentially providing

opportunities for intervention for the alleviation of this core symptom of CFS.

ABBREVIATIONS

BMI, body mass index
CFS, chronic fatigue syndrome
ECG, electrocardiography
EEG, electroencephalography
HF, high frequency
HFnu, high frequency normalized units
HR, heart rate
HRV, heart rate variability
LF, low frequency
LMM, linear mixed models
NREM, non-rapid eye movement
PSG, polysomnography
REM, rapid eye movement
SWS, slow-wave sleep
VLF, very low frequency

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