Gotts ZM, Deary V, Newton JL, Ellis JG. [A comparative polysomnography analysis of sleep in healthy controls and patients with chronic fatigue syndrome](#). *Fatigue: Biomedicine, Health and Behavior* 2016, 4(2), 80-93.

Copyright:

This is an Accepted Manuscript of an article published by Taylor & Francis in *Fatigue: Biomedicine, Health and Behavior* on 13-4-2016, available online:

<http://www.tandfonline.com/10.1080/21641846.2016.1167470>

Date deposited:

22/06/2016

Embargo release date:

13 April 2017

This work is licensed under a [Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International licence](#)

A comparative polysomnography analysis of sleep in healthy controls and patients with chronic fatigue syndrome

Zoe M. Gotts, PhD^{a*}, Vincent Deary, PhD^a, Julia L. Newton, MD, PhD^b and Jason G. Ellis, PhD^a

^aNorthumbria Centre for Sleep Research, Faculty of Health and Life Sciences, Northumbria University, Newcastle-upon-Tyne, United Kingdom

^bInstitute for Cellular Medicine, Medical School, Newcastle University & Newcastle Hospitals NHS Foundation Trust and UK NIHR Biomedical Research Centre in Ageing, Newcastle-upon-Tyne, United Kingdom

***Correspondence:**

Dr Zoe Gotts
Northumbria Centre for Sleep Research (NCSR)
Faculty of Health & Life Sciences
Northumbria University
Newcastle-upon-Tyne
NE1 8ST
United Kingdom
Tel: +44 (0)191 227 4363
Email: zoe.gotts@ncl.ac.uk

Abstract

Background: Sleep disturbance affects almost 95% of people with chronic fatigue syndrome (CFS).

However, existing studies of sleep in CFS have shown mixed results and methodological issues prevent between-study comparisons.

Purpose: To redress this, the present study aimed to investigate whether there are differences in the sleep of patients with CFS and healthy controls, using a comparative analysis of Polysomnography over three consecutive nights.

Methods: 22 patients with CFS (1994 Centers for Disease Control and Prevention criteria) and 22 healthy controls underwent three nights of polysomnographic sleep assessment. Groups were compared on their objective sleep variables derived from the third night of assessment, to allow for participant adaptation to the sleep study.

Results: 9.1% of patients met criteria for an objectively verifiable sleep disorder. Differences in sleep were observed between CFS patients and healthy controls on four objectively-derived sleep variables (wake after sleep onset, sleep efficiency, percentage wake and REM Latency). In addition, people with CFS reported more severe symptoms of insomnia than healthy controls.

Conclusions: The study reports on key differences in sleep between people with CFS and healthy individuals. The potential presence of a sleep disorder in this patient population is high, it is therefore important that during early evaluation, a detailed history of sleep is taken to rule out a sleep disorder in CFS. In addition, patients with CFS show poorer sleep as defined by objectively-derived measures and also self-report poorer quality sleep. Improving sleep is a potential treatment target in CFS.

Key Words: chronic fatigue syndrome, sleep, polysomnography

Introduction

Chronic Fatigue Syndrome (CFS) affects between 0.2% - 4% of the UK population¹, making it a significant healthcare issue. Characterized by intense persistent or relapsing fatigue of at least 6 months in duration, CFS affects both physical and cognitive functioning and is associated with other symptoms such as myalgia, concentration difficulties and sleep disturbance². CFS has the largest prevalence of an objective sleep disorder in any single illness population³⁻⁶, with rates as high as 65%⁷, and 87-95% of patients continue to report unrefreshing sleep as a principle complaint after excluding individuals with diagnosable sleep disorders⁸⁻¹¹.

Polysomnography (PSG) is considered the gold standard objective sleep assessment. Despite the prevalence of sleep problems in CFS, studies using PSG in CFS populations have not been uniform in their data reporting or methodological practices¹²⁻¹³. As such, there remains no clear pattern of sleep abnormality in this population. One characteristic of PSG research in CFS that may account for this is the high degree of variability in sleep continuity and sleep architecture features that are reported in CFS studies, making it difficult to interpret results and determine the nature and extent of patients' sleep difficulties. Furthermore, PSG studies in CFS have mostly been carried out over one night^{6, 7, 14-21}, or two²²⁻³⁰, which may present a potential 'first night effect' (i.e, when a person has a different sleeping pattern to usual, as a result of a sleep study)²⁴. The assumptions regarding the variability and lack of consistency in objective sleep patterns of patients with CFS rests on the idea that patients experience the first-night-effect. A seminal study explored this phenomenon in 83 CFS patients without an objectively verifiable sleep disorder and observed clear differences between the first and second night sleep parameters²⁵, all indicating a poorer first night sleep, in comparison to night two.

Both the first night effect and the potential for rebound sleep (better sleep resulting from a previous poor night) highlight the need for at least a 3-night assessment for PSG research with CFS patients.

CFS diagnosis is based on a collection of symptoms, which creates difficulties in making definitive conclusions, however, given the probable reciprocal effects of disturbed sleep on existing CFS symptoms, the sleep of patients with CFS should be looked at in as much detail as possible. This study aimed to redress the inconsistencies in previous studies reporting polysomnographic-derived results from CFS populations and compare the sleep of individuals with CFS and healthy controls on the *third* recorded night of sleep.

Methods

Recruitment of participants

22 CFS patients were recruited from a specialist CFS Service in the North of England, and fulfilled the CDC 1994 diagnostic criteria². 22 healthy controls were recruited from a bank of participants held by the Northumbria Centre for Sleep Research (NCSR). All included subjects were aged between 18 and 65 and free from any sleeping medication for at least 3 weeks prior to recording (Table 2). Six CFS patients (40%) were taking sleep-altering medications at participation (selective serotonin re-uptake inhibitors, N = 6; gabapentin, N = 1). Five were taking one sleep-altering medication and one participant was on both a selective serotonin re-uptake inhibitor (SSRI) and Gabapentin.

Exclusion criteria for all subjects were: a) those currently seeing a sleep medicine specialist, b) a diagnosis of Obstructive Sleep Apnoea (OSA), Periodic Limb Movement Disorder (PLMD) or Narcolepsy, c) those who had travelled beyond one time zone within three months of study participation, and d) shift-workers. Regular sleep-wake schedules and circadian normality were assessed through Actigraphy and adjunct sleep diaries two weeks prior to the start of the study. Actigraphy was used to complement the sleep diary, and was not used in any further analyses. Sleep Disorders (OSA, PLMD) were ruled out following night one of the PSG assessment, if individuals met AASM exclusionary criteria (i.e, if the Apnoea Hypopnoea Index (AHI; number of Apnea or Hypopnea events per hour of sleep) was greater than 5, and/or a Periodic Limb Movement Index (PLMI; rate of

leg movements per hour of sleep) greater than 5).

Ethical approval was granted by the Newcastle and North Tyneside local research ethics committee, and all participants provided written informed consent.

Procedure

Prior to the 3-day assessment, participants were required to complete a sleep diary over a 14-day pre-assessment period. During this time, participants were also required to complete the Pittsburgh Sleep Quality Index (PSQI) and the Insomnia Severity Index (ISI). To assess daytime symptoms in the CFS group, the Chalder Fatigue Questionnaire and Short Form-36 Health Survey (SF-36) were completed by patients. All participants underwent three consecutive nights of polysomnography assessment, to reduce the potential for a 'first-night' effect and a rebound night. To allow for greater participation, the CFS cohort underwent ambulatory PSG assessment in their homes.

Objective Sleep Assessment

Polysomnography. Polysomnography (PSG) was carried out over 3 consecutive nights. The first two study nights served as screening and an opportunity for participant adaptation. Recordings were conducted in accordance with International 10/20 standards on all 3 nights³¹, and an extended montage was used on night 1 (Figure 1). Oral and nasal airflow were measured by a nasal cannula, capillary oxygen saturation by finger-oxymetry and respiratory effort by thoracic and abdominal belts (See eMethods1 in the supplement for details of the PSG recording).

[Insert Figure 1 here]

Outcome Measures

The *Pittsburgh Sleep Quality Index (PSQI)*³³ evaluated sleep quality over the previous month. 19 self-rated items are combined to form 7 component scores (subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, daytime dysfunction), responses are rated on 4-point Likert scale (0=no difficulty, 3=severe difficulty). Component scores are summed to yield a global score that has a possible range of 0-21 (0=no difficulty, 21=severe difficulties in all areas). A global PSQI score greater than 5 suggests poor quality sleep.

The *Insomnia Severity Index (ISI)* is a reliable and valid tool for detecting cases of insomnia in a population³⁴. 7 items evaluate the severity of sleep onset, sleep maintenance, early morning awakening problems, sleep dissatisfaction, interference of sleep difficulties with daytime functioning, noticeability of sleep problems by others, and distress caused by the sleep difficulties. Responses are rated on a 5-point Likert scale (0 = no problem; 4 = very severe problem) yielding a total score (0 -28). Scores can determine an absence of insomnia (0-7), subthreshold insomnia (8-14) or 'caseness' for clinical insomnia (15-21), with 10 or more considered optimal for detecting insomnia cases³⁴. Convergent validity is supported by high ISI scores being significantly correlated with QoL and fatigue³³. The *Ford Insomnia Response to Stress Test (FORD)* is a 9-item screening tool to identify individuals predisposed to developing insomnia, testing the likelihood that an individual will have sleep disturbances following stressful events.

Objective Sleep Variables included Sleep onset latency (SOL), Total sleep period (TSP), Total sleep time (TST), Number of awakenings (NWAK), Sleep efficiency index (SEI), REM (Non Rapid Eye Movement) sleep, REM (Rapid Eye Movement) latency (REML) (See Table 1) (See eMethods 1 in the supplement for detailed sleep variable parameters).

(Insert Table 1 Here)

Daytime symptoms

The *Chalder Fatigue Questionnaire (CFQ)*³⁵ was used to measure symptomatic fatigue experienced by patients in this study. Four response options are available, ranging from “less than usual” to “much more than usual”. The Likert system for scoring was used (0-3) with a total possible score ranging from 0-33. A higher score indicates more fatigue. The test has been shown by its authors to have good reliability ($r = .86$ for physical fatigue, and $r = .85$ for mental fatigue) and has high internal consistency as measured by Cronbach’s alpha (.89)³⁵. The *Short Form Health Survey (SF-36)*³⁶ was used to assess health status, functioning, and well-being as a measure of Quality of Life (QoL) across eight domains, both physically and emotionally based. Lower values reflect more impairment.

Statistical analysis

Statistical analyses were performed using IBM SPSS version 22. An independent samples *t*-test was used to examine which demographic variables and polysomnography-derived sleep variables differentiated the groups. Multiple Regression analyses examined the extent to which sleep predicted patient’s daytime symptoms (see eResults 1). All values are expressed as mean $\pm$ SD unless otherwise stated.

Results

Following the first night of recording, 2 (9.1%) CFS patients were excluded from the study, having met the exclusionary criteria for sleep apnea (A+H Indexes: 15.5 and 7.1). Data for one CFS patient was excluded due to no nocturnal sleep having been recorded, due to daytime sleep, following the third study night. There were no further exclusions. The final dataset included 19 CFS patients, and 22 healthy control participants. All patients completed the three overnights of home-based polysomnographic assessment including morning sleep diary completion. This 0% rate of attrition indicates that this 3-day sleep assessment protocol was both feasible and acceptable to patients who were eligible to take part in this study.

There were no between-group differences on sex ($p=0.12$) or BMI ($p=0.46$). There were no significant differences in sleep parameters between the second and third nights of assessment (data not shown) and therefore the third night data is presented. In relation to the polysomnography variables, differences in objective sleep were observed between CFS patients and healthy controls on four objectively-derived sleep variables (wake after sleep onset ($p<0.05$), sleep efficiency ($p<0.05$), percentage of wake ($p<0.01$) and REM Latency ($p<0.05$) (see Table 2), and six self-reported facets of sleep quality (PSQI), including insomnia severity (ISI) (see Table 3). There were no group differences in sleep onset latency (SOL) ($p=0.06$), TST ($p=0.57$), percentage of stage 1 ($p=0.28$) sleep, percentage of stage 2 sleep ($p=0.71$), percentage of stage 3 (SWS) ($p=0.26$) sleep, or percentage of REM ($p=0.60$). There were also no differences between CFS patients and healthy controls on number of awakenings (NWAK) ($p=0.08$).

(Insert Table 2 Here)

Self-reported sleep

There were significant group differences on all but one component of the PSQI. Global scores were poorer for CFS patients than healthy controls ($p<.001$). In addition, CFS patients had poorer scores on 'sleep Latency' ($p<.001$), 'Subjective Sleep Quality' ($p<.001$), 'Sleep Duration' ($p<.05$), 'Sleep Efficiency' ($p<.05$), and 'Sleep Disturbances' ($p<.001$), and 'Daytime Dysfunction' ($p<.01$). There were no significant differences observed on the 'Medication Use' ($p=0.07$) component (Table 3). 100% of patients had PSQI global scores of 5 or more, exceeding the threshold that is indicative of poor quality sleep (≥ 5). Scores ranged from 5 to 17 points (mean=8.75, SD=3.45). For individual components (subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of

sleeping medication, daytime dysfunction), each with a possible range of 0-3, the observed ranges were 0-3 (Table 3).

There were significant differences in self-reported insomnia severity between CFS patients and healthy controls ($p < .001$). Observation of self-reported sleep difficulties showed CFS patients had mean ISI scores (13.74, $SD=4.81$) which indicated 'sub-threshold insomnia', with 52.6% (10/19) of patients reporting sleep difficulties meeting criteria for this range (8-14). 42.1% of patients (8/19) met 'caseness' for clinically defined insomnia (ISI score 15-21), and one patient's sleep difficulties were classified as 'severe' (>21)³⁴.

(Insert Table 3 Here)

Subjective vs Polysomnographic assessment of sleep

Interestingly, based on the retrospective measures of sleep (PSQI, ISI, FIRST), patients scored highly across all assessments for reporting sleep difficulties and poor quality sleep. On the other hand, the objectively-derived PSG measures shed a different light; patients' sleep profiles on the whole appeared to reflect 'normal sleep' parameters, presenting abnormalities on the continuity variable WASO, and in the architectural variables of %WAKE and REM latency.

It is therefore of interest to explore this discrepancy further. To evaluate the level of concordance between the two assessment modalities; self-reported measures of sleep based on the sleep diary; and the objectively derived Polysomnographic variables (PSG), a Pearson product-moment correlation was carried out to determine the level of agreement between corresponding sleep variables (TST, SOL, WASO) derived from the two assessment modalities.

(Insert Table 4 Here)

TST as measured by the PSG (453.91 ± 73.74 minutes) and TST self-reported on the sleep diary (448.68 ± 101.31 minutes) were significantly correlated, $r = .65$, $p < .01$, indicating a strong positive relationship between objectively derived (PSG) measures of total sleep time and total sleep time as self-reported (sleep diary) by patients (See Table 4). Patients were therefore accurately estimating their sleep duration. However, there was a nonsignificant correlation of $.21$ ($p = n.s$) between SOL measured by the PSG (mean= 22.47 , SD= 20.49 minutes) and SOL self-reported on the sleep diary (mean= 33.95 , SD= 21.67 minutes). There was also a nonsignificant correlation of $.32$ ($p = n.s$) between WASO measured by the PSG (mean= 37.13 , SD= 24.32 minutes) and WASO self-reported on the sleep diary (mean= 41.58 , SD= 56.48 minutes) (Table 4). This indicates that patients were overestimating the amount of time it took them to get to sleep and the amount of time they were spending awake during the night.

Discussion

The study aimed to investigate objective differences in the sleep of patients with CFS and healthy controls, using Polysomnography over three consecutive nights. Sleep on the third night allowed for adaptation and potential rebound sleep was compared. Patients with CFS differed from the healthy healthy control group on four objectively-derived sleep variables with significant differences observed on WASO, SE, REML and %Wake; the CFS patient group had the highest amount of wake after sleep onset and percentage of wake, and longer REM latencies than the healthy control group. Although differences in sleep efficiency were observed, these were in the normal range ($>85\%$) for both groups. CFS patients also reported significantly poorer sleep quality and more severe insomnia-related symptoms than the healthy control group.

A key clinical observation in the study was the longer REM latency in the CFS group. REM sleep

is the period by which learning and memory consolidation are believed to occur, it therefore seems plausible to consider this stage of sleep and how it may be involved in CFS, as this condition features key symptoms such as brain fog, memory and concentration difficulties. REM sleep represents the most highly aroused brain state during sleep and appears the most vulnerable to fragmentation in individuals who demonstrate persistent hyperarousal - a potential contributor to the experience of disrupted and nonrestorative sleep - a result of enhanced arousal and more conscious perception of the environment during sleep³⁷. REM sleep should be a focus for future sleep research in CFS, given its association with poor quality sleep³⁸ and a potential perpetuating factor for other symptoms. Such disruptions in the normal sleep process suggest that a potential 'REM Sleep Instability' (RSI) may be an objective marker for CFS³⁹.

Prior to the sleep assessment, patients self-reported their sleep as disturbed and of poor quality, as demonstrated by the retrospective self-report measures. However, on initial examination of patients' sleep profiles, based on objectively derived measures (PSG), on average they fell into the parameters of 'normal' sleep. The variability in values derived on each of the sleep parameters is of relevance; it highlights how a significant minority of the sample fell outside of the 'normal' parameters, a reflection of the heterogeneity of sleep, and is also characteristic of patient's sleep profiles as identified in the previous studies. For example, increased amounts of stage 2 sleep mirrors what has been shown in patients characterised by the second phenotype identified in the cluster analysis of CFS patients from our recent study⁵, and its association with information processing, arousability and the perception of sleep in fibromyalgia patients has also been demonstrated⁴¹. Alpha activity (a shallow form of sleep), has been associated with an increased tendency to arouse to external stimuli in fibromyalgia patients, and to the perception of more shallow sleep, but interestingly not related to pain⁴¹. This increased arousability could be trans-diagnostic for functional symptoms; the tendency for patients to arouse more during sleep may

result in more fragmented sleep, as suggested by Shneider-Helmert and colleagues⁴³, which in turn has been implicated in daytime fatigue and nonrestorative sleep⁴⁴, fundamental symptom complaints of patients with CFS.

Combining methods of sleep assessment enabled the examination of sleep variables derived from the different assessment modalities (subjective sleep diary vs objective PSG). Patients were accurate in their estimation of sleep duration. However, estimations of wake duration and the time it took them to get to sleep were not concordant with the objectively derived measures. This finding mirrors the discrepancy found between subjective and objective measures of sleep, previously seen in CFS; Watson and colleagues⁴⁵ demonstrated no differences between the healthy and CFS twins on objective measures of sleep abnormalities despite significant self-reported sleep complaints from the CFS twins. This suggests CFS patients require an objective assessment of their sleep pattern, and these objective methods have been shown to be feasible in this population.

The protocol was possible in all eligible patients that took part, which emphasises the feasibility of incorporating all the included procedures of a detailed 3-night PSG sleep assessment. Overall, the protocol was well tolerated, with only minor issues relating to individuals and their experience of the equipment (sensitivity, planning, energy depletion). Also it is worth emphasising how several patients brought to light of the issue of daytime sleep, and this also posed a problem with regard to analyses, where a night of PSG data for one patient had to be excluded due to no nocturnal sleep having been recorded, **and the possible presence of a sleep disorder in this patient. Daytime sleep is recognisable in this population⁴⁶, and it has been associated with having a negative impact on daytime symptoms⁴⁷, this warrants further study.**

In addition to establishing protocol feasibility in this patient group, we established a profile of sleep in patients, derived from sleep in a naturalistic setting across 3 consecutive nights. The temporal

stability of sleep continuity and main architectural variables across two consecutive nights of assessment was also confirmed. This PSG protocol therefore affords, if needed, the efficacy to carry out two rather than three nights of recording. Of note, variability of sleep was confirmed to exist in this population, and, as such, the establishment of a successful protocol for effective and thorough sleep assessment is a key advancement in this domain .

There are some limitations to the design of this study. The CFS group underwent sleep assessment in the home setting. This enabled greater participation and generalizability to a patient group whose symptoms are often disabling, and allowed participation of the more severely affected, a sub-group often overlooked in research. Ideally a healthy control group should have also been studied in the home setting, given that people may sleep differently in the lab to how they would usually in their own home. Despite the potential for differences in sleep between the unattended home and the attended laboratory PSG setting, previous home vs lab investigations have observed only modest effects on sleep parameters, an overall difference similar to that expected based on night-to-night variation in sleep^{40,41}. Of note, participants in the study significantly differed on age. **And, by not including those with sleep apnea, sleep phase disorders or narcolepsy, it is plausible that a crucial subgroup of patients are being missed, with sleep disorders that may be contributing to fatigue, or comorbid to CFS.** Future work may want to age-match the control participants to the CFS patient group, and also look at comparing CFS patients with and without a comorbid sleep disorder, **or the presence of OSA**. Although participants were free from sleep medication prior to taking part, those taking anti-depressants were not excluded. Anti-depressant medication increases REM latency, which makes it difficult to determine whether the longer REM latencies observed in patients are due to the sleep altering medication or a feature of CFS.

Despite patients' demonstrating impairments in symptoms of fatigue and social functioning, there was no relationship between objective sleep and symptoms in patients (see eResults1 in

supplement), suggesting that further work is needed to explore the relationship between sleep abnormalities and fatigue in this patient group, and that formal sleep studies are needed.

Moving forward in advancing sleep research in CFS populations, this study afforded the opportunity to establish an objective profile of sleep in a group of CFS patients, based on assessment of sleep in a naturalistic setting, over 3 consecutive nights. By carrying out home sleep studies with people with CFS, the findings are more generalizable to patients, who may otherwise not be able to participate in such research studies. It is important to note the exclusion of one patient's data due to an absence of nocturnal sleep recorded, **and also, with PSG there is always the potential for day-to-day variability in objective sleep variables, which should be considered⁴⁸. Future objective sleep studies in CFS may wish to explore sleep fragmentation, where there have been advances in methods to quantify this aspect of sleep.** Studies should also consider *daytime* PSG assessment, thus extending the monitoring of patient's sleep to ensure their entire sleep period is characterized, given sleeping during the day, is highly likely in a CFS patient group. It would also be of value for future studies to incorporate daytime multiple sleep latency tests (MSLT) to measure excessive sleepiness during the day, **in trying to determine a problem with sleep, and identify and rule out possible narcolepsy as an underlying sleep disorder, where it can often mistakenly be labelled as CFS. Future, more complete studies should also look in more detail at the demographics of sleep disorders in this group of patients, which can present more than one syndrome.**

In summary, the objective data show that the sleep of people with CFS is different from those without the condition, particularly in relation to sleep efficiency, wake and REM latency. Those with CFS also self-report poorer sleep quality and more severe insomnia ratings than healthy controls. In CFS, detailed sleep evaluation and systematic PSG screening early on will help to identify and exclude diagnosable sleep disorders, which are important contributors to fatigue.

Contributorship Statement

ZMG, VD, JLN and JGE were involved in the design of the study. ZMG conducted the study and JGE and ZMG analysed the data. The first draft was written by ZMG and was edited by all authors. All authors approved the final version of the manuscript.

Competing Interests

The authors have declared that no competing interests exist

Funding

This work was supported by Action for ME, ME Research UK, and the ME Association Ramsay Research Fund. The organizations had no role in the study design, data collection and analysis, decision to publish and preparation of the manuscript.

Data Sharing Statement

No additional data are available.

References

1. Fernandez AA, Martin AP, Martinez MI, *et al.* Chronic fatigue syndrome: aetiology, diagnosis and treatment. *Bmc Psychiatry* 2009; 9.
2. Fukuda K, Straus SE, Hickie I, *et al.* The Chronic Fatigue Syndrome: A Comprehensive approach to its definition and study. *Annals of Internal Medicine* 1994; 121: 953-9.
3. Decker MJ, Eyal S, Shinar Z, Fuxman Y, Cahan C, Reeves WC, Baharav A. Validation of ECG-derived sleep architecture and ventilation in sleep apnea and chronic fatigue syndrome. *Sleep and Breathing* 2010; 14: 233-9.
4. Devasahayam A, Lawn T, Murphy M, White PD. Alternative diagnoses to chronic fatigue syndrome in referrals to a specialist service: service evaluation survey. *JRSM short reports* 2012; 3: 4.
5. Gotts ZM, Deary V, Newton J, Van der Dussen D, De Roy P, Ellis JG. Are there sleep-specific phenotypes in patients with chronic fatigue syndrome? A cross-sectional polysomnography analysis. *BMJ Open* 2013; 3.
6. Fossey M, Libman E, Bailes S, Baltzan M, Schondorf R, Armsel R, Fichten CS. Sleep quality and psychological adjustment in chronic fatigue syndrome. *Journal of Behavioral Medicine* 2004; 27: 581-605.

7. Creti L, Libman E, Baltzan M, Rizzo D, Bailes S, Fichten CS. Impaired Sleep in Chronic Fatigue Syndrome How Is It Best Measured? *Journal of Health Psychology* 2010; 15: 596-607.
8. Nisenbaum R, Jones JF, Unger ER, Reyes M, Reeves WC. A population-based study of the clinical course of chronic fatigue syndrome. *Health Qual Life Outcomes* 2003; 1: 49.
9. Hamaguchi M, Kawahito Y, Takeda N, Kato T, Kojima T. Characteristics of chronic fatigue syndrome in a Japanese community population : chronic fatigue syndrome in Japan. *Clin Rheumatol* 2011; 30: 895-906.
10. Jason LA, Porter N, Brown M, Anderson V, Brown A, Hunnell J, Lerch A. CFS: A Review of Epidemiology and Natural History Studies. *Bulletin of the IACFS/ME* 2009; 17: 88-106.
11. Mariman A, Vogelaers D, Hanouille I, Delesie L, et al. Subjective sleep quality and daytime sleepiness in a large sample of patients with chronic fatigue syndrome (CFS). *Acta Clinica Belgica* 2012; 67(1):19-24.
12. Gotts ZM, Ellis JG, Newton JL, Deary V. The role of sleep in chronic fatigue syndrome: a narrative review. *Fatigue: Biomedicine, Health & Behavior* 2014; 2: 163-84.
13. Mariman, A. N., Vogelaers, D. P., Tobback, E., Delesie, L. M., Hanouille, I. P., & Pevernagie, D. A. Sleep in the chronic fatigue syndrome. *Sleep medicine reviews* 2013; 17(3), 193-199.
14. Buchwald D, Pascualy R, Bombardier C, Kith P. Sleep disorders in patients with chronic fatigue. *Clin Infect Dis* 1994; 18: S68-72.
15. Guilleminault C, Poyares D, da Rosa A, Kirisoglu C, Almeida T, Lopes MC. Chronic fatigue, unrefreshing sleep and nocturnal polysomnography. *Sleep Medicine* 2006; 7: 513-20.
16. Kishi A, Struzik ZR, Natelson BH, Togo F, Yamamoto Y. Dynamics of sleep stage transitions in healthy humans and patients with chronic fatigue syndrome. *American Journal of Physiology-Regulatory Integrative and Comparative Physiology* 2008; 294: R1980-R7.
17. Krupp LB, Jandorf L, Coyle PK, Mendelson WB. Sleep disturbance in chronic fatigue syndrome. *Journal of Psychosomatic Research* 1993; 37: 325-31.
18. Morriss R, Sharpe M, Sharpley AL, Cowen PJ, Hawton K, Morris J. Abnormalities of sleep in patients with the chronic fatigue syndrome. *British Medical Journal* 1993; 306: 1161-4.
19. Sharpley A, Clements A, Hawton K, Sharpe M. Do patients with "pure" chronic fatigue syndrome (neurasthenia) have abnormal sleep? *Psychosom Med* 1997; 59: 592-6.
20. Stores G, Fry A, Crawford C. Sleep abnormalities demonstrated by home polysomnography in teenagers with chronic fatigue syndrome. *Journal of Psychosomatic Research* 1998; 45: 85-91.
21. 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 Research & Therapy* 2008; 10.
22. Ball N, Buchwald DS, Schmidt D, Goldberg J, Ashton S, Armitage R. Monozygotic twins discordant

for chronic fatigue syndrome - Objective measures of sleep. *Journal of Psychosomatic Research* 2004; 56: 207-12.

23. Decker MJ, Tabassum H, Lin JMS, Reeves WC. Electroencephalographic correlates of Chronic Fatigue Syndrome. *Behavioral and Brain Functions* 2009; 5.

24. Fischler B, LeBon O, Hoffmann G, Cluydts R, Kaufman L, DeMeirleir K. Sleep anomalies in the chronic fatigue syndrome - A comorbidity study. *Neuropsychobiology* 1997; 35: 115-22.

25. Le Bon O, Minner P, Van Moorsel C, *et al.* First-night effect in the chronic fatigue syndrome. *Psychiatry Research* 2003; 120: 191-9.

26. Neu D, Hoffmann G, Moutrier R, Verbanck P, Linkowski P, Le Bon O. Are patients with chronic fatigue syndrome just 'tired' or also 'sleepy'? *Journal of Sleep Research* 2008; 17: 427-31.

27. Neu D, Cappeliez B, Hoffmann G, Verbanck P, Linkowski P, Le Bon O. High Slow-Wave Sleep and Low-Light Sleep: Chronic Fatigue Syndrome is Not Likely to be a Primary Sleep Disorder. *Journal of Clinical Neurophysiology* 2009; 26: 207-12.

28. Reeves WC, Heim C, Maloney EM, *et al.* Sleep characteristics of persons with chronic fatigue syndrome and non-fatigued controls: results from a population-based study. *BMC Neurol* 2006; 6.

29. Watson NF, Jacobsen C, Goldberg J, Kapur V, Buchwald D. Subjective and objective sleepiness in monozygotic twins discordant for chronic fatigue syndrome. *Sleep* 2004; 27: 973-7.

30. Van Hoof E, De Becker P, Lapp C, Cluydts R, De Meirleir K. Defining the occurrence and influence of alpha-delta sleep in chronic fatigue syndrome. *American Journal of the Medical Sciences* 2007; 333: 78-84.

31. Harner P, Sannit T. *A review of the international ten-twenty system of electrode placement*. Grass Instrument Company. 1974.

32. Medicine AAoS, Iber C. *The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications*. American Academy of Sleep Medicine. 2007.

33. Buysse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Research* 1989; 28: 193-213.

34. Morin CM, Belleville G, Bélanger L, Ivers H. The insomnia severity index: psychometric indicators to detect insomnia cases and evaluate treatment response. *Sleep* 2011; 34: 601.

35. Chalder T, Berelowitz G, Pawlikowska T, Watts L, Wessely S, Wright D, Wallace, E. P. Development of a fatigue scale. *Journal of Psychosomatic Research* 1993; 37: 147-153.

36. Ware Jr JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36): I. Conceptual framework and item selection. *Med Care* 1992: 473-83.

37. Drake C, Richardson G, Roehrs T, Scofield H, Roth T. Vulnerability to stress-related sleep disturbance and hyperarousal. *SLEEP* 2004; 27: 285-92.

38. Drake C JC, Roehrs T, *et al.* . Vulnerability to chronic insomnia: a longitudinal population-based

prospective study. . *Sleep*. 2004; (Abstract Supplement): A270-A1.

39. Riemann D, Spiegelhalder K, Nissen C, Hirscher V, Baglioni C, Feige B. REM Sleep Instability-A New Pathway for Insomnia? *Pharmacopsychiatry* 2012; 45: 167.

40. Iber C, Redline S, Gilpin AK, *et al*. Polysomnography performed in the unattended home versus the attended laboratory setting-Sleep Heart Health Study methodology. *Sleep* 2004; 27: 536-40.

41. Hirscher V, Unbehauen T, Feige B, Nissen C, Riemann D, Spiegelhalder K. Patients with primary insomnia in the sleep laboratory: do they present with typical nights of sleep? *Journal of Sleep Research* 2015.

42. Perlis ML, Giles DE, Bootzin RR, Dikman ZV, Fleming GM, Drummond SP, Rose MW. Alpha sleep and information processing, perception of sleep, pain, and arousability in fibromyalgia. *International journal of neuroscience* 1997; 89: 265-80.

43. Schneider-Helmert D, Kumar A. Sleep, its subjective perception, and daytime performance in insomniacs with a pattern of alpha sleep. *Biological Psychiatry* 1995; 37: 99-105.

44. Stepanski E, Lamphere J, Badia P, Zorick F, Roth T. Sleep Fragmentation and Daytime Sleepiness. *Sleep* 1984; 7: 13-26.

45. Watson NF, Kapur V, Arguelles LM, Goldberg J, Schmidt DF, Armitage R, Buchwald D. Comparison of subjective and objective measures of insomnia in monozygotic twins discordant for chronic fatigue syndrome. *Sleep* 2003; 26: 324-8.

46. Spitzer AR, Broadman M. A Retrospective Review of the Sleep Characteristics in Patients with Chronic Fatigue Syndrome and Fibromyalgia. *Pain Practice*. 2010;10(4):294-300.

47. Gotts ZM, Ellis JG, Deary V, Barclay N, & Newton JL. The Association between Daytime Napping and Cognitive Functioning in Chronic Fatigue Syndrome. *PloS one*, 2015; 1-12. doi e0117136.

48. Tobback E *et al*. Polysomnographic and multiple sleep latency data in a large sample of patients with chronic fatigue syndrome and their relationship with subjective scores. *Fatigue: biomedicine, health and behavior*. 2015; 1-10. DOI: 10.1080/21641846.2015.1106176

Table 1: Description of sleep variables

Abbreviated Variable	Sleep Variable (measure)	Description
AHI	Apnea /Hypopnea Index	Number of Apnea or Hypopnea events during sleep
TST	Total Sleep Time (minutes)	Amount of time asleep
SOL	Sleep Onset Latency (minutes)	Length of time from lights out to first episode of stage 2 sleep
WASO	Wake After Sleep Onset (minutes)	Number of minutes of recorded wake following first episode of stage 2 sleep
NWAK	Number of Awakenings (over TSP)	Number of wake bouts following first episode of stage 2 sleep
NoA	Number of Arousals	Number of arousals over the entire sleep period
REML	REM Latency	Length of time to first REM stage
SE (%)	Sleep Efficiency	Percentage of time spent asleep from the amount of time spent in bed ($TST/TIB \times 100$)
%N1	Percentage of Stage 1 (of TST)	Percentage of recorded stage 1 sleep over the total time asleep
%N2	Percentage of Stage 2 (of TST)	Percentage of recorded stage 2 sleep over the total time asleep
%SWS	Percentage of SWS (of TST)	Percentage of recorded slow wave sleep over the total time asleep
%REM	Percentage of REM (of TST)	Percentage of recorded Rapid Eye Movement sleep over the total time asleep
%WAKE	Percentage of WAKE (of TSP)	Percentage of recorded wake over the whole sleep period (from lights out to lights on)

Notes: REM, rapid eye movement; TSP, total sleep period; TST, total sleep time; arousal defined as an abrupt shift in EEG frequency (alpha, theta waves and/or frequencies greater than 16 Hz, but not sleep spindles), lasting at least 3s, after at least 10 continuous seconds of sleep, and is associated with sleep fragmentation (Iber et al., 2007).

Table 2: Characteristics of study participants, and sleep variables derived from nocturnal polysomnography for the two groups, from the third recorded night.

	CFS (N=19)	HC (N=22)	t- test	P Value
Demographics				
Sex	5 males (26.32%)	11 males (50%)	1.56	ns
Age (years)	44.63 (9.74)	25.18 (5.86)	7.87	p<.001
BMI	26.09 (3.89)	25.18 (3.57)	0.75	ns
Sleep Variables				
Total Sleep Time (min)	442.39 (85.85)	430.43 (30.08)	0.61	ns
Sleep Onset Latency (min)	28.95 (29.55)	14.73 (11.41)	2.09	ns
Wake After Sleep Onset (min)	42.16 (42.26)	15.86 (12.41)	2.79	p<.05
Number of Awakenings (over TSP)	18.37 (10.34)	13.64 (4.88)	1.92	ns
REM Latency (min)	140.00 (84.33)	89.45 (30.91)	2.62	p<.05
Percentage of N1 (of TST)	4.33 (2.11)	3.70 (1.39)	1.15	ns
Percentage of N2 (of TST)	53.15 (11.58)	52.08 (4.47)	0.40	ns
Percentage of N3 (SWS) (of TST)	17.07 (10.38)	20.02 (4.43)	-1.21	ns
Percentage of REM (of TST)	25.45 (8.11)	24.33 (4.92)	0.54	ns
Percentage of Wake (of TSP)	13.01 (9.39)	6.54 (3.75)	2.97	p<.01
Sleep Efficiency Index (%)	91.64 (7.35)	96.52 (2.37)	-2.95	p<.05

Notes: BMI, body mass index; CFS, chronic fatigue syndrome; HC, healthy controls; TSP, total sleep period; TST, total sleep time; REM, rapid eye movement.

Values are given as Mean (SD); values are from the third recorded night (night 1 and night 2 data not shown).

Table 3: Retrospective sleep disturbances, self-reported by patients with CFS and healthy controls.

Self-reported sleep disturbance	CFS (N=19)	HC (N=22)	<i>t-test</i>	P Value
SF-36 (global)	29.50 ± 17.91	na	-	-
SF-36 (physical)	25.00 ± 14.42	na	-	-
SF-36 (energy/fatigue)	19.00 ± 15.78	na	-	-
PSQI (subjective sleep quality)	1.53 ± 0.70	0.64 ± 0.49	4.77	p<.001
PSQI (sleep latency)	1.89 ± 0.94	0.82 ± 0.59	4.47	p<.001
PSQI (sleep duration)	0.68 ± 0.95	0.18 ± 0.39	2.28	p<.05
PSQI (habitual sleep efficiency)	0.84 ± 1.07	0.18 ± 0.50	2.59	p<.05
PSQI (sleep disturbances)	1.74 ± 0.45	1.00 ± 0.44	5.30	p<.001
PSQI (use of sleep medication)	0.63 ± 1.11	0.09 ± 0.43	2.03	ns
PSQI (daytime dysfunction)	1.53 ± 0.96	0.59 ± 0.50	3.97	p<.01
PSQI (global)	8.84 ± 3.51	3.45 ± 1.77	6.33	p<.001
ISI	13.74 ± 4.81	2.64 ± 2.19	9.74	p<.001

Notes: CFS, chronic fatigue syndrome; HC, healthy controls; PSQI, Pittsburgh sleep quality index; ISI, insomnia severity index.

Values are given as Mean ± SD

Table 4: Comparison of Sleep Parameters: PSG vs. Sleep Diary: Pearson Product- Moment Correlation Coefficients.

Sleep Parameters	Means ^a		Correlation	
	PSG	Diary	Pearson <i>r</i>	<i>p</i> (2-tailed)
TST (min)	453.91 (73.74)	448.68 (101.31)	.65	.003*
SOL (min)	22.47 (20.49)	33.95 (21.67)	.21	.379
WASO (min)	37.13 (24.32)	41.58 (56.48)	.32	.179

Notes: *N* = 19 ^aValues are means; values in parentheses are standard deviations. **p* < .01
TST, total sleep time; SOL, sleep onset latency; WASO, wake after sleep onset; PSG, polysomnography
Values based on an average of night 2 and night 3.

Figure1: The Polysomnogram

Notes: EEG, electroencephalography; EOG, electrooculography, EMG, electromyography; ECG, electrocardiography PSG, polysomnography